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Cholecalciferol: A potent fat soluble vitamin to combat insomnia (A mini review)

Shahnai Basharat, Aiman Ijaz*, Fatima Abid, Faiza Iftikhar, Syed Amir Gilani

University Institute of Diet & Nutritional Sciences, The University of Lahore, Lahore, Pakistan

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Abstract

The Significance of active form of vitamin D is much beyond its classical role in bone health. It performs different functions in the body and included in fat soluble class of vitamins. Insomnia is a sleeping disorder which affects the quality and quantity of sleep. Sleeping disorders are increasing tremendously among the developing countries. About one third population of Pakistan is suffering from chronic insomnia. The previous scientific data revealed that a significant relation persist between vitamin D deficiency, insomnia and inflammation resulted in low immunity health complications included; inflammatory bowel disease (IBD), rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis (MS), atherosclerosis, or asthma. Furthermore, it has a potential role in the strengthening of the immune system and its associated health disorders that may increase the overall health care cost. Therefore, the aim of this article is to highlight the possible mechanism between the vitamin D in the betterment of sleep disorder and low immunity health risk factors.

* **Corresponding Author:** Aiman Ijaz ✉ aiman.ijaz@dncs.uol.edu.pk

Introduction

Brain stimulation during wakefulness cycle is governed by many arousal systems. There are different types of sleep disorders that affect the sleep included rapid eye movement sleep behavior disorder (REM), restless legs syndrome (RLS), obstructive sleep apnea (OSA) and Insomnia etc. Insomnia is a most common sleep disorder. (Silva *et al.*, 2016). It may be acute or chronic and coupled with daytime consequences such as fatigue, difficulty in concentrations and mood instability (Silva *et al.*, 2016).

Approximately 50% and 6% population in high income countries suffer from acute and chronic insomnia respectively. According to the survey research 30% Pakistanis reported that they have difficulties with sleep, 5% never sleep well and 64% had sound sleep (Kidwai and Ahmed *et al.*, 2013). According to National Sleep Foundation a person should get 6-7 hours of sleep in a day. It is caused by the excess use of social media, television, stress, Anxiety, use of Caffeine, alcohol, drug abuse and many other metabolic disorders (Gao *et al.*, 2018).

Vitamin D also called cholecalciferol is a fat soluble vitamin and has both exogenous and endogenous sources. Its presence in the body can be affected by different factors such as low intake of the sun bath, dark skin color and low intake in the food. Its deficiency play important role in the development of CVDs, infectious diseases and sleep disorders (Batool *et al.*, 2018). Deficiency of vitamin D is a global issue and affecting one billion populations in the world. In the Pakistan a study was conducted and the results showed that only 15.5% of the people living in Pakistan have optimal vitamin D levels (Riaz *et al.*, 2016).

Receptors of vitamin D₃ are present in various parts of the central nervous system, which stimulate the sleep cycle and play role in the regulation of sleep pattern. High intake of vitamin D is directly related to improvement of the sleep cycle (McCarty *et al.*, 2012).

Another study reveals that insomnia is strongly associated with the serum 25 (OH) D₃ level. Vitamin D and insomnia might be inter-related through

inflammation, disease, homeostatic imbalance and a non-specific immune system response to injury (de Lourdes *et al.*, 2012).

Vitamin D works as an immunosuppressant and serve to suppress pro inflammatory cytokines in the brain as well as in the body (Etten and Mathieu, 2005). The previous studies showed significant results in ameliorating the immune related and neurological disorders. The present study focuses to establish a more strong and long-lasting relation between vitamin D consumption and its outcomes.

Review of Literature

The Basal ganglia, is a major production site for dopamine in the brain, was the site for strongest perfusion irregularities in insomnia. Persons with insomnia had significant hyperarousal of the basal ganglia during the measured portion of non rapid eye movement sleep (REM). Thus the dopamine dysfunctioning is also a contributor in etiology and maintenance of insomnia (Smith *et al.*, 2006). According to these mechanisms, vitamin D deficiency may contribute to dopamine dysregulation, thereby increasing vulnerability to hyper-arousal and insomnia, thereby increasing inflammation and subsequent deleterious health outcomes (Smith *et al.*, 2002).

Chronic pain due to deficiency of active vitamin D (D₃) and insomnia

Nonspecific chronic pain in the body is an inflammatory marker of vitamin D deficiency (Abbasi *et al.*, 2013). According to a study, people with non-specific chronic pain having higher risk of shorter duration sleep. Increased in sensation of chronic pain is associated to low quality sleep duration is reported to be linked with an increase in Interleukin L-6 (Okura *et al.*, 2008). It is an inflammatory marker which is increased in the patient suffering from sleep apnea and low level of cholecalciferol. Their pain, quality of life significantly improved when supplements of vitamin D were given. In a study proportion of night time IL -6levels have been elevated in the individuals with insomnia as compared to duration of sleep (Toujani *et al.*, 2017).

The stimulation to major neurotransmitter occurs in ventrolateralpreoptic nucleus of hypothalamus by the interaction of circadian and homeostatic factors (de Oliveira, Hirotsu, Tufik and Andersen, 2017). Sleep disturbance is an important condition directly linked with the increased sensitivity to pain (hyperglasia) (Finan *et al.*, 2013). In the Peripheral Nervous System, immune system also takes part in the inflammatory process which contributes to hyperglasia. Sleep disturbance is directly associated with hyperglasia and now recently it has been linked with various values of active form of vitamin D. It has an inverse relationship with painfull manifestations caused such as fibromyalgia and rheumatic diseases. Fig. 1 (Jablonski *et al.*, 2011).

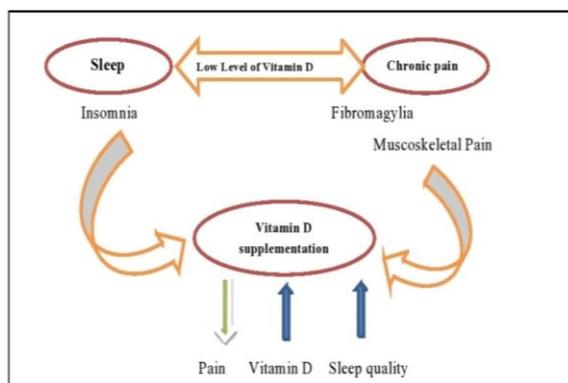


Fig. 1. Chronic pain due to vitamin D deficiency and insomnia.

The short sleep duration significantly associated with low level of vitamin D (<20ng/ml). It has bidirectional relationship between sleep and pain. In a study Supplementation of 1200IU /day of vitamin D were given to a group of people having serum vitamin D level between 20-29ng/ml and 50,000IU/weekly to those having serum vitamin D <20ng/ml in veterans with different areas of the chronic pain. The result showed that reduction in both pain and improvement of sleep pattern as well as duration of sleep (Huang *et al.*, 2013).

Another study 3,048 men >68 years old were selected to check their serum level 25(OH) D and their sleep pattern for an average of 24-h consecutively. Result showed that 16% of population had low serum vitamin D level (<20ng/mL) and short sleep duration (<5 h). While the men having high serum vitamin D level (>20ng/mL)

having good quality sleep duration. The findings of different studies showed a potential role of vitamin D in regulating healthy sleep (Massa *et al.*, 2015).

A Study found that presence of nonspecific pain is a valid marker for the presence of vitamin D deficiency. It has a reliable biological potential to contribute to sleep apnea through myopathy (Massa *et al.*, 2015). Another study showed that individual with musculoskeletal pain had low level of vitamin D and suffering from sleeping disorders as compared to healthy control. Chronic musculoskeletal pain is an indicator of hypovitaminosis of VDD (McCarty *et al.*, 2012).

According to an experimental study 89 individuals 20-50 years old with sleeping disorders were selected and divided into interventional and control group. Treatment group received a 50,000IU of vitamin D supplements on in a fortnight in two months. Control group received the placebo. Before and after the intervention sleep quality, physical activity, Sun exposure and three day food record questionnaires were assessed. Findings showed that sleep score decrease in vitamin D recipients as compared to control group. Findings showed that supplementation of vitamin D improve the quality of the sleep and duration of the sleep as well as reduction in the latency of the sleep (Majid, Ahmad, Bizhan, Hosein and Mohammad, 2017).

A study entitled sleep become epidemic due to vitamin D deficiency was performed for a 2 years to determine the effect of vitamin D supplementation in the improvement of sleep pattern. 1500 patients with neurological symptoms also suffer from the insomnia were selected. Many patients had recovered from the neurological symptoms and sleeping disorders by maintaining 60-89ng/mL vitamin D level. Results of this study found that patients had improvements in neurological symptoms including the good quality sleep by maintain a 60-80ng/mL blood level of 25 (OH) D₃ (Gominak & Stumpf, 2012).

In another finding depression is ameliorated with the supplementation of Vitamin D in adolescents. 54 Swedish adolescents were selected and individuals

identified with vitamin D deficiency were given supplements of vitamin D₃ for the 3 months. Mean serum level was 41 in the depressed individual which was increased to 91nmol/L. Result showed that vitamin D supplementation improved the depression and associated symptoms such as mood swings and feelings (Högberg *et al.*, 2012). In a study approximately 0.5mg/day melatonin was given combined with oral supplementation of vitamin D 50,000IU/week and 1000IU/day for three weeks to the individuals suffering from musculoskeletal pain and fatigue. Result of this study showed that symptoms improved within the first week and there was no need to increase the dosage (Sahakyan 2018).

Vitamin D is also correlated with the regulation of dopamine. Moreover, vitamin D might be involved in the regulation of the tyrosine hydroxylase gene expression, an enzyme which is involved in the production of dopamine and norepinephrine (Ganji *et al.*, 2010). Thus, the vitamin D gives protection against the activity of dopaminergic neurotoxins, thereby controlling the dopamine levels in the brain (Cass *et al.*, 2006).

Restless leg syndrome (RLS) is commonly linked with insomnia, has been correlated with reduced D₂ receptors in the putamen and dysfunction in the nigrostriatal DA areas (Connor *et al.*, 2009). A study which is conducted by Finan and Smith *et al.*, 2013 resulted that low dose dopamine was positively affects the RLS (Restless leg Syndrome) (Ganji *et al.*, 2010). Various observational studies indicated that insomnia is associated with chronic hyperarousal (Bonnet and Arand., 2010) and the insomniac individuals have more chances to develop depression as compared to the good sleepers (Taylor *et al.*, 2005). Chronic stress might be correlated with reduce ability to stimulate dopamine production in response to natural rewards (Abercrombie *et al.*, 1989) thereby increasing vulnerability to major depressive disorder while psychological stress has been found to activate dopamine production (Horvitz., 2002) (Seyedi and Gholami, 2019) (Fig. 2).

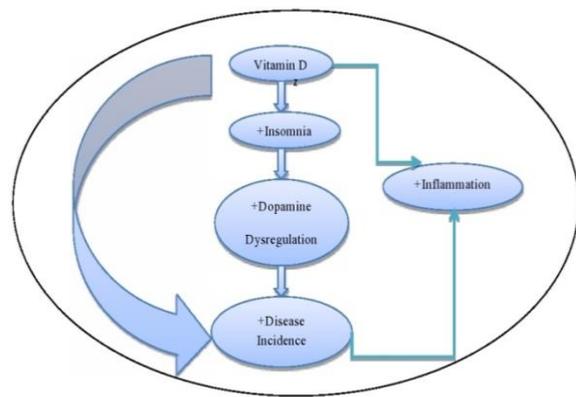


Fig. 2. Insomnia, Vitamin D and inflammation.

Vitamin D has a positive impact in the formation of serotonin, dopamine and many other neurotrophic factors (Holick, 2012). A research was conducted to analyze the impact of cholecalciferol supplementation on serum levels of dopamine, serotonin and Brain Derived Neurotrophic Factor (BDNF) among school going children with Attention deficient/Hyperactivity Disorder. Eighty-six children were selected in this study. Two groups were made on the base of randomized permuted blocks. Subjects received 2000IU cholecalciferol per day for 12 weeks. Dopamine, serotonin, 25-hydroxyvitamin D [25(OH) D] and BDNF serum levels were measure at the beginning and at the end of the study. Finding of this study revealed that the dopamine and 25-hydroxyvitamin D serum levels were significantly increased in the group who take 2000IU vitamin D₃ per day as compared to the experimental group ($p < 0.05$). Moreover, serum levels of BDNF and serotonin did not change significantly (Seyedi *et al.*, 2019).

Vitamin D plays an important role in the prevention and pathogenesis of insomnia (Espie *et al.*, 2019). Insomnia has a absolute link with vitamin D deficiency (Espie *et al.*, 2019). JOSEPH 2018 conducted a research to analyze the vitamin D serum levels in patients with insomnia. In this study, vitamin D serum levels of 50 subjects with insomnia have been assessed from the outpatient clinic. 5ml of blood was collected from the subjects for the measurement of 25-OH vitamin D total levels using fully automated chemiluminescent immunoassay. Result of this study concluded that 80% subjects were in deficient state (i.e., >20ng/ml) (insomniac) because of vitamin D

deficiency and the rest 20% were in the insufficient state (i.e., 20-30ng/ml) (Joseph *et al.*, 2018).

Another study related to vitamin D levels with the association of sleep duration is conducted by de Oliveria, Hirotsu *et al.*, 2018. In Brazil. It was a cross sectional study and also the part of the prospective EPISONO cohort. In this study seven hundred and twelve individuals were selected. Selected individuals answers sleep questionnaire and had their blood collected for serum 25OHD quantification and underwent polysomnography. Result of this study showed that individuals with a sleep duration of <6 hours had a 2-fold Increased odds of 25OHD<20ng/mL (OR=2.06, 95% CI 1.04-4.09, p=0.03) as compared to those who reported 6 or more hours of sleep. Furthermore, gender analysis indicated that men with a sleep duration of <6 hours had a 4-fold increased odds of 25OHD<20ng/mL (OR=4.10, 95% CI 1.37-12.23, p=0.01). In addition, a woman with short sleep duration was not correlated with lower levels of 25-hydroxy vitamin D. Study finding indicated that the time span of sleep <6 hours, but not obstructive sleep apnea, was an unrestrained factor correlated with 25-hydroxy

vitamin D serum levels <20ng/mL, particularly in men (de Oliveira *et al.*, 2018).

Vitamin D signaling and immune/inflammation system
 Vitamin D receptor is a crucial cell type in the non specific response which has been documented in macrophages. In macrophages, activation of the toll-like receptor helps to upregulate VDR, leading to control the TLR signaling which creates a negative feedback mechanism to control non-specific immunity (Krutzik *et al.*, 2008), (Christmas., 2010).

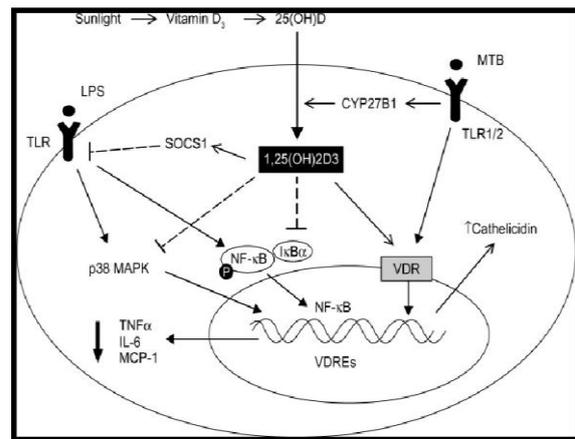


Fig. 3. Primary mechanisms through which vitamin D regulates the macrophage-mediated innate immune.

Table 1.

Source	Study design	Condition	Population (cases)	Main outcomes
MacCarty <i>et al.</i> ,	Cross sectional prospective	Serum 25(OH)D3 level	153 consecutive individuals	Individual with musculoskeletal pain had low level of vitamin D and suffering from insomnia
Majid <i>et al.</i> , 2017)	Double blind clinical trial	Supplementation of vitamin D	89 individuals 20-50 years old	Supplementation of vitamin D improves the quality of sleep
GretSahakyan., 2018)	Experimental study	0.5g melatonin combined with oral Supplementation of vitamin D 1000IU/day 50,000IU/week	10 women 60-65 years	Reduce musculoskeletal pain and fatigue
Seyedi <i>et al.</i> , 2019	Experimental Study	2000IU vitamin D/per day Serum level of BDNF, Dopamine, Serotonin, [25(OH)D] were measured	86 children with ADHD	Serum dopamine levels were significantly increase in children with ADHD who take 2000 IU vitamin D/per day
Maria Jai Joseph, 2018)	Prospective, Cross sectional, analytical study	Serum 25-OH vitamin D- Radioimmunoassay (RIA Kit method)	50 subjects (Male, Female, age 20-70 years)	80% subjects were insomniac due to vitamin D deficiency
De Oleveria DL <i>et al.</i> , 2018)	Cross-Sectional	Serum 25OHD quantification	712 individuals	the time span of sleep <6 hours was an unrestrained factor correlated with 25-hydroxy vitamin D serum levels <20 ng/mL

Evidence regarding Level of vitamin D and insomnia

Intake of Vitamin D enhances the toll like receptors (TLR) signaling, TLR belongs to the class of proteins. They play a key role in stimulating the non-specific immunity (Chan *et al.*, 2010). These single membrane receptors are expressed on cell macrophages and dendritic cells, with the help of SOCS1 (suppressor of cytokine signalling). This gene encodes suppressor of cytokine signaling and creates negative feedback mechanism which regulates cytokine signal transduction. It regulates the Proinflammatory cytokines and acts as a leukemia inhibitory factor (Zarubin and Jiahui., 2005). High levels of vitamin D is also associated with inhibition of P38 MAPK also known as mitogen activated protein kinase family which mediates wide variety of cellular activities in response to the extracellular stimulus (Coulthard *et al.*, 2009). They are activated by environmental stresses and inflammatory cytokines. 1, 25(OH)₂D₃ helps in activation of NF-KB signaling in human macrophages, which reduces the gene expression and protein release of proinflammatory mediators, such as TNF α , IL-6, and MCP-1, leading to decreased recruitment of monocytes/macrophages and overall inflammation within tissue (Kato, 2000). (Fig. 3) Evidence from the previous studies revealed that Inflammation accelerates neurological disorders, sleep disorders and chronic fatigue syndrome (ME). Thus, it is concluded that the presence of 1,25(OH)₂D₃ and vitamin D receptors represses inflammatory cytokine expression which further leads in treatment of insomnia, prostate cancer, cancer risk reduction, obesity and other diseases. (Table 1).

Conclusion

Vitamin D has a potential role in the strengthening of the immune system and its associated health disorders that may increase the overall health care cost. Vitamin D deficiency associated with inflammatory response in the body which affects the immune system as well as sleep disorders such as insomnia. Intake of vitamin D according to recommended dietary allowance per day play important role in the modulation of the immune/inflammatory system. It regulates the system with control of the production of inflammatory

cytokines and anti-inflammatory cytokines, as well as C-reactive protein (CRP) and inhibiting the proliferation of pro-inflammatory cells that leads to many health disorders.

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