

## Review Article

# Is Vitamin D Deficiency Implicated in Autonomic Dysfunction?

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ABSTRACT

Dysautonomia, dysfunction of the autonomic nervous system, presents with heterogeneous clinical features from an imbalanced regulation of the sympathetic and parasympathetic nervous systems. Low Vitamin D levels can explain the heterogeneous clinical features of migraine headaches, cardiac and gastrointestinal dysfunction, and oxidative stress evident in dysautonomia patients. The role of Vitamin D in modulating pain sensitivity has been recently established. However, there is a lack of research and understanding regarding the association between Vitamin D deficiency and autonomic dysfunction. Vitamin D is a neuroactive hormone that modulates autonomic balance, regulating the sympathetic and parasympathetic nervous systems, and has multisystem benefits. The following review explores the literature and addresses the relationship between Vitamin D deficiency and autonomic dysfunction. Overall, this literature review implicates Vitamin D deficiency in autonomic dysfunction and elucidates the potential therapeutic role of Vitamin D in autonomic disorders. PubMed search was performed for English articles from 1996 to 2016. Following keywords: Vitamin D, autonomic dysfunction and orthostatic hypotension, Vitamin D receptor, migraine and traumatic brain injury, Vitamin D, cardiac and gastrointestinal disease, Vitamin D, glutathione, oxidative stress, and serotonin were included. Only articles reporting primary data relevant to the above question were included in the study.

**KEYWORDS:** *Autonomic dysfunction and orthostatic hypotension, cardiac and gastrointestinal disease, glutathione and oxidative stress, migraine and traumatic brain injury, serotonin, Vitamin D, Vitamin D receptor*

## INTRODUCTION

Dysautonomia, dysfunction of the autonomic nervous system, impairs the differentiating neural crest that gives rise to neurons of the sympathetic and the parasympathetic nervous system affecting cardiac, enteric, osteocytes, and connective tissue. It presents with multiple symptoms including headaches, lightheadedness with orthostatic intolerance, palpitations, gastrointestinal dysfunction, generalized muscular pains, and exercise intolerance. Oxidative stress with increased pro-inflammatory markers and low levels of cerebrospinal fluid serotonin and dopamine metabolites-5HIAA, and HVA are evident in a subset of patients with juvenile neurocardiogenic syncope with dysautonomia based on abnormal tilt table test.<sup>[1,2]</sup>

Autonomic dysfunction has also been associated with increased pain sensitivity as in reflex sympathetic dystrophy with pain out of proportion to the cause.<sup>[3]</sup> Often increased pain sensitivity and nonspecific muscular aches can be a sign of Vitamin D deficiency. Headaches in dysautonomia patients may be explained by Vitamin D deficiency. A case series of three premenarchal girls with chronic tension-type headaches and generalized body pain were evaluated with Vitamin D deficiency. Symptoms improved with Vitamin D therapy suggesting a single symptom complex with Vitamin D deficiency as an etiology.<sup>[4]</sup> This literature review illustrates Vitamin D deficiency in autonomic dysfunction by demonstrating

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the role of Vitamin D in autonomic regulation, pain modulation and muscle function, gastrointestinal functioning, and as an antioxidative agent and thereby implicates Vitamin D deficiency in autonomic dysfunction. Figure 1 illustrates the role of Vitamin D deficiency in autonomic dysfunction.

### METHODOLOGY OF REVIEW

Studies published between 1996 and 2016 were reviewed through PubMed. The search was restricted to English. Following keywords were included: Vitamin D, autonomic dysfunction, orthostatic hypotension, Vitamin D receptor (VDR), migraine, traumatic brain injury (TBI), Vitamin D, cardiac and gastrointestinal disease, serotonin, glutathione, and oxidative stress. Only articles reporting primary data relevant to the association between Vitamin D deficiency and autonomic dysfunction were included in the study. Articles irrelevant to the role of Vitamin D and autonomic dysfunction were excluded with the rationale that these articles would lead to digression from this specific study. Table 1 summarizes the major studies reviewed.

### VITAMIN D FOR AUTONOMIC BALANCE

Vitamin D plays a crucial role in autonomic balance and may act as a central neuroactive substance. In a case report of a patient diagnosed with postural orthostatic tachycardia syndrome by tilt table studies, 1,25-dihydroxyvitamin D [1,25(OH) 2D] [1,25(OH) D3, calcitriol] – the main biologically active form of Vitamin D was found to be below normal. Supplementation with calcitriol resulted in improvement of orthostatic intolerance and palpitations. This suggests the potential therapeutic role of Vitamin D in autonomic dysfunction.<sup>[5]</sup>

Low Vitamin D status is associated with an increased risk of orthostatic hypotension. The association of hypovitaminosis D with orthostatic hypotension was

confirmed in a meta-analysis of five cross-sectional studies including 3646 participants (1270 with hypovitaminosis D and 2376 without). The participants with hypovitaminosis D had a higher prevalence of orthostatic hypotension (odds ratio = 1.88; 95% confidence interval [CI]: 1.25–2.84; I = 68%) that was not affected by adjusting for a median of five potential confounders. People with orthostatic hypotension had significantly reduced serum Vitamin D concentrations (standardized mean difference = -0.42; 95% CI: -0.72–-0.12).<sup>[6]</sup>

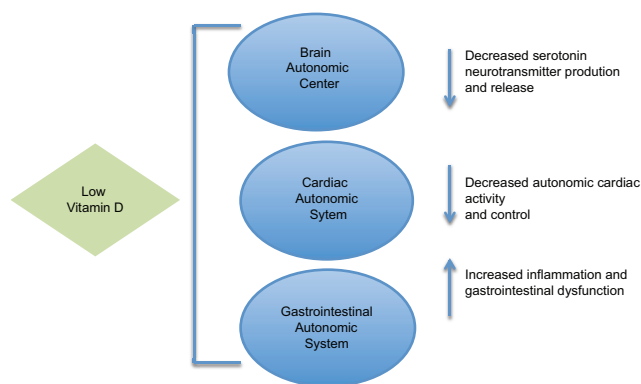
Low 1,25(OH) D3 levels are associated with unfavorable cardiac autonomic activity with suppression of resting cardiac autonomic activity.<sup>[7]</sup> A study of 84 healthy adolescents evaluating serum Vitamin D levels with myocardial function using tissue Doppler imaging showed subtle systolic and diastolic myocardial dysfunction in Saudi adolescents with low Vitamin D.<sup>[8]</sup> These studies suggest the crucial role of Vitamin D in the maintenance of cardiac autonomic balance.

### VITAMIN D FOR PAIN MODULATION, MIGRAINES, AND MUSCLE FUNCTION

The association of Vitamin D deficiency with increased pain sensation, migraine headaches, and poor muscle function are evident in several studies. Vitamin D receptors are found in the hypothalamus, a region of migraine pain sensation. There has been an association between migraines without aura and two VDR polymorphisms (Taq1 and FokI) in Iranian patients. Furthermore, headache severity was found to be worse in FokI heterozygote patients than homozygote patients.<sup>[9]</sup> Vitamin D binding to the VDR may be important in pain modulation. Vitamin D deficiency could lead to increased excitability and sensitization.

Vitamin D supplementation has been shown to reduce the frequency of migraine attacks. In the study by Cayir, Vitamin D supplementation in addition to antimigraine treatment reduced the number of migraine attacks in pediatric patients.<sup>[10]</sup> Vitamin D is known to have a neuroprotective role in patients with TBI.<sup>[11]</sup> There is a correlation between serum Vitamin D levels and severity of TBI. In a prospective observational study, Vitamin D was significantly lower in patients with severe TBI compared to patients with mild TBI ( $n = 95$ ,  $P = 0.03$ , CI 95% -23.60–-1.21, mean effect size 12.40 nmol/L).<sup>[12]</sup>

Vitamin D reduces pain severity and improves mobility and daily functioning. In a prospective pilot study of 35 children (18 males; age  $10.48 \pm 3.87$  years) with different musculoskeletal/orthopedic conditions and Vitamin D deficiency, Vitamin D therapy for 6 months



**Figure 1:** Vitamin D deficiency and autonomic dysfunction - Vitamin D stimulates release of serotonin and acts as an antioxidant, influencing the autonomic activities of the brain, cardiac, and gastrointestinal systems

**Table 1: The role of Vitamin D deficiency in autonomic dysfunction**

Role of Vitamin D	List of studies	Major study	Method	Main conclusion
Autonomic Balance	Chaudhari Ometto <i>et al.</i> Mann <i>et al.</i> Matter <i>et al.</i>	Chaudhari <i>et al.</i> Matter <i>et al.</i>	Case study Prospective study evaluating serum Vitamin D levels with myocardial function using tissue Doppler imaging  <i>n</i> =84 healthy adolescents divided into vitamin D deficient group with 25-hydroxy vitamin D (25(OH) D) levels less than 20 ng/mL and normal vitamin D (control group) versus 25(OH) D equal or more than 30 ng/mL	Supplementation with calcitriol resulted in improvement of orthostatic intolerance in a patient with postural orthostatic tachycardia syndrome (POTS) diagnosed by tilt table studies  Subtle systolic and diastolic myocardial dysfunction in Saudi adolescents with low Vitamin D
Migraines, Pain Modulation and Muscle Function	Mohammad Lawrence Toman <i>et al.</i> Cayir Blagojevic <i>et al.</i> Bezrati <i>et al.</i>	Cayir	Prospective trial Group 1 ( <i>n</i> =13): normal 25(OH) D levels and amitriptyline therapy Group 2 ( <i>n</i> =13): normal 25(OH) D levels and vitamin D+amitriptyline therapy Group 3 ( <i>n</i> =14): mildly deficient 25(OH) D levels and vitamin D + amitriptyline therapy Group 4 ( <i>n</i> =13): severely deficient 25(OH) D levels and vitamin D + amitriptyline therapy	Vitamin D supplementation in addition to amitriptyline therapy reduced the number of migraine attacks in pediatric patients
Gastrointestinal Function	Kedar <i>et al.</i> Kwon <i>et al.</i> Ahlawat Veit	Veit	Retrospective case control study <i>n</i> =59 pediatric patients with inflammatory (age 16.4±2.2 y) versus 116 controls (age 14.6±4.4 y)	Higher prevalence of vitamin D deficiency in pediatric patients with inflammatory bowel disease (42.4% versus 26.7%; <i>P</i> =0.04)
Antioxidant	Patrick Alvarez <i>et al.</i> Kanikarla Tao Bhat Dulla <i>et al.</i> Shinpo <i>et al.</i>	Alvarez <i>et al.</i>	Cross-sectional study <i>n</i> =50 PICU patients	Vitamin D sufficiency was associated with more reduced plasma EhCySS, indicative of lower oxidative stress in critically ill children

resulted in decreased pain intensity ( $P \leq 0.03$ ) as well as decreased functioning problems related to pain ( $P \leq 0.01$ ).<sup>[13]</sup> In a cross-sectional study of 125 healthy children who practiced football as a leisure activity, low plasma 25(OH)D levels were associated with decreased muscle strength and decreased exercise performance.<sup>[14]</sup> Vitamin D status may be a key factor in muscle function and pain intensity in patients with autonomic dysfunction.

## VITAMIN D FOR GASTROINTESTINAL FUNCTION

Vitamin D deficiency is associated with gastrointestinal dysfunction. Vitamin D is important for health of the enteric nervous system and influences gastric emptying. Patients with gastric dysmotility have low serum Vitamin D levels.<sup>[15]</sup> Low serum 25(OH)D levels are

associated with delayed gastric emptying time (GET) assessed by scintigraphy in Parkinson's disease patients that were divided into a delayed-GET group and a normal-GET group.<sup>[16]</sup>

Vitamin D deficiency is common in pediatric patients with gastrointestinal symptoms. The anti-inflammatory role of Vitamin D plays a protective role in gastrointestinal function. There is evidence to suggest an inverse relationship between Vitamin D status and inflammatory bowel disease (IBD).<sup>[17]</sup> In a retrospective case-control study of 59 pediatric patients with IBD (age 16.4 ± 2.2 years) versus 116 controls (age 14.6 ± 4.4 years) demonstrated that patients with IBD had a higher prevalence of Vitamin D deficiency (42.4% vs. 26.7%;  $P = 0.04$ ) with inflammation being the key determinant of Vitamin D status in IBD.<sup>[18]</sup>

## VITAMIN D AS AN ANTIOXIDANT

Interestingly, Vitamin D has been shown to have antioxidant properties along with its role in the production of serotonin, an antioxidant. The active form of Vitamin D, calcitriol activates the synthesis of serotonin-synthesizing gene tryptophan hydroxylase 2 in the brain at a Vitamin D response element.<sup>[19]</sup> Vitamin D sufficiency is associated with lower oxidative stress in critically ill children suggesting the crucial role of Vitamin D in maintaining redox status and in protecting against oxidative stress.<sup>[20]</sup>

Vitamin D inhibits oxidative stress and has anti-inflammatory properties.<sup>[21]</sup> In a study evaluating the association of cord blood levels of 25(OH)D with an inflammatory marker, C-reactive protein (CRP) in 1491 neonates in Heifei China, it was shown that the CRP decreased by 1.42 mg/L (95% CI: 0.90, 1.95) per 10 nmol/L increase in 25(OH)D among neonates with 25(OH)D <25.0 nmol/L, and CRP decreased by 0.49 mg/L (95% CI: 0.17, 0.80) among neonates with 25(OH)D between 25.0 nmol/L and 49.9 nmol/L.<sup>[22]</sup> The antioxidant potential of Vitamin D was evident in a rat model where treatment with Vitamin D caused a reversal of oxidative stress in the muscle tissue.<sup>[23]</sup> Vitamin D has been shown to inhibit production of several pro-inflammatory molecules including nitric oxide, interleukin (IL)-1 $\beta$ , and IL-6 from microglia.<sup>[24]</sup> The biologically active form of Vitamin D, 1,25(OH)<sub>2</sub>D<sub>3</sub>, has been reported to enhance intracellular glutathione concentration in the central nervous system.<sup>[25]</sup> Vitamin D as an antioxidative agent may serve to protect against autonomic dysfunction.

## CONCLUSION

Dysautonomia, dysfunction of the autonomic nervous system, affects the expression of genes involved in calcium metabolism before and after differentiation of the neural cells that gives rise to neurons of the sympathetic and the parasympathetic nervous system. Vitamin D is crucial for the effective functioning of the sympathetic and parasympathetic nervous systems. Low Vitamin D levels can explain the symptom complex of migraine headaches, cardiac and gastrointestinal dysfunction, and oxidative stress as evident in dysautonomia patients. This literature review elucidates the potential therapeutic role of Vitamin D for autonomic dysfunction. More research is needed to investigate the role of Vitamin D in autonomic disorders.

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## Conflicts of interest

There are no conflicts of interest.

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