



Shining Light on Dysautonomia: The Role of Vitamin D in Cardiac Autonomic Regulation

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Abstract

Purpose of review Traditionally recognized for its role in calcium homeostasis and bone metabolism, vitamin D is increasingly acknowledged for its broader physiological effects, particularly in cardiovascular health. One area of growing interest is its influence on cardiac autonomic function. Cardiac autonomic dysfunction, characterized by an imbalance between sympathetic and parasympathetic activity, is a well-established predictor of adverse cardiovascular outcomes. This narrative review aims to synthesize the current literature on the association between vitamin D status and cardiac autonomic function.

Recent findings Accumulating observational data indicate that individuals with vitamin D deficiency exhibit poorer cardiac autonomic function, reflected by reduced heart rate variability indices, compared to vitamin D-sufficient individuals. Interventional trials, though limited, suggest that vitamin D supplementation may improve autonomic balance, especially in those with baseline deficiency. The relationship appears to be affected by factors such as glycemic control, disease state, and vitamin D binding protein levels.

Summary Vitamin D may modulate autonomic regulation largely via the vitamin D receptor, which activation influences multiple downstream pathways, including central nervous system effects, neurotrophic properties, regulation of the renin-angiotensin-aldosterone system, calcium-parathyroid hormone axis, and immune modulation. However, inconsistencies in study design, population characteristics, and assessment methods limit the strength of current evidence. Further longitudinal and interventional studies are warranted to establish causality and determine whether vitamin D repletion can reduce cardiovascular risk by restoring autonomic balance.

Keywords Heart rate variability · Autonomic neuropathy · Vitamin D deficiency · Sympathetic nervous system · Parasympathetic nervous system

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Introduction

Traditionally recognized for its essential role in calcium regulation and bone homeostasis, vitamin D has gained growing attention for its influence on cardiovascular health, supported by the presence of vitamin D receptors (VDR) in cardiomyocytes and various cells of the cardiovascular and nervous systems [1, 2]. Observational studies have reported an inverse relationship between serum 25-hydroxyvitamin D [25(OH)D] levels and the risk of cardiovascular events, such as myocardial infarction, heart failure, and cardiac arrhythmias [3–6]. However, intervention trials using vitamin D supplementation have not consistently demonstrated a reduction in cardiovascular events or all-cause mortality [7], possibly due to variations in treatment duration, dosages, and study populations.

One emerging yet under-explored mechanism that may link vitamin D deficiency (VDD) to cardiovascular morbidity

is the impact of vitamin D levels on cardiac autonomic function. Cardiac arrhythmias, which are frequently observed in vitamin D-deficient individuals, may be partly attributed to autonomic imbalance, characterized by heightened sympathetic activity and reduced parasympathetic tone. Vitamin D is believed to modulate autonomic output, but direct evidence linking vitamin D status to cardiac autonomic regulation remains limited in the literature. Moreover, the relationship between vitamin D status and cardiac autonomic function remains inconclusive, with findings in the literature demonstrating mixed results. Similarly, interventional studies investigating the impact of vitamin D supplementation on cardiac autonomic function have produced conflicting outcomes.

Given these gaps and inconsistencies, this review aims to synthesize current evidence on the association between vitamin D and cardiac autonomic function. By examining both mechanistic pathways and clinical findings, we aim to determine whether vitamin D serves as a key modulator of cardiac autonomic regulation, potentially shedding light on its broader role in cardiovascular health.

Methodology

A structured literature search was conducted using MEDLINE via PubMed, CINAHL via EBSCOhost, and Cochrane library from inception to April 2025 (Supp. Figure 1). Search terms included “vitamin D”, “25-hydroxyvitamin D”, “cholecalciferol”, “calcitriol”, “ergocalciferol”, “25-OHD”, “cardiac autonomic”, “heart rate variability”. Observational studies, interventional trials, and experimental studies were included in this review. Non-English publications, case reports, animal studies, and abstracts were excluded. The search yielded 183 results, from which 25 relevant articles were identified through titles and abstracts screening. Following full-text review, 23 studies met the inclusion criteria: 8 involved apparently healthy individuals, 8 focused on patients with pre-diabetes or diabetes mellitus, and 7 examined other patient groups, including those with sleep apnea, multiple sclerosis, or heart failure. Of these, 7 studies assessed the effects of vitamin D supplementation on cardiac autonomic function. A manual search of the reference lists of all included articles was performed; however, no additional eligible studies were identified. Given the narrative nature of this review, data were synthesized qualitatively.

Vitamin D

Vitamin D is a secosteroid obtained primarily through cutaneous synthesis with sun exposure as previtamin D₃. It is then metabolized into 25(OH)D in the liver, which is the

main circulating compound, with a half-life of 2–3 weeks. Subsequently, it is hydroxylated by 1- α hydroxylase in the kidneys into the biologically active form of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)₂D], with a shorter half-life of 4–6 h. Vitamin D is weakly bound to vitamin D binding protein (VDBP) which is synthesized in the liver for transportation and acts on various tissues in the body which express VDR. Activated vitamin D facilitates calcium absorption from the gastrointestinal tract, while its activation is influenced by parathyroid hormones.

Serum 25(OH)D is used widely as the main measure of vitamin D level. Although to date, there is no consensus on the normal range of 25(OH)D and levels of VDD and insufficiency, a level of 30 ng/mL and above is considered sufficient, while a level of below 20 ng/mL is defined as VDD [8].

The Cardiac Autonomic Nervous System

The cardiac autonomic nervous system (ANS) is a component of the peripheral nervous system which functions without conscious effort. It controls cardiac muscle contraction and regulates heart rate and blood pressure (BP). The ANS consists of the sympathetic and parasympathetic systems and is controlled by centres in the spinal cord, brain stem, and hypothalamus. The sympathetic system prepares the body for stressful situations, and its stimulation increases the heart rate and myocardial contractility. On the other hand, the parasympathetic system counteracts the sympathetic system, and its stimulation decreases the heart rate. Therefore, autonomic imbalance is characterized by a hyperactive sympathetic system and a hypoactive parasympathetic system, which is associated with increased risk of cardiac arrhythmias and sudden cardiac death [9].

The nerves of the sympathetic system originate from the spinal cord, whereas the parasympathetic system nerves originate from the brainstem and sacral region of the spinal cord. While the postganglionic endings of the parasympathetic system secrete acetylcholine, most of the endings of the sympathetic system release norepinephrine.

Autonomic regulation of the cardiovascular function is complex, involving baroreflex and chemoreflex pathways, neural modulation of heart rate and BP, bidirectional relationship with endothelial function, and interactions with humoral systems like the renin–angiotensin–aldosterone system (RAAS) [10]. In addition, calcium channels in the plasma membrane and sarcoplasmic reticulum membrane in cardiac myocytes play an important role in electrophysiological properties of the heart and control of cardiac contractility [11]. As the parathyroid hormone and vitamin D play crucial roles in calcium regulation, disruptions in calcium and parathyroid hormone levels can also significantly

impact cardiac function and autonomic nervous system function.

Cardiac autonomic dysfunction is associated with increased mortality particularly among those with diabetes [12, 13] and end stage renal failure [14]. Although the exact mechanism of the increased mortality in autonomic dysfunction is unknown, a few of the possible causes include prolongation of the QT interval [15], asymptomatic myocardial ischemia [16], and cardiac arrhythmias [17].

The cardiac autonomic function can be assessed by a few non-invasive tests. One of the more commonly used assessment is heart rate variability (HRV) [18–20], which represents a measure of the variations in heart rate. The time-domain measures analyze beat-to-beat (NN) intervals over time, whereas the frequency-domain measures reflect how much power or variance exists in specific frequency bands, such as high- and low-frequencies. The low frequency to high frequency (LF:HF) ratio is used as an index of sympathovagal balance. Other assessments include autonomic reflex testing (Ewing's manoeuvres) [21], baroreflex sensitivity [22, 23], heart rate recovery post-exercise, heart rate turbulence, and plasma or urine catecholamine measurements with or without tilt test [24, 25]. The summary of these measures is displayed in Table 1.

Clinical Evidence of the Association Between Vitamin D and Cardiac Autonomic Function

Clinical Studies Exploring Vitamin D and Cardiac Autonomic Function

Apparently Healthy Individuals

Individuals with VDD were demonstrated to have lower HRV parameters on 24-h Holter monitoring compared to vitamin D sufficient individuals [26]. This observation was also demonstrated among those with vitamin D insufficiency (VDI) using short term HRV monitoring [27]. Moreover, serum 25(OH)D was positively correlated with heart rate recovery indices post-exercise stress test [26] and HRV parameters [27, 28] in both groups of patients. These findings suggest that individuals with VDD and VDI exhibit impaired cardiac autonomic regulation and highlight the potential role of vitamin D in cardiac function.

When angiotensin II (AngII) was infused to simulate a stress response, the LF:HF ratio demonstrated an increasing trend in individuals with VDD and VDI [29, 30], although the change was statistically significant only among those with VDI [29]. An elevated LF:HF ratio is often interpreted as a shift toward sympathetic dominance or reduced parasympathetic modulation. This observation suggests the

Table 1 Cardiac autonomic function tests

Test	Measures	Interpretation
Heart rate variability	Variations in heart rate	Higher readings reflect better autonomic function
1. Time domain	SDNN, SDANN, ASDNN, rMSSD, NN50, pNN50	LF is a marker of both sympathetic and parasympathetic activity modulation
2. Frequency domain	ULF, VLF, LF, HF, LF:HF	HF reflects parasympathetic activity; higher readings reflect better autonomic function
		LF:HF ratio is index of sympathovagal balance; higher ratio suggests sympathetic dominance; lower ratio indicates vagal predominance
Autonomic reflex testing (Ewing's manoeuvres)	Heart rate and blood pressure responses to physiological stimuli, eg deep breathing, Valsalva manoeuvre, standing, and sustained handgrip	≥ 3 abnormal tests indicate definite autonomic neuropathy
	Particularly in detecting cardiac autonomic neuropathy	
Baroreflex sensitivity	Effectiveness of heart rate changes in response to BP fluctuations	Higher sensitivity reflects greater HRV and better autonomic function
Heart rate recovery	Speed at which heart rate drops after peak exercise, reflecting sympathetic withdrawal and parasympathetic reactivation	Blunted heart rate recovery indicates impaired vagal tone and autonomic imbalance
Heart rate turbulence	Short-term fluctuations in heart rate following premature ventricular contraction	≥ 0% turbulence onset and ≤ 2.5 ms/RR turbulence slope indicates impaired baroreflex and vagal activity
Plasma or urine catecholamine with or without tilt test	Sympathetic activity	Elevated levels reflect over-activity while low levels indicate autonomic failure at baseline
		Blunted response with tilt test suggests sympathetic activity failure
		*Can be influenced by stress, medications, and acute conditions, therefore, to be interpreted alongside other cardiac autonomic function measures

SDNN standard deviation of the NN intervals, *SDANN* standard deviation of 5-min average NN intervals, *ASDNN* mean of the standard deviations of all NN intervals for all 5-min segments of entire recording, *rMSSD* square root of the mean of the squares of successive NN interval differences, *NN50* the number of interval differences of successive NN intervals greater than 50 ms, *pNN50* proportion of NN50 to the total number of NN intervals, *ULF* ultra-low frequency, *VLF* very low frequency, *LF* low frequency, *HF* high frequency

possibility of RAAS activation contributing to autonomic dysfunction among those with hypovitaminosis D (deficient or insufficient vitamin D levels), potentially worsening cardiovascular complications in this group of individuals. Moreover, autonomic dysfunction in VDD and VDI may become more apparent with the presence of physiological stressors. This is exemplified by a greater increase in serum norepinephrine during the head-up tilt test in a group of young patients with vitamin D sufficiency compared to those who had hypovitaminosis D [31], suggesting a more robust sympathetic nervous system (SNS) response to orthostatic stress in those with adequate vitamin D levels. Inadequate orthostatic sympathetic activation, as seen in hypovitaminosis D, has been linked to increased cardiovascular risks [32].

Conversely, among 54 individuals with VDD who underwent 1-h Holter performed in sitting position after a 30-min rest, the HRV parameters did not differ compared to the control group of healthy individuals [33]. Nevertheless, it is important to note that the subjects studied were younger than those in previous studies. Additionally, the supposedly healthy control group had a mean 25(OH)D level in the deficient and insufficient range, which may have contributed to the lack of significant difference. Moreover, a lack of physiological stressors and a shorter assessment of HRV in a resting state may not fully capture the autonomic dysfunction.

In summary, most evidence in the healthy populations indicates that VDD is associated with poorer cardiac autonomic function.

Diabetes or Pre-Diabetes

Among patients with type 2 diabetes, those with VDD and VDI demonstrated more deranged HRV compared to those with higher serum 25(OH)D levels, although the correlation results were inconsistent between studies [34–36]. The calculated cardiac autonomic neuropathy (CAN) score was also higher among those with lower vitamin D concentrations, particularly those involving Valsalva manoeuvre, implying poorer cardiac autonomic function among those with hypovitaminosis D [34]. Similarly, those with presence of cardiac autonomic dysfunction exhibited lower serum 25(OH)D levels [37]. Additionally, serum 25(OH)D levels were found correlated with HF and LF:HF ratio among type 1 diabetes patients with cardiac autonomic dysfunction [38]. Nevertheless, the inconsistent correlation results in the studies suggest that additional factors may play a role in modulating this relationship, including glycemic control, duration of diabetes, and presence of inflammation [19]. Interestingly, an inverted U-shaped association was observed between serum 25(OH)D level and autonomic function indices [39]. In that study [79 patients with type 1 and 34 with type 2 diabetes], increasing 25(OH)D levels from 10 to 20 ng/mL

was associated with improved autonomic function, but levels beyond 50 ng/mL were linked to worsening outcomes. This finding aligns with an earlier study showing increased cardiovascular morbidity and mortality at both low and high 25(OH)D levels [40]. This suggests the importance of an optimal vitamin D range to avoid potential adverse effects on cardiovascular autonomic function in diabetes.

Conversely, the relationship between vitamin D level and cardiac autonomic function is scarce and inconsistent in individuals with pre-diabetes. One study ($n=126$) found no significant difference in vitamin D levels between individuals with cardiac autonomic dysfunction and those without, nor any correlation between 25(OH)D levels and cardiac autonomic function parameters [41]. However, another study ($n=113$) reported lower vitamin D levels in those with autonomic dysfunction, and demonstrated that severe VDD [25(OH)D < 10 ng/mL] was associated with significantly lower standard deviation of the NN intervals (SDNN) and square root of the mean of the squares of successive NN interval differences (rMSSD), and a higher LF:HF ratio, compared to higher vitamin D statuses [42]. This was further confirmed on regression analysis, which demonstrated 25(OH)D level to be positively correlated with SDNN and negatively correlated with LF:HF ratio. Moreover, the calculated odds ratio of developing cardiac autonomic dysfunction for those with severe VDD was 2.38 (95% CI 1.21, 4.69) and 1.88 (95% CI 1.06, 3.75) for those with VDD [serum 25(OH)D 10–20 ng/mL].

Additionally, VDBP levels were elevated in individuals with cardiac autonomic dysfunction, and showed a positive correlation with markers of parasympathetic activity [41]. This suggests that vitamin D transport and bioavailability might influence autonomic function independently of serum 25(OH)D levels.

Overall, in patients with diabetes, lower vitamin D levels are generally associated with worse autonomic function, although this relationship may be influenced by glycemic control and other factors. This association may be bidirectional. Diabetes mellitus is an established cause of cardiac autonomic dysfunction, primarily mediated by chronic hyperglycemia, oxidative stress, and diabetes-related neuropathy [43]. In contrast, the relationship between VDD and impaired autonomic regulation is largely derived from observational studies, suggesting an association rather than a definitive causal effect. In individuals with diabetes, VDD may exacerbate this risk, potentially through VDR-mediated pathways. The co-existence of chronic low-grade inflammation and persistent metabolic dysregulation may further amplify these effects, thereby increasing the susceptibility to cardiac autonomic dysfunction. Notably, excessively high vitamin D levels may also be detrimental in diabetes, underscoring the importance of maintaining an optimal vitamin D range.

Other Groups

Obstructive sleep apnea (OSA) patients with VDD were noted to have poorer HRV parameters in both 24-h Holter monitoring and 5-min short term HRV using the Polar device compared to those without VDD [44]. Additionally, serum 25(OH)D level was negatively correlated with SNS and stress indices. These findings highlight the role of vitamin D in autonomic regulation in OSA, where deficiency may contribute to heightened sympathetic activity and diminished parasympathetic tone. These features are commonly observed in this group of patients, contributing to the risk of hypertension and cardiovascular complications [45]. Although there was no significant difference demonstrated in the HRV parameters between congestive heart failure patients with VDD compared to the healthy controls, serum 25(OH)D level was found to be positively correlated with SDNN and standard deviation of 5-min average NN intervals (SDANN) among those with non-ischaemic dilated cardiomyopathy [46], which may suggest the potential role of vitamin D in cardioprotective mechanisms and autonomic stability in these patients. In contrast, there seems to be no correlation between vitamin D level and HRV parameters in patients with multiple sclerosis [47] and adults who were born pre-term [48]. This may be explained by the small sample sizes [47, 48], lack of vitamin D sufficiency as a control group [48], and the presence of immunomodulating drug use at the time of cardiac autonomic function assessment [47].

The studies investigating the relationship between vitamin D and autonomic function are summarized in Table 2. These findings collectively suggest that while this association may vary across populations, individuals with chronic diseases and low vitamin D levels exhibit impaired HRV when compared to those who are vitamin D sufficient.

Effect of Vitamin D Supplementation on Cardiac Autonomic Function

Studies examining the effects of vitamin D supplementation on cardiac autonomic function remain limited. Nevertheless, despite the inconsistencies in the correlation between vitamin D levels and cardiac autonomic function parameters, supplementation appears to have a potential beneficial effect in improving cardiac dysautonomia.

The use of high dose vitamin D3 at 300,000 IU given as a single dose was shown to improve HRV parameters among those with VDD to a level similar to the vitamin D-sufficient group [28]. Likewise, administering vitamin D3 at a dose of 30 mcg (~1200 IU) daily for 180 days resulted in a reduction in serum norepinephrine levels among vitamin D-deficient patients, bringing them to levels comparable to those with

vitamin D sufficiency [31]. Furthermore, vitamin D supplementation improved the serum norepinephrine response to physiological stress during the head-up tilt test in individuals with hypovitaminosis D eliminating the differences in the levels of norepinephrine between groups [31].

These benefits were similarly seen among type 1 diabetes patients with cardiac autonomic dysfunction given a total of 12-week duration of cholecalciferol at 10,000 IU daily for those with serum 25(OH)D level of <30 ng/mL, or 4,000 IU daily otherwise [38]. The improvement in the HRV parameters seems to be more pronounced among OSA patients only when they had VDI at baseline and achieved sufficient vitamin D levels at the end of the 16-week treatment duration with 4,000–6,000 IU daily of vitamin D3 depending on their vitamin D statuses [49]. Although no difference was observed among patients with end stage renal disease on regular hemodialysis given vitamin D supplementation, an increment of LF:HF ratio was observed among those who remained vitamin D-deficient after treatment [50]. Furthermore, AngII infusion, given to simulate a stress response, mitigated the increment in LF:HF ratio among healthy patients with VDI [30], as well as patients with IgA nephropathy [51], after 4 weeks of vitamin D3 supplementation.

The studies exploring the effect of vitamin D supplementation on cardiac autonomic function are summarized in Table 3. Despite limited studies, some small interventional studies suggest possible improvement in selected autonomic indices, particularly in individuals with baseline deficiency, highlighting its potential therapeutic role in restoring autonomic balance and reducing cardiovascular risks.

Sources of Heterogeneity

The current body of literature presents inconsistent findings regarding the association between vitamin D status and cardiac autonomic function, as well as the therapeutic benefits of vitamin D supplementation across various populations. Several factors may account for these discrepancies:

1. Variations and limitations in study design.

The majority of existing studies are cross-sectional or observational in nature, limiting the ability to infer causality between vitamin D status and autonomic function. Longitudinal studies assessing the impact of dynamic changes in vitamin D levels over time on autonomic outcomes are lacking. Additionally, heterogeneity in study populations, disease severity, baseline vitamin D statuses, small sample sizes, control group not in the vitamin D-sufficient range, and differences in supplementation regimes (dose, duration, and form of vitamin D) contribute to inconsistent findings. Besides,

Table 2 Correlation studies between vitamin D and cardiac autonomic function

Study	Country	Study population	Age	Sex (M:F)	25(OH)D level, ng/mL	Control group	Measurement tool	Main findings
<i>Study group: Apparently healthy</i>								
Mann 2013 [29]	Canada	7 VDD	37±5	2:5	15.2±0.8	27 non-VDD	180-min ECG with graded AngII infusion	Lower LF:HF in VDD; Increasing trend of LF:HF with AngII graded infusion in VDD but not statistically significant
Canpolat 2014 [26]	Turkey	24 VDD	38.2±6.6	12:12	13.8±2.3	50 VDS	24-h Holter for HRV, heart rate recovery index post-exercise stress test	VDD lower SDNN, SDANN, rMSSD, pNN50, HF, higher LF, LF/HF; Serum 25(OH)D positively correlated with heart rate recovery indices
Tak 2014 [79]	Korea	50 VDD	55.9±10.9	19:31	11.4±2.5	126 non-VDD	5-min ECG	Lower SDNN in VDD group, 25(OH)D positively correlated with SDNN and LF
Lopez 2017 [27]	USA	44 VDI	62.7±5.2	18:26	23.25±4.44	51 VDS	TM-Oxi for HRV	VDD independently correlated with low SDNN, OR 3.07 (95% CI 1.32, 7.14) rMSSD, HF, TP lower in VDI than VDS
Nalbant 2017 [33]	Turkey	54 VDD	27.8±5.54	7:47	6.1±3.3	51 healthy	1-h Holter in sitting position after 30-min rest	Serum 25(OH)D positively correlated with rMSSD, HF, negatively correlated with LF:HF
<i>Study group: Diabetes/pre-diabetes</i>								
Jung 2015 [34]	Korea	257 type 2 diabetes	56.8±11.6	84:79	15.1±7.5	Nil	DICAN Medi-core for HRV	Longer QTc in VDS, no difference in HRV parameters (SDNN, SDANN, SDNNI, rMSSD, pNN50)
Maser 2015 [36]	USA	26 type 2 diabetes + VDI	60±10	11:15	21.4±5.1	24 type 2 diabetes + VDS	ECG for RR (MCR, E/I ratio), heart rate response to Valsalva	Lower supine SDNN and rMSSD, higher LF:HF in 25(OH)D < 10 ng/mL than 25(OH)D 10–20 ng/mL and 25OHD ≥ 20 ng/mL; Higher prevalence of CAN (Valsalva manoeuvre) among those with lower 25(OH)D; No correlation between 25(OH)D with HRV parameters
Hansen 2017 [39]	Denmark	79 type 1 diabetes, 34 type 2 diabetes	54.3±13.5 60.8±10.4	47:32 18:16	33.7±13.1 32.5±14.3	Nil	5-min HRV, CART	Lower MCR and E/I ratio in VDI than VDS; VDI negatively correlated with MCR and E/I ratio
								Inverted U-shaped association between 25(OH)D and CART (lying to standing ratio, deep breathing test), rMSSD, SDNN, HF

Table 2 (continued)

Study	Country	Study population	Age	Sex (M:F)	25(OH)D level, ng/mL	Control group	Measurement tool	Main findings
Dimova 2020 [41]	Bulgaria	126 pre-diabetes (50 IFG, 25 IGT, 51 IFG+IGT)	50.9±11.9	43:83	13.6 (10.4, 18.0)	48 normal glucose tolerance	CART	No difference in 25(OH)D level with cardiac dysautonomia; No correlation between 25(OH)D with ANS activity; VDBP lower in cardiac dysautonomia, positively correlated with parasympathetic activity
Bai 2022 [42]	China	113 pre-diabetes with CAN	59.5±9.91	60:53	14.0±4.12	180 pre-diabetes without CAN	CAN score from cardiovascular autonomic reflex test, 24—h Holter for HRV	25(OH)D lower in CAN group; Lower SDNN, rMSSD, higher LF:HF in VDD; 25(OH)D positively correlated with SDNN, negatively correlated with LF:HF Risk of CAN in 25(OH)D < 10 ng/mL: OR 2.38 (95% CI 1.21, 4.69); Risk of CAN in 25(OH)D 10—20 ng/mL: OR 1.88 (95% CI 1.06, 3.75)
Chen 2022 [35]	China	55 VDD with type 2 diabetes, 89 VDI with type 2 diabetes	60.4±11.7; 57.9±9.8	22:33; 48:41	9.27±1.95; 15.56±2.41	47 VDS with type 2 diabetes	24-h Holter for HRV	SDNN, ASDNN, pNN50, LF, HF, SDANN, rMSSD lower in VDD than VDS; pNN50, rMSSD lower in VDI than VDS; LF:HF higher in VDD and VDI than VDS; 25(OH)D positively correlated with rMSSD
Zhang 2023 [37]	China	116 type 2 diabetes+cardiac dysautonomia	65.6±8.5	60:56	24.9±9.4	160 type 2 diabetes with no cardiac dysautonomia	CART	25(OH)D lower in cardiac dysautonomia than without
<i>Study group: Others</i>								
Cetin 2014 [80]	Turkey	71 CCF (36 NIDCM, 35 IDCM)	59±14 62±10	22:14 26:9	14.3±6.2 15.8±6.5	25 healthy	24-h Holter for HRV and heart rate turbulence	No significant differences in HRV parameters between NIDCM and IDCM with VDD compared to control; 25(OH)D positively correlated with SDNN, SDANN, negatively correlated with QTc in NIDCM; 1,25(OH) ₂ D level lower in NIDCM with abnormal TS
Akturk 2019 [47]	Turkey	26 Multiple Sclerosis	35.6±6.1	11:15	24.98 (9.74, 47.94)	24 healthy	Orthostatic hypotension, 24-h blood pressure	25(OH)D, VDBP, VDR no correlation with orthostatic hypotension, supine hypertension, 24-h systolic blood pressure variability

Table 2 (continued)

Study	Country	Study population	Age	Sex (M:F)	25(OH)D level, ng/mL	Control group	Measurement tool	Main findings
Bjorkman 2023 [48]	Finland	30 born pre-term	24.4±0.9	11:19	29.4±11.4	16 born full-term	2 weeks of multisensory ring sleep tracer for heart rate and HRV	25(OH)D no correlation with cardiac autonomic function parameters
Loh 2025 [44]	Malaysia	118 OSA+VDD	41.6±11.7	39:79	14.2±3.6	86 OSA non-VDD	24-h Holter for HRV, 5-min Polar for HRV	ASDNN, SDANN, SDNN, rMSSD, PNS index lower, SNS index higher in VDD than non-VDD; 25(OH)D negatively correlated with SNS and stress indices

Continuous variables are presented as mean±SD or median (IQR)

M male, *F* female, *25(OH)D* 25-hydroxyvitamin D, *VDD* vitamin D deficiency, *AngII* Angiotensin II, *LF* low frequency, *HF* high frequency, *VDS* vitamin D sufficiency, *HRV* heart rate variability, *SDNN* standard deviation of the NN intervals, *SDANN* standard deviation of 5-min average NN intervals, *rMSSD* square root of the mean of the squares of successive NN interval differences, *pNN50* proportion of the number of interval differences of successive NN intervals greater than 50 ms to the total number of NN intervals, *OR* odds ratio, *CI* confidence interval, *TP* total power (area under the curve of frequency domain), *VDI* vitamin D insufficiency, *SDNNI* SDNN index, *MCR* mean circular resistant, *E/I* expiration/inspiration, *CART* cardiovascular autonomic reflex test, *IFG* impaired fasting glucose, *IGT* impaired glucose tolerance, *ANS* autonomic nervous system, *CAN* cardiac autonomic neuropathy, *ASDNN* mean of the standard deviations of all NN intervals for all 5-min segments of entire recording, *CCF* congestive cardiac failure, *NIDCM* non-ischemic dilated cardiomyopathy, *IDCM* ischemic dilated cardiomyopathy, *1,25(OH)₂D* 1,25-dihydroxyvitamin D, *OSA* obstructive sleep apnea, *SNS* sympathetic nervous system

including patients who are on treatment which affect cardiac autonomic function may have affected the association.

2. Variability in autonomic assessment methods.

A wide range of methodologies has been employed to evaluate cardiac autonomic function, including differing HRV metrics, test durations (short-term vs. 24-h), and testing conditions (rest vs. physiological stress). The absence of standardized protocols hinders the ability to compare outcomes across studies and may partially explain the conflicting results observed.

3. Limited focus on bioavailable vitamin D.

Most studies have focused on total serum 25(OH)D concentrations without accounting for the bioavailable or free vitamin D fraction, which is influenced by VDBP. Conditions such as pre-diabetes may alter VDBP concentrations, thereby modulating the biological activity of vitamin D and potentially affecting autonomic outcomes. The under-representation of bioavailable vitamin D in research limits the understanding of its true physiological impact.

4. Influence of genetic polymorphism.

Genetic variability in VDR, VDBP, and enzymes involved in vitamin D metabolism can influence individual responses

to vitamin D. Ethnic differences in these polymorphisms may contribute to inter-individual variability in both vitamin D status and cardiac autonomic function measures, adding another layer of complexity to the interpretation of study findings.

Overall Summary of the Clinical Findings

Collectively, these findings highlight the interplay between vitamin D status and cardiac autonomic function across diverse populations. Observational studies suggest that cardiac dysautonomia is generally more pronounced in individuals with VDD and VDI, and that serum 25(OH)D level is correlated with the majority of the HRV parameters. Both VDR and VDBP may play essential roles in modulating cardiac autonomic function. However, due to scarcity of data, it remains uncertain whether high vitamin D levels might harm autonomic function. The conflicting results between pre-diabetes and type 1 or type 2 diabetes suggest that autonomic dysfunction may occur only in the later stages of metabolic diseases. Nevertheless, it is notable that, despite mixed correlational evidence in the subgroups, some small interventional studies demonstrated improvements in autonomic function with vitamin D repletion, particularly benefiting individuals with VDD and VDI, leading to improvements in cardiac autonomic function. However, whether this translates to mitigation of cardiovascular risks observed with VDD and VDI is yet to be determined.

Table 3 Interventional trials on impact of vitamin D supplementation on cardiac autonomic function

Study	Country	Study population	Mean age	Sex (M:F)	Baseline 25(OH)D, ng/mL	Control group	Measurement tool	Intervention	Main findings
<i>Study group: Apparently healthy</i>									
Mann 2014 [30]	Canada	13 VDI	33±3	3:10	22±2	-	180-min ECG with graded AngII infusion	Vitamin D3 5000 IU (n=11) or 10,000 IU (n=2) for 28 days	Increased LF:HF with AngII infusion from baseline without vitamin D3; No significant change in LF:HF with AngII infusion from baseline with vitamin D3
Tonnesen 2018 [31]	Denmark	13 VDD	21.7±2	7:6	12.8±6.6	14 VDS	Serum epinephrine and norepinephrine with head-up tilt test	Vitamin D3 30 mcg (~1200 IU) daily for 180 days	Higher serum norepinephrine at rest in VDD group, no difference from VDS group after 90 days of vitamin D supplementation; Higher increase in norepinephrine in VDS group in head-up tilt test, no difference between groups after 30 days of vitamin D supplementation
Dogdus 2019 [28]	Turkey	52 VDD	34.6±7.4	24:28	9.2 (5.04, 16.2)	50 VDS	24-h Holter for HRV	Vitamin D3 300,000 IU stat dose	SDNN, SDANN, rMSSD, pNN50 lower in VDD, improved after vitamin D replacement with no significant difference in HRV parameters compared to VDS group; Serum 25(OH)D positively correlated with SDNN, SDANN, rMSSD, pNN50, HF
<i>Study group: Diabetes/ pre-diabetes</i>									
Silva 2020 [38]	Brazil	23 type 1 diabetes with CAN	29.8±10.7	11:12	26±9	Nil	CART, VNS-MICRO analysis for HRV	Cholecalciferol 10,000 IU daily for 25(OH)D<30 ng/mL; 4000 IU daily for 25(OH)D≥30 ng/mL for 12 weeks	Improvement in VLF, LF, HF, TP, RRmax, RRNN, SDNN with vitamin D supplementation; 25(OH)D positively correlated with HF %, negatively correlated with LF:HF
<i>Study group: Others</i>									
Mann 2015 [51]	Canada	15 IgA nephropathy	41±4	13:2	25.2±2.8	-	180-min ECG with graded AngII infusion	Vitamin D3 10,000 IU/d for 28 days	Reduced LF:HF response to AngII infusion with vitamin D supplementation; 1,25(OH) ₂ D levels associated with graded increase in cardioprotective parasympathetic activity with AngII infusion

Table 3 (continued)

Study	Country	Study population	Mean age	Sex (M:F)	Baseline 25(OH)D, ng/mL	Control group	Measurement tool	Intervention	Main findings
Mann 2016 [50]	Canada	56 end-stage renal failure	66±2	41:15	21±4	-	4 to 24-h ECG within 1st hour of first weekly dialysis	Group 1: 0.25 mcg alfalcidol 3 times a week for 6 weeks then 12 weeks washout then 0.25 mcg alfalcidol 3 times a week + 50,000 IU ergocalciferol once weekly for 12 weeks Group 2: reverse regime	No difference in LF:HF with vitamin D treatment; Increase in LF:HF in those who remained VDD after treatment
Loh 2025 [49]	Malaysia	41 OSA	48.1±11.6	19:22	19.6±9.1	37 OSA (no vitamin D3 given)	24-h Holter for HRV, 5-min Polar for HRV	Vitamin D3 6000 IU daily for 8 weeks then 4000 IU daily if VDS or 6000 IU daily if still VDI/VDD for 8 weeks	Improvement in ASDNN with vitamin D3 only among those with 25OHD<30 ng/mL at baseline and achieved>30 ng/mL at end of visit

Continuous variables are presented as mean±SD or median (IQR)

M male, *F* female, *25(OH)D* 25-hydroxyvitamin D, *VDI* vitamin D insufficiency, *AngII* angiotensin II, *LF* low frequency, *HF* high frequency, *VDD* vitamin D deficiency, *VDS* vitamin D sufficiency, *HRV* heart rate variability, *SDNN* standard deviation of the NN intervals, *SDANN* standard deviation of 5-min average NN intervals, *rMSSD* square root of the mean of the squares of successive NN interval differences, *pNN50* proportion of the number of interval differences of successive NN intervals greater than 50 ms to the total number of NN intervals, *CAN* cardiac autonomic neuropathy, *CART* cardiovascular autonomic reflex test, *VLF* very low frequency, *TP* total power (area under the curve of frequency domain), *RRmax* maximum RR interval, *1,25(OH)₂D* 1,25-dihydroxyvitamin D, *OSA* obstructive sleep apnea, *ASDNN* mean of the standard deviations of all NN intervals for all 5-min segments of entire recording

These clinical observations naturally raise the question: through which physiological pathways might vitamin D status influence autonomic function? This is explored in the following sections.

Mechanistic Insights from Animal Studies

Experimental animal studies provide important mechanistic insights into the role of vitamin D in cardiac autonomic regulation. Vitamin D has been shown to modulate autonomic neurotransmission by influencing acetylcholine synthesis, thereby contributing to heart rate reduction and vasodilation, as well as regulating tyrosine hydroxylase expression, which is the rate-limiting enzyme in catecholamine synthesis [52]. Additionally, vitamin D affects cardiac electrophysiology through regulation of potassium channel proteins, including acetylcholine sensitive potassium channels (IKACH) and delayed rectifying potassium channel (I_k), which affect cardiac excitability and automaticity, and are responsible in heart action potential repolarization, maintaining stable rhythm, and responding to sympathetic and parasympathetic signals [52]. Importantly, VDR-knockout mice exhibited increased renin expression, suggesting that vitamin D

signalling modulates RAAS activity and supporting a central role of VDR in neurohormonal regulation [53, 54].

Furthermore, vitamin D supplementation in animal models has been shown to improve HRV, partly through attenuation of pro-inflammatory cytokines such as IL-6, TNF- α , and TGF- β [55]. It also improves the bradycardic (parasympathetic) component of the baroreflex sensitivity, suggesting a shift toward vagal predominance [56]. In hypertensive models, chronic administration of active vitamin D attenuates sympathoexcitation, reduces oxidative stress and inflammation within the paraventricular nucleus, and preserve cardiovascular function [57].

Experimental evidence in animals supports a biological plausible role for vitamin D, likely via VDR pathways, in regulating autonomic tone through integrated neurochemical, electrophysiological, and anti-inflammatory mechanisms.

Possible Mechanisms Explaining the Association Between Vitamin D and Cardiac Autonomic Function in Humans

While animal studies provide important mechanistic insights into the role of vitamin D in autonomic regulation, translating these findings into human physiology

requires consideration of additional clinical and systemic factors. Emerging evidence in human studies suggests that vitamin D may influence autonomic balance, potentially through effects on sympathetic and parasympathetic activity, whereas VDD has been associated with endothelial dysfunction [58], which can impair baroreflex sensitivity and disrupt autonomic balance [59]. As illustrated in Fig. 1, several interrelated mechanisms may explain this association:

1. Vitamin D receptors

The effects of vitamin D on cardiac autonomic regulation are largely mediated through activation of the VDR, a nuclear receptor expressed in cardiomyocytes, vascular smooth muscle cells, endothelial cells, and key autonomic regulatory centres [60, 61]. Upon activation by $1,25(\text{OH})_2\text{D}$, VDR modulates gene transcription and influences multiple pathways involved in autonomic regulation [62], affecting myocardial contractility, vascular tone, and central autonomic networks.

2. Central effect

VDR is abundantly located in adrenergic neurons of the central nervous system, particularly the hypothalamus, brainstem, and spinal cord [63]. It is postulated that vitamin D metabolites can cross the blood brain barrier to bind to VDR in these regions [64], thereby modulating ANS activity.

3. Neurotrophic properties

Vitamin D is shown to induce nerve growth factor, which plays a crucial role in the growth, maintenance, and survival of the neurons [65]. Additionally, vitamin D contributes to the health of Schwann cells, which are essential for myelin sheath formation and nerve regeneration [66]. These neurotrophic effects may help preserve autonomic nerve integrity and function. Notably, VDD is associated with increased risk of CAN, particularly in individuals with pre-diabetes as demonstrated above [42], underscoring the potential role of vitamin D in maintaining nerve health and autonomic function.

4. Renin–angiotensin–aldosterone system (RAAS)

The RAAS plays a significant role in autonomic regulation, particularly through the action of AngII, which enhances sympathetic outflow and impairs baroreflex sensitivity [67]. Vitamin D has been increasingly recognized as a negative regulator of RAAS. This effect is largely mediated through VDR-dependent suppression of renin gene expression in the juxtaglomerular apparatus as demonstrated in animal studies where VDR-knockout mice exhibited elevated renin and AngII levels whereas vitamin D supplementation down-regulated renin gene transcription [54, 68, 69]. A recent review of human studies similarly suggests that VDD

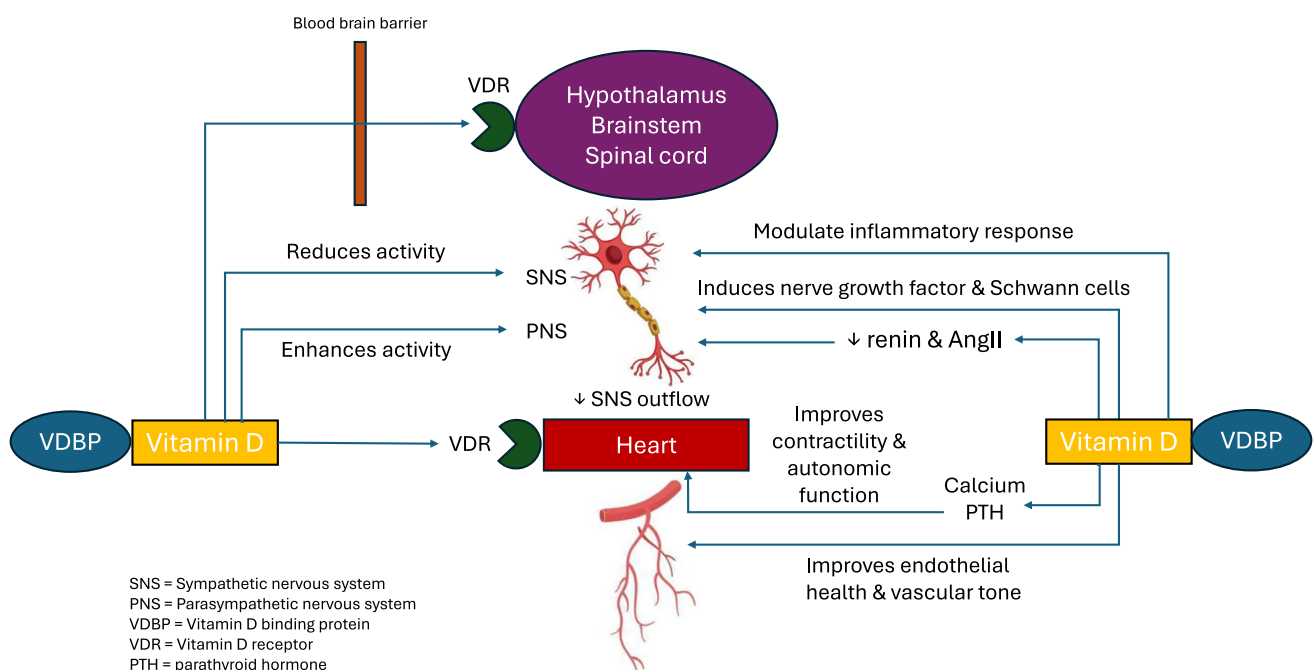


Fig. 1 Mechanisms explaining the association between vitamin D and cardiac autonomic regulation

leads to RAAS overactivation especially in individuals with hypertension [70]. This pathway represents a potential link between low vitamin D status and autonomic dysfunction, which is reflected in the rise of LF:HF ratio in individuals with hypovitaminosis D, and subsequently mitigated with vitamin D supplementation [29, 30].

5. Calcium-parathyroid hormone axis

Vitamin D plays a key role in maintaining calcium homeostasis, primarily by promoting intestinal calcium absorption and regulating parathyroid hormone secretion. Calcium ions are essential for both neurotransmitter release and cardiac muscle contraction, processes tightly controlled by autonomic inputs [11]. VDR signalling has been implicated in regulating intracellular calcium handling in cardiomyocytes, thereby contributing to electrophysiological stability and autonomic responsiveness [71, 72]. Additionally, elevated parathyroid hormone levels were associated with decreased HRV in ESRD patients [73]. Thus, the interplay between vitamin D, calcium, and parathyroid hormones not only affect cardiac muscle contraction, but also the modulation of cardiac autonomic function.

6. Vitamin D Binding Protein (VDBP)

VDBP is the primary carrier of vitamin D and its metabolites in circulation. By regulating the transport, distribution, and bioavailability of vitamin D to target tissues – including the heart and central nervous system – VDBP indirectly affects cardiac autonomic function [74]. Variations in VDBP levels and binding affinity may also influence individual responsiveness to vitamin D and its physiological effects. The role of VDBP in autonomic function is supported by a lower level of VDBP among pre-diabetes with cardiac autonomic dysfunction, which correlated with parasympathetic activity [41].

7. Inflammation or immune modulation

Oxidative stress leads to increased production of reactive oxygen species, which can disrupt the balance of ANS by affecting the SNS and PNS pathways [75]. Inflammatory cytokines, such as TNF- α and interleukins, which are elevated in oxidative stress and VDD, can affect the autonomic regulation of the heart by impairing heart rate regulation and promoting sympathetic dominance [76]. Vitamin D has immunomodulatory effects which have been shown to influence the inflammatory pathways by modulating the inflammatory response [77]. Vitamin D has been demonstrated to exert anti-inflammatory and anti-oxidative effects through VDR signalling [78], thus improving autonomic function.

These mechanistic insights suggest that vitamin D status could potentially be a modifiable factor in preserving autonomic

balance through modulation of VDR-mediated pathways. If vitamin D indeed suppresses sympathetic activity, maintaining adequate levels could form part of a broader strategy to prevent autonomic neuropathy, particularly in high-risk populations. However, this hypothesis remains to be validated in future outcome-driven studies. The inconsistencies observed across the literature warrant further discussion, as outlined below:

Research Gap and Future Directions

Despite emerging evidence suggesting that vitamin D may play an important role in modulating cardiac autonomic function, only a subset of studies has demonstrated significant associations. These discrepancies highlight the need for more rigorous and comprehensive research in this area. Additionally, evidence in other high-risk groups, such as essential hypertension, is lacking and warrant further investigation.

Future studies should prioritize well-designed randomized controlled trials that utilize standardized vitamin D supplementation protocols, including consistent dosing regimens and clearly defined target serum 25(OH)D levels. Such trials are essential to establish causality and determine optimal supplementation strategies for improving autonomic function.

Longitudinal cohort studies are also warranted to assess how temporal changes in vitamin D status influence cardiac autonomic outcomes. These studies can provide valuable insights into the trajectory of autonomic function relative to fluctuations in vitamin D levels over time.

In addition, the use of standardized and validated protocols for assessing cardiac autonomic function, such as consistent HRV measurement methods, testing durations, and conditions, will help reduce variability and enhance comparability across studies.

Further exploration into the role of genetic and epigenetic factors is needed. This includes investigating polymorphisms in VDR, VDBP, and enzymes involved in vitamin D metabolism, as well as potential gene-environment interactions that may affect individual responsiveness to vitamin D.

Finally, it is important to define threshold levels of vitamin D that are associated with cardiac dysautonomia. Identifying a clinically relevant cut-off may guide early intervention and help optimize cardiovascular outcomes.

Conclusions

This review addresses a notable gap in the literature, as no previous meta-analyses have specifically examined the relationship between vitamin D and cardiac autonomic function. Our findings provide new insights into the potential role of vitamin D as a modulator of autonomic balance, particularly

in individuals with chronic conditions, such as diabetes and OSA. While the evidence suggests a meaningful association, further research is needed to confirm its impact on clinical outcomes. This association is likely mediated predominantly through activation of the VDR, which regulates multiple downstream pathways, including endothelial function and the RAAS.

While observational studies generally support an inverse association between vitamin D levels and improved cardiac autonomic function, interventional studies with vitamin D supplementation have yielded some promising yet inconsistent results. Nevertheless, vitamin D repletion may improve selected autonomic markers in some high-risk groups, but clinical cardiovascular benefit remains unproven.

Future research should address these gaps by prioritizing studies that focus on cardiac autonomic endpoints to better define vitamin D's role in autonomic regulation. In particular, well-designed prospective and interventional studies targeting vitamin D-deficient individuals and assessing autonomic outcomes are needed to determine whether supplementation can reduce the risk of arrhythmia and adverse cardiac event. Such evidence will be essential for guiding therapeutic strategies aimed at reducing cardiovascular morbidity and mortality in high-risk populations.

Key References

- Zhang Y, Bai J, Li L, Yang H, Yang Y, Lv H. Research for correlation between heart rate variability parameters and bone mineral density in patients of type 2 diabetes mellitus. *J Endocrinol Invest*. 2023;46[1]:79–88.

This paper provides mechanistic insights into the broader cardiovascular and metabolic effects of vitamin D by demonstrating its influence on bone–metabolic and endocrine pathways in patients with type 2 diabetes. These findings support the hypothesis that vitamin D modulates systemic homeostasis and autonomic balance, offering indirect evidence for its potential role in HRV regulation.

- Bai J, Zhang Y, Li L, Yang H, Yang Y, Lv H. Relationship between vitamin D status and cardiac autonomic neuropathy in prediabetes. *Asia Pac J Clin Nutr*. 2022;31[4]:759–67.

This study in prediabetic individuals demonstrated that lower serum vitamin D levels were associated with reduced HRV and heightened sympathetic activity, independent of glycemic control. It reinforces

the broader link between vitamin D deficiency and impaired autonomic regulation beyond OSA, providing mechanistic support for vitamin D's role in cardiovascular autonomic modulation.

- Loh HH, Tay SP, Koa AJ, Yong MC, Said A, Chai CS, et al. Cardiac Autonomic Dysfunction in Obstructive Sleep Apnea: The Hidden Role of Vitamin D Deficiency. *J Evid Based Med*. 2025:e70071.

This cross-sectional study showed that OSA patients with vitamin D deficiency had lower HRV, higher sympathetic tone, and elevated hsCRP compared with those with sufficient vitamin D levels. It identifies hypovitaminosis D as an independent correlate of cardiac autonomic dysfunction in OSA, supporting the hypothesis that vitamin D status influences autonomic balance and cardiovascular risk

- Loh HH, Tay SP, Koa AJ, Yong MC, Said A, Chai CS, et al. Unveiling the benefits of Vitamin D3 with SGLT-2 inhibitors for hypertensive obese obstructive sleep apnea patients. *J Transl Med*. 2025;23[1]:296.

This randomized controlled trial demonstrated that combining vitamin D3 with SGLT-2 inhibitors improved metabolic parameters, nocturnal heart rate, and prevented HRV deterioration in hypertensive obese OSA patients. It provides strong interventional evidence that vitamin D supplementation, particularly when used synergistically with cardiometabolic agents, can beneficially modulate cardiac autonomic function and cardiovascular risk in OSA.

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Data Availability No datasets were generated or analysed during the current study.

Compliance with Ethical Standards

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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