RESEARCH PAPER

Vitamin D Deficiency and Cardiovascular Autonomic Function: Exploring Early Physiological Alterations in Apparently Healthy Adults

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ABSTRACT

Background: Vitamin D deficiency has been associated with cardiovascular abnormalities, but its relationship with cardiac autonomic regulation in apparently healthy adults remains unclear.

Objective: To investigate the association between serum 25-hydroxyvitamin D [25(OH)D] and cardiovascular autonomic function assessed by heart rate variability (HRV).

Methods: This cross-sectional analytical study included 204 apparently healthy adults categorized as vitamin D deficient (<20 ng/mL), insufficient (20–<30 ng/mL), or sufficient (≥30 ng/mL). Short-term HRV was assessed using time-domain and frequency-domain parameters. Associations between serum 25(OH)D and HRV were evaluated using correlation and multivariable regression analyses.

Results: Vitamin D-deficient participants had significantly lower SDNN, RMSSD, pNN50, high-frequency power and higher resting heart rate and LF/HF ratio than vitamin D-sufficient participants ($P<0.05$). Serum 25(OH)D correlated positively with SDNN ($r=0.39$), RMSSD ($r=0.36$), pNN50 ($r=0.31$), and high-frequency power ($r=0.34$), and inversely with resting heart rate ($r=-0.29$) (all $P\leq0.001$). After multivariable adjustment, 25(OH)D remained independently associated with SDNN ($\beta=0.31$, $P<0.001$) and RMSSD ($\beta=0.27$, $P<0.001$).

Conclusion: Lower vitamin D status was associated with reduced overall and predominantly vagally mediated HRV in apparently healthy adults. These findings suggest subtle alterations in cardiovascular autonomic regulation associated with vitamin D deficiency and warrant prospective investigation.

Keywords: Vitamin D Deficiency, 25-hydroxyvitamin D, Heart Rate Variability, Cardiac Autonomic Function, Cardiovascular Physiology

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INTRODUCTION

The role of vitamin D as a biologically active secosteroid hormone with multiple physiological roles that are well beyond its role in regulating calcium and skeletal health is gaining increasing recognition. Cardiomyocytes, vascular endothelial cells, vascular smooth muscle cells and other cardiovascular-regulatory organs express vitamin D receptors (VDRs) and vitamin D–metabolizing enzymes. These mechanisms suggest vitamin D may play a role in regulating vascular tone, endothelial function, inflammation signaling, glucose metabolism and the renin–angiotensin–aldosterone system (RAAS). This has led to poor vitamin D being a subject of much interest as potentially modifiable risk factor for cardiovascular and metabolic abnormalities [1, 2].

Vitamin D deficiency is still prevalent in various populations and may be relevant in people who do not have clinically obvious cardiovascular disease. There are several

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biological pathways that may explain the association between vitamin D deficiency and early cardiovascular changes. Low vitamin D signal has been linked to enhanced RAAS activation, endothelial dysfunction, reduced nitric oxide bioavailability, vascular inflammation, impaired calcium control, and impaired myocardial remodeling [1–3]. Mechanistic evidence recently supports the role for vitamin D signaling in regulating blood pressure, vascular function, and myocardial homeostasis. However, the magnitude of these biological effects in a normal population to translate to measurable cardiovascular dysfunction is not fully understood.

Disturbance of autonomic nervous system regulation is one way that vitamin D deficiency may be related to cardiovascular risk. S/P activity is a dynamic balance that continually regulates HR according to physiological and environmental demands is essential for cardiovascular homeostasis. An imbalance with increased sympathetic influence and decreased vagal modulation or impaired autonomic adaptability can precede overt cardiovascular manifestations. The identification of such subclinical physiological changes could therefore offer the possibility of identifying people who might be at high cardiovascular risk prior to the onset of traditional clinical disease.

Heart rate variability (HRV) is a simple and non-invasive method for assessing cardiac autonomic modulation, based on the variability of normal cardiac cycles. Time domain indices, like the SDNN (standard deviation of normal-to-normal intervals), are mainly associated with overall variability, while RMSSD (root mean square of successive differences) and the percentage of NN intervals longer than 50 ms (pNN50) are mainly associated with parasympathetic modulation. Frequency domain measures are complementary to those for oscillatory components of cardiovascular autonomic regulation. Thus, lowered HRV has been studied as a marker of autonomic dysfunction and bad cardiovascular physiology.

However, there is limited and inconsistent evidence connecting vitamin D status with HRV. Canpolat et al. found vitamin D deficiency in apparently healthy persons was linked with decreased SDNN, RMSSD and vitamin D deficiency-related same high-frequency HRV and increased vitamin D deficiency-related indices of sympathetic predominance [4]. A population-based study also showed positive correlation between serum 25-hydroxyvitamin D [25(OH)D] and SDNN and reported that those with severe vitamin D deficiency had around 3-fold risk for decreased SDNN [5]. In contrast, a study of low-risk coronary artery disease patients did not report any difference in any of the major HRV indices between the low vitamin D group and the controls [6]. The conflicting results suggest that this association could be affected by population-related factors, extent of vitamin D deficiency, cardiovascular risk factors, adiposity, and other factors that might represent a confounding variable.

This is further supported by the observation that HRV parameters significantly improved after vitamin D replacement in those with vitamin D deficiency but otherwise apparently healthy. Vitamin D deficiency has been corrected in one observational intervention study, which demonstrated significant enhancement of indices such as SDNN, SDANN, RMSSD and pNN50 [7]. While the results are interesting, they do not prove that a vitamin D deficiency directly leads to autonomic dysfunction. The connection between low vitamin D and cardiovascular abnormalities is still discussed in contemporary cardiovascular literature, while the evidence of an effect of vitamin D supplementation on cardiovascular outcomes is still discussed as a benefit.

The relevance of this relationship to apparently healthy adults is especially important given the possibility of subtle alterations in autonomic regulation already present in apparently normal subjects, who may have normal conventional cardiovascular measures. Therefore, a simultaneous measurement of serum 25(OH)D levels, HRV, RHR, blood pressure and related anthropometric variables may represent a more comprehensive assessment of the physiologic link between vitamin D status and CVAR.

The goal of the present study was therefore to examine the relationship between 25(OH)D and cardiovascular autonomic function as measured mainly by HRV in apparently healthy adults. It further set out to investigate the difference in autonomic indices among the vitamin D groups and to see if serum 25(OH)D was independently related to HRV after adjusting for pertinent demographic, anthropometric and cardiovascular parameters. We hypothesized that lower vitamin D status would be related to lower overall and parasympathetic HRV, which could be an early physiological change prior to cardiovascular disease.

MATERIALS AND METHODS

To assess the relationship between serum vitamin D status and cardiovascular autonomic function in apparently healthy adults, a cross-sectional analytical study was conducted at Department of Physiology, Liaquat University of Medical and Health Sciences (LUMHS) Jamshoro, Pakistan. The individuals aged 18–45 years were selected by non-probability consecutive sampling with a signed informed consent. Persons were eligible to participate if they appeared to be healthy and did not have a known history of cardiovascular or major systemic diseases. The history of diabetes mellitus, hypertension requiring treatment, ischemic heart disease, cardiac arrhythmias, heart failure, chronic kidney or liver disease, thyroid dysfunction and other important systemic diseases were exclusion criteria. In addition, pregnant women, those taking medications that significantly affect heart rate or autonomic function such as beta-blockers and antiarrhythmic drugs, and those taking therapeutic doses of vitamin D were not included.

Relevant clinical data and demographic details such as age, sex, smoking history, physical activity, drug regime, and vitamin D supplementation was recorded on a structured

data collection proforma. Body weight was determined on a calibrated digital weighing scale in which the subjects were dressed in light-weight clothes and without shoes and height was measured on a stadiometer. BMI (body mass index) was defined as weight in kg/m² (kg per square metre). The waist circumference was measured with a non-stretch tape measure, and anthropometric measurements were taken in a standard manner.

Standard rest was used to perform the cardiovascular assessment. Participants were asked not to engage in exercise or beverages containing caffeine before assessment. After a period of seated rest of at least 5–10 minutes, resting heart rate and systolic and diastolic blood pressure were taken using a cuff size appropriate to the size of the arm and the arm was supported at the level of the heart. A minimum of two blood pressures was taken, and the average blood pressure was analysed. The mean arterial blood pressure was derived from systolic and diastolic blood pressure readings.

Short term heart rate variability (HRV) analysis was used to assess cardiovascular autonomic function. Participants were given the opportunity to rest in a quiet environment prior to the recording, and then a continuous ECG was recorded in the relaxed supine position, with spontaneous breathing. Technically acceptable normal-to-normal (NN) intervals were used for HRV analysis and averaged around 5 minutes. Any recording that had excessive artefacts, ectopic beats, and/or technically poor signals were not analysed or repeated if possible. The time-domain parameters used were standard deviation of normal-to-normal intervals (SDNN), root mean square of successive differences (RMSSD), and the percentage of successive NN intervals longer than 50 ms (pNN50). The SDNN was a measure of overall short-term HRV, while the RMSSD and pNN50 mainly reflected parasympathetic cardiac modulation. Low frequency power (LF), high frequency power (HF), and the low frequency/high frequency ratio were analysed in the frequency domain. HF was interpreted as mostly related to vagally mediated respiratory modulation, and LF and LF/HF were interpreted with caution, as the measures do not reflect isolated sympathetic activity.

Venous blood samples were taken under sterile conditions, and the serum was isolated for the measurement of biochemical indicator of vitamin D status, 25 hydroxyvitamin D [25(OH)D]. Serum 25(OH)D was measured as a continuous variable and was stratified for group comparisons. Participants were categorized as vitamin D deficient (< 20 ng/mL), sufficient (≥ 30 ng/mL), or insufficient (20– < 30 ng/mL). Laboratory assay to determine serum 25(OH)D was conducted in line with the manufacturer's recommended procedure and routine laboratory quality-control procedures.

Serum 25(OH)D level was the main exposure and HRV indices, specifically SDNN and RMSSD were the main physiological outcomes. Secondary outcomes were pNN50, LF, HF, LF/HF ratio, resting heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure. Possible co-variates included: age, sex, BMI, waist circumference, smoking status, physical activity, resting heart rate, and blood pressure.

IBM SPSS Statistics was used for data analysis. The continuous variables were given as mean ± SD for data with a normal distribution, and as median with IQR for skewed data. Categorical data were reported in frequencies and percentages. Graphical methods and Shapiro–Wilk test were used to evaluate distributional assumptions. One-way analysis of variance (ANOVA) was used to determine differences across vitamin D status groups for continuous variables with a normal distribution, with appropriate post-hoc tests performed when the main effect of vitamin D status was significant. For data that were not normally distributed, the Kruskal–Wallis test with adjusted pairwise comparisons was used. The chi-square test or Fisher's exact test was used for the comparison of categorical variables, depending on the distribution of the variables. The correlations between the serum 25(OH)D and cardiovascular and HRV parameters were analyzed by Pearson or Spearman correlation depending on the distribution of variables. A multivariable linear regression analysis was then conducted to evaluate for the independent association of serum 25(OH)D concentration to HRV parameters after adjusting for other relevant demographic, anthropometric and cardiovascular covariates. Regression coefficients with 95% CIs were presented and P-values <0.05 were regarded as significant.

RESULTS

A total of 204 apparently healthy adults were included finally. The mean age of the participants was 30.8 ± 7.1 years, and 108 (52.9%) were male. Based on serum 25-hydroxyvitamin D [25(OH)D] concentrations, 82 (40.2%) participants were vitamin D deficient, 67 (32.8%) were insufficient, and 55 (27.0%) had sufficient vitamin D levels. Mean serum 25(OH)D concentration increased from 14.2 ± 3.8 ng/mL in the deficient group to 24.7 ± 2.8 ng/mL in the insufficient group and 36.9 ± 6.1 ng/mL in the sufficient group (P<0.001). Age and sex distribution were comparable across the three groups. BMI and waist circumference tended to be higher among participants with vitamin D deficiency, although the difference between-group differences were modest. Resting heart rate was significantly higher in the vitamin D-deficient group, whereas systolic and diastolic blood pressures did not differ significantly across vitamin D categories (Table 1).

Table 1: *Demographic, anthropometric, and cardiovascular characteristics according to vitamin D status*

Variable	Deficient (n=82)	Insufficient (n=67)	Sufficient (n=55)	P-value
Age (years)	31.2 ± 7.3	30.6 ± 6.9	30.4 ± 7.0	0.781

Male, n (%)	45 (54.9)	35 (52.2)	28 (50.9)	0.891
25(OH)D (ng/mL)	14.2 ± 3.8	24.7 ± 2.8	36.9 ± 6.1	**<0.001**
BMI (kg/m²)	25.7 ± 3.5	24.9 ± 3.3	24.4 ± 3.2	0.073
Waist circumference (cm)	86.8 ± 9.5	84.2 ± 9.1	82.9 ± 8.7	0.052
Resting heart rate (beats/min)	78.6 ± 8.7	75.4 ± 8.1	72.9 ± 7.5	**<0.001**
Systolic BP (mmHg)	119.3 ± 10.5	117.8 ± 10.1	116.9 ± 9.8	0.372
Diastolic BP (mmHg)	76.8 ± 7.9	75.6 ± 7.5	74.9 ± 7.3	0.344
Mean arterial pressure (mmHg)	91.0 ± 7.8	89.7 ± 7.5	88.9 ± 7.1	0.251

Values are mean ± SD unless otherwise indicated. BMI: body mass index; BP: blood pressure; 25(OH)D: 25-hydroxyvitamin D.

HRV analysis demonstrated a progressive increase in overall and parasympathetic variability with increasing vitamin D status. Mean SDNN was lowest among vitamin D-deficient participants (34.8 ± 10.2 ms) and highest among vitamin D-sufficient participants (46.7 ± 12.1 ms; P<0.001). A similar pattern was observed for RMSSD, which increased from 29.6 ± 10.8 ms in the deficient group to 40.9 ± 13.0 ms in the sufficient group (P<0.001). pNN50 and HF power were also significantly lower in participants with vitamin D deficiency. LF/HF ratio was comparatively higher in the deficient group, although this parameter was interpreted as a composite spectral index rather than a direct measure of sympathetic activity (Table 2).

Table 2: *Heart rate variability according to vitamin D status*

HRV parameter	Deficient (n=82)	Insufficient (n=67)	Sufficient (n=55)	P-value
SDNN (ms)	34.8 ± 10.2	40.3 ± 10.9	46.7 ± 12.1	**<0.001**
RMSSD (ms)	29.6 ± 10.8	34.8 ± 11.5	40.9 ± 13.0	**<0.001**
pNN50 (%)	10.8 ± 7.4	14.5 ± 8.1	19.1 ± 9.5	**<0.001**
LF power (ms²)*	521 (382–698)	556 (410–735)	579 (428–762)	0.168
HF power (ms²)*	396 (272–548)	482 (335–635)	598 (419–775)	**<0.001**
LF/HF ratio*	1.42 (1.09–1.78)	1.20 (0.94–1.53)	1.03 (0.81–1.35)	**0.002**

Values are mean ± SD unless otherwise indicated. *Median (interquartile range). SDNN: standard deviation of NN intervals; RMSSD: root mean square of successive differences; pNN50: percentage of successive NN intervals differing by >50 ms; LF: low-frequency power; HF: high-frequency power.

Post-hoc analysis showed that SDNN and RMSSD were significantly lower in the vitamin D-deficient group than in the sufficient group (both P<0.001). Differences between deficient and insufficient participants were also significant for SDNN and resting heart rate, while the greatest separation in parasympathetic HRV indices was observed between deficient and sufficient participants. These findings demonstrated a graded rather than exclusively threshold-dependent relationship between vitamin D status and autonomic parameters.

When serum 25(OH)D was analyzed as a continuous variable, significant positive correlations were observed with SDNN (r=0.39, P<0.001), RMSSD (r=0.36, P<0.001), pNN50 (r=0.31, P<0.001), and HF power (r_s=0.34, P<0.001). Serum 25(OH)D was inversely correlated with resting heart rate (r=−0.29, P<0.001) and LF/HF ratio (r_s=−0.24, P=0.001). No significant association was identified between 25(OH)D and systolic or diastolic blood pressure (Table 3).

Table 3: *Correlation of serum 25(OH)D with cardiovascular and HRV parameters*

Parameter	Correlation coefficient	P-value
SDNN	0.39	<0.001
RMSSD	0.36	<0.001
pNN50	0.31	<0.001
HF power	0.34*	<0.001
LF/HF ratio	−0.24*	0.001
Resting heart rate	−0.29	<0.001
Systolic BP	−0.10	0.158
Diastolic BP	−0.08	0.247

*Spearman correlation coefficient; remaining values represent Pearson correlation coefficients.

Multivariable linear regression was performed to determine whether serum 25(OH)D remained associated with HRV after adjustment for potential confounding factors. In the adjusted model, serum 25(OH)D was independently and positively associated with SDNN (β=0.31, P<0.001) after adjustment for age, sex, BMI, waist circumference, resting heart rate, blood pressure, smoking status, and physical activity. Vitamin D concentration was similarly independently associated with RMSSD (β=0.27, P<0.001). Increasing age and higher resting heart rate demonstrated independent inverse relationships with HRV, whereas the associations of BMI and blood pressure were attenuated after multivariable adjustment (Table 4).

Table 4: *Multivariable linear regression for determinants of HRV*

Predictor	SDNN standardized β	P-value	RMSSD standardized β	P-value
Serum 25(OH)D	0.31	<0.001	0.27	<0.001
Age	−0.18	0.008	−0.20	0.004
Male sex	0.06	0.342	0.04	0.518
BMI	−0.09	0.181	−0.08	0.226
Waist circumference	−0.07	0.294	−0.06	0.351
Resting heart rate	−0.28	<0.001	−0.32	<0.001
Systolic BP	−0.05	0.438	−0.03	0.647
Smoking	−0.11	0.083	−0.10	0.112
Physical activity	0.13	0.041	0.14	0.032

Overall, the results demonstrated a graded association between lower serum vitamin D status and reduced cardiovascular autonomic variability, particularly indices reflecting overall and parasympathetic modulation. Importantly, the association persisted after adjustment for major demographic, anthropometric, and cardiovascular factors, while conventional blood pressure measurements remained largely comparable across vitamin D categories.

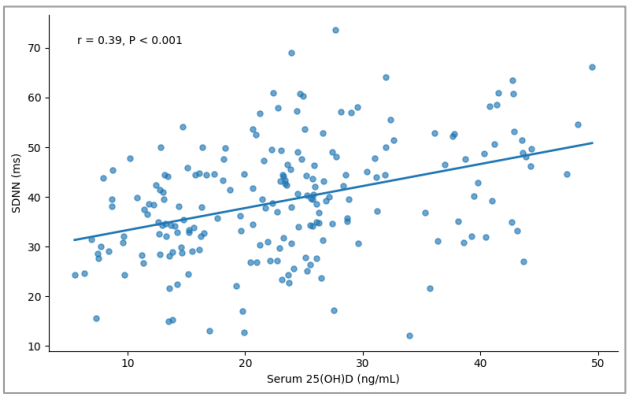

Figure 1

Comparison of SDNN and RMSSD across vitamin D status categories. Both indices demonstrated progressively higher values with increasing vitamin D status. Values are presented as mean ± SD.

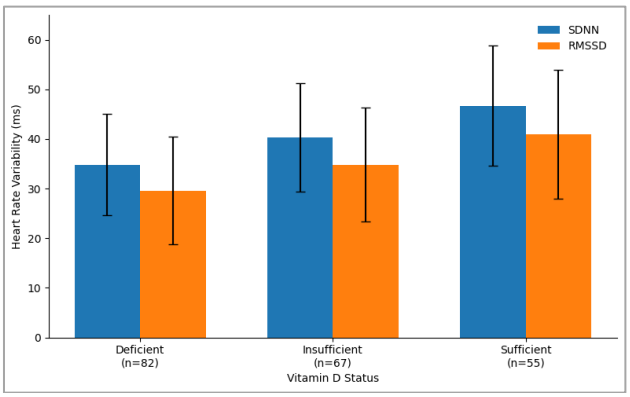

Figure 2

Relationship between serum 25-hydroxyvitamin D [25(OH)D] concentration and SDNN among apparently healthy adults. Higher serum 25(OH)D concentrations were associated with greater overall heart rate variability ($r = 0.39$, $P < 0.001$).

DISCUSSION

This current study showed that vitamin D status is strongly correlated with cardiovascular autonomic function in apparently healthy adults. Vitamin D deficient participants had significantly lower SDNN, RMSSD, pNN50 and HF power than those who were sufficient vitamin D and higher resting heart rate and LF/HF ratio. Positive correlations were found between 25(OH)D and indices of overall and predominantly vagally mediated heart rate variability (HRV) and the associations with SDNN and RMSSD remained significant after adjusting for relevant demographic, anthropometric, lifestyle and cardiovascular variables. Systolic and diastolic blood pressures, on the other hand, were similar between vitamin D levels. The results are consistent with the hypothesis that low levels of vitamin D may be linked to subtle changes in the functioning of cardiovascular autonomic regulation even in people who do not have clinically evident cardiovascular disease.

The changes in HRV for the participants who were vitamin D deficient are like those observed in other studies of healthy populations. Canpolat et al. [4] reported significantly decreased SDNN, RMSSD, pNN50, and HF in apparently healthy subjects with vitamin D deficiency, suggesting that vitamin D deficiency may cause cardiac autonomic modulation alteration. Likewise, Tak et al. [5] reported that serum 25(OH)D was correlated positively with SDNN, while serum 25(OH)D deficiency was correlated positively with a higher risk of decreased HRV. The present study confirms these findings and shows a dose-dependent relationship between the three vitamin D status groups and SDNN and RMSSD. This scheme indicates that there may be a continuum between the actions of vitamin D and autonomic function, and that the effect may only be noted when levels fall below a certain point.

These are lower RMSSD, pNN50 and HF power, which mainly reflect vagally mediated cardiac modulation, and are of particular interest when evaluating the vitamin D deficient group. Concomitant decreases in these parameters yield a physiologically consistent pattern indicating decreased parasympathetic modulation of cardiac rhythm. Similarly, Dogdus et al. [7] reported decreased values of SDNN, RMSSD, and pNN50 for vitamin D deficient (VDD) apparently healthy subjects and noted that these indices improved after vitamin D replacement. These results suggest a possible modifiable association of vitamin D levels with autonomic regulation. But because this was an observational study and the current study has a cross-sectional design, conclusions can only be made of a descriptive nature and not causal or therapeutic.

Contrary to the above results, Nalbant et al. [6] found no significant differences in SDNN, RMSSD, pNN50 or other HRV parameter between the patients with low vitamin D levels and controls. This difference could be due to a variety of factors including study population, severity and definition of vitamin D deficiency, duration of HRV recording, age distribution, adiposity, physical activity, sunlight exposure, or other unmeasured factors. HRV is strongly affected by methodological and physiological factors, such as respiration, posture, recording time, physical activity, and resting HR [8,9]. Standardized short-term recordings and evaluation of serum 25(OH)D level as a categorical and continuous variable in the present study might have allowed relatively subtle autonomic differences to be detected.

This increase in resting heart rate in the vitamin D deficient group also reinforces the idea that there is a cardiac autonomic dysfunction. Together with low RMSSD, pNN50 and HF power, this pattern fits with decreased vagal modulation. This higher LF/HF ratio in the deficient group should, however, be taken with a pinch of salt. Traditionally this ratio was thought to reflect sympathovagal balance, however there are complex interactions of sympathetic and parasympathetic systems that influence LF power, and LF/HF is not a direct quantitative measure of sympathetic activity [9,10]. Thus, the present results should not be taken as a sign of a predominance of the sympathetic side but rather as indicator of a change in autonomic modulation.

There are several mechanisms that could account for the relationship between Vitamin D status and cardiovascular autonomic function. There is evidence that Vitamin D receptors are present in cardiovascular tissues and Vitamin D signaling in these tissues is associated with regulation of the renin–angiotensin–aldosterone system, endothelial function, inflammatory response, oxidative stress, and myocardial physiology [11,12]. Increased vitamin D deficiency could augment renin–angiotensin activity and negatively affect vascular and neurohumoral regulation. There are also suggestions that Vitamin D may act via non-genomic and genomic pathways to affect autonomic pathways [12]. In addition, vitamin D could play a role in maintaining endothelial NO bioavailability and vascular homeostasis [13]. These mechanisms offer biological plausibility for the association observed but were not directly measured in the present study and should therefore be considered as possible mechanisms rather than established mechanisms.

Contrary to the authors had one interesting finding, that there were no significant differences in the systolic and diastolic blood pressure despite significant differences in several HRV parameters. This would suggest that autonomic changes due to low vitamin D levels can be detectable prior to the appearance of persistent changes in standard resting hemodynamics. Blood pressure is an integrated cardiovascular endpoint which is influenced by several compensatory mechanisms, while HRV is a dynamic beat-to-beat autonomic regulation. This is echoed

by intervention studies, which failed to demonstrate consistent evidence of a clinically important effect of vitamin D on BP [14]. In this regard, HRV could be used as an additional physiological marker that is not measured by resting blood pressure.

These results are supported by the independent association between serum 25(OH)D and SDNN and RMSSD after multivariable adjustment. Tak et al. [5] showed that after adjusting for important cardiovascular and lifestyle parameters, vitamin D concentration was not associated with SDNN. However, one must take note of the medium strength of the correlations found in the present study. HRV is multifactorial, with age, sex, resting heart rate, physical activity, adiposity, smoking, respiration, psychological state, and many environmental factors contributing to HRV [8]. Vitamin D status should thus be regarded as one variable among several that may correlate with autonomic physiology but is not necessarily the primary one.

The current findings can be viewed in the context of the larger epidemiological association of vitamin D and cardiovascular health. Inverse relationships between circulating levels of 25(OH)D and cardiovascular events and mortality have been shown in prospective studies and meta-analyses [15,16]. But there has not been a consistent link to benefits from vitamin D supplements. In generally healthy adults, the large Vitamin D and OmegA-3 Trial (VITAL) found no significant benefit of vitamin D3 supplementation for major cardiovascular events [17]. A similar meta-analysis of RCTs with over 83,000 participants also showed no significant decrease in MACE, myocardial infarction, stroke, or cardiovascular mortality with vitamin D supplementation [18].

This difference between observational and interventional evidence is significant for the interpretation of the present results. Low vitamin D concentration could be part of a general physical activity, adiposity, nutrition, sun exposure, or general health difference, and not just be a separate causal cardiovascular risk factor. There has also been some evidence from observational and Mendelian randomization studies that vitamin D-cardiovascular relationships might be non-linear and more relevant at very low levels of 25(OH)D [19]. Current reviews thus highlight the importance of separating correction of existing vitamin D deficiency from the practice of vitamin D supplementation for cardiovascular disease prevention [20]. Therefore, the current association between vitamin D status and HRV should not be used as a justification for the use of vitamin D supplementation to prevent cardiovascular disease or to affect autonomic function.

The present study had several strengths: the assessment of apparently healthy adults, assessment of several complementary time- and frequency-domain HRV parameters, the use of 25(OH)D levels as both a continuous and categorical variable, and the adjustment for important potential confounders. However, there are several drawbacks to note. As there is no temporal sequence or causality, the cross-sectional design is a limitation. One 25(OH)D level may not be representative of the vitamin D status of individuals and may be affected by seasonality and the type of dietary vitamin D intake. There are various factors that can affect short-term HRV (respiration, caffeine, physical activity, psychological state, recording conditions). In addition, mechanistic interpretation was limited as parathyroid hormone, calcium, inflammatory biomarkers, oxidative stress markers, and components of the renin–angiotensin system was not evaluated. Additionally, the single center design could restrict the generalizability of the study results to populations with varying environmental, nutritional, and demographic characteristics.

In conclusion, the present study suggests that low serum vitamin D levels are linked to decreased overall and mainly vagal HRV in healthy adults. Overall, the results are like those of Canpolat et al. [4], Tak et al. [5], and Dogdus et al. [7] and different from the lack of significant autonomic differences reported by Nalbant et al. [6]. The present study indicates that the association remained in multivariable analyses and conventional BP levels were only modestly affected, suggesting that HRV may provide a window to detect subtle changes in physiology linked to vitamin D status prior to the manifestation of cardiovascular disease. Causality studies and therapeutic intervention trials specifically targeting patients with confirmed vitamin D deficiency would help elucidate whether vitamin D deficiency causes lasting changes in cardiovascular autonomic function and if vitamin D correction can restore normal function.

CONCLUSION

Apparently healthy adults with vitamin D deficiency had lower overall and parasympathetic HRV indexes. Significant independent positive correlations were observed between serum 25-hydroxyvitamin D and SDNN and RMSSD after accounting for the various demographic, anthropometric, lifestyle and cardiovascular risk factors. Even though there are blood pressure comparisons that are quite similar, the autonomic changes observed indicate that HRV may be a better way to detect subtle physiological changes that are linked to low vitamin D status prior to the more prominent cardiac abnormalities. The cross-sectional design of the study does not enable it to prove causality or therapeutic effect, however. Future studies with prospective and interventional design will be needed to assess the effects of correction of vitamin D deficiency on cardiovascular autonomic regulation over a longer time.

The clinical and physiological implications

Results indicated that vitamin D may be important in the regulation of cardiovascular autonomic physiology, even in the absence of clinically recognized cardiovascular diseases. HRV could serve as a valid non-invasive physiological tool that could be used to examine subtle autonomic changes related to nutritional and metabolic conditions. The current findings, however, are not to be taken as a recommendation for routine vitamin D supplementation to prevent cardiovascular disease.

Additional longitudinal trials are required to establish if the association demonstrated is causal and clinically significant.

Recommendations

For future research, a prospective design with repeated measurement of serum 25(OH)D and HRVs with standardized assessment is recommended. The inclusion of markers of calcium–parathyroid hormone homeostasis, inflammation, oxidative stress, and renin–angiotensin activity may shed more light on the mechanisms underlying the association between vitamin D status and autonomic regulation. Randomized intervention trials specifically in patients with proven deficiency of vitamin D would be highly useful to assess if correction of vitamin D deficiency improves HRV.

REFERENCES

1. de la Guía-Galipienso F, Martínez-Ferran M, Vallecillo N, Lavie CJ, Sanchis-Gomar F, Pareja-Galeano H. Vitamin D, and cardiovascular health. Clin Nutr. 2021;40(5):2946-2957. doi:10.1016/j.clnu.2020.12.025.
2. Haider F, Ghafoor H, Hassan OF. Vitamin D and cardiovascular diseases: an update. Cureus. 2023;15(11):e49734. doi:10.7759/cureus.49734.
3. Latic N, Erben RG. Vitamin D and cardiovascular disease, with emphasis on hypertension, atherosclerosis, and heart failure. Int J Mol Sci. 2020;21(18):6483. doi:10.3390/ijms21186483.
4. Canpolat U, Özcan F, Özeke Ö, Turak O, Yayla Ç, Açıkgöz SK, et al. Impaired cardiac autonomic functions in apparently healthy subjects with vitamin D deficiency. Ann Noninvasive Electrocardiol. 2015;20(4):378-385. doi:10.1111/anec.12233.
5. Tak YJ, Lee JG, Kim YJ, Lee SY, Cho BM. 25-Hydroxyvitamin D and its relationship with autonomic dysfunction using time- and frequency-domain parameters of heart rate variability in Korean populations: a cross-sectional study. Nutrients. 2014;6(10):4373-4388. doi:10.3390/nu6104373.
6. Nalbant A, Vatan MB, Varım P, Varım C, Kaya T, Tamer A. Does vitamin D deficiency effect heart rate variability in low cardiovascular risk population? Open Access Maced J Med Sci. 2017;5(2):197-200. doi:10.3889/oamjms.2017.041.
7. Dogdus M, Burhan S, Bozgun Z, Cinier G, Koyuncu I, Karabay CY, et al. Cardiac autonomic dysfunctions are recovered with vitamin D replacement in apparently healthy individuals with vitamin D deficiency. Ann Noninvasive Electrocardiol. 2019;24(6):e12677. doi:10.1111/anec.12677.
8. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation. 1996;93(5):1043-1065.
9. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Front Public Health. 2017;5:258. doi:10.3389/fpubh.2017.00258.
10. Billman GE. The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. Front Physiol. 2013;4:26. doi:10.3389/fphys.2013.00026.
11. Pilz S, Verheyen N, Grübler MR, Tomaschitz A, März W. Vitamin D, and cardiovascular disease prevention. Nat Rev Cardiol. 2016;13(7):404-417. doi:10.1038/nrcardio.2016.73.
12. Mann MC, Exner DV, Hemmelgarn BR, Turin TC, Sola DY, Ellis L, et al. Vitamin D supplementation is associated with improved modulation of cardiac autonomic tone in healthy humans. Int J Cardiol. 2014;172(2):506-508. doi:10.1016/j.ijcard.2014.01.058.
13. Kim DH, Meza CA, Clarke H, Kim JS, Hickner RC. Vitamin D and endothelial function. Nutrients. 2020;12(2):575. doi:10.3390/nu12020575.
14. Beveridge LA, Struthers AD, Khan F, Jorde R, Scragg R, Macdonald HM, et al. Effect of vitamin D supplementation on blood pressure: a systematic review and meta-analysis incorporating individual patient data. JAMA Intern Med. 2015;175(5):745-754. doi:10.1001/jamainternmed.2015.0237.
15. Wang L, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes. 2012;5(6):819-829. doi:10.1161/CIRCOUTCOMES.112.967604.
16. Zhang R, Li B, Gao X, Tian R, Pan Y, Jiang Y, et al. Serum 25-hydroxyvitamin D and the risk of cardiovascular disease: dose-response meta-analysis of prospective studies. Am J Clin Nutr. 2017;105(4):810-819. doi:10.3945/ajcn.116.140392.
17. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. N Engl J Med. 2019;380(1):33-44. doi:10.1056/NEJMoa1809944.
18. Barbarawi M, Kheiri B, Zayed Y, Barbarawi O, Dhillon H, Swaid B, et al. Vitamin D supplementation and cardiovascular disease risks in more than 83,000 individuals in 21 randomized clinical trials: a meta-analysis. JAMA Cardiol. 2019;4(8):765-776. doi:10.1001/jamacardio.2019.1870.
19. Emerging Risk Factors Collaboration/EPIC-CVD/Vitamin D Studies Collaboration. Estimating dose-response relationships for vitamin D with coronary heart disease, stroke, and all-cause

mortality: observational and revised Mendelian randomization analyses. Lancet Diabetes Endocrinol. 2024;12(1):e2-e11. doi:10.1016/S2213-8587(23)00287-5.

20. Shu L, Huang K. Effect of vitamin D supplementation on blood pressure parameters in patients with vitamin D deficiency: a systematic review and meta-analysis. J Am Soc Hypertens. 2018;12(7):488-496. doi:10.1016/j.jash.2018.04.009