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VITAMIN D INSUFFICIENCY IS ASSOCIATED WITH REDUCED PARASYMPATHETIC NERVE FIBER FUNCTION IN TYPE 2 DIABETES

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Abstract

Objective—Vitamin D insufficiency is prevalent in type 2 diabetes mellitus (T2DM) and is associated with peripheral neuropathy. There is little data, however, for cardiovascular autonomic neuropathy. Our objective was to evaluate the association of cardiovascular autonomic function, 25-hydroxyvitamin D (25(OH)D) insufficiency (i.e., levels <30 ng/mL), and multiple metabolic parameters in T2DM.

Methods—We examined 50 individuals with T2DM. Cardiovascular autonomic function was assessed by RR-variation during deep breathing (i.e., mean circular resultant (MCR), expiration/inspiration (E/I) ratio). These measures assess parasympathetic function. Metabolic parameters included measures of adiposity, glycemic control, insulin resistance, calcium metabolism and 25(OH)D.

Results—Participants with 25(OH)D insufficiency (n=26) were younger (66±9 vs. 60±10 years, $p<0.05$), more insulin resistant, had a higher body mass index and lower adiponectin levels. The MCR (39.5±26.3 vs. 27.6±17.2, $p<0.01$) and E/I ratio (1.21±0.17 vs. 1.15±0.09, $p<0.01$) were lower for those with 25(OH)D insufficiency, after controlling for age. A stepwise selection procedure regressing MCR and E/I ratio on a number of metabolic parameters resulted in a model identifying age and 25(OH)D insufficiency as significant determinants for both measures. The interaction of age×25(OH)D insufficiency was also included (MCR model, $R^2=0.491$, $p<0.001$; E/I ratio, $R^2=0.455$, $p<0.001$). Neither glycemic control nor other metabolic parameters were selected.

Conclusion—Our results suggest that 25(OH)D insufficiency is associated with reduced parasympathetic function, the association being stronger in younger persons with T2DM. Studies

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are needed to determine if vitamin D supplementation into the sufficient range could prevent or delay the onset of cardiovascular autonomic dysfunction.

Keywords

Vitamin D; Type 2 diabetes mellitus; Cardiovascular autonomic neuropathy; Parasympathetic nerve function

INTRODUCTION

Low serum levels of 25-hydroxyvitamin D (25(OH)D) are prevalent in diabetes and have been shown to be associated with various complications, for example cardiovascular disease. Recent studies have suggested that low 25(OH)D levels may be related to the development of diabetic peripheral neuropathy (1–3). The etiology of diabetic neuropathy is multifactorial with metabolic and neurovascular involvement. Potential etiologies include increased activity of the polyol pathway, oxidative stress, the formation of advanced glycation end products, inflammatory changes, and neurohormonal growth-factor deficiency (4, 5). Accumulating evidence supports pleiotropic effects of vitamin D. For example, results from animal models suggest that vitamin D induces nerve growth factor (6) and may be neuroprotective through antioxidative mechanisms (7).

Recently the potential association of low vitamin D levels and cardiovascular autonomic nerve function in healthy adults was examined (8). These investigators showed that low 25(OH)D levels were associated with depressed resting cardiac autonomic activity (8). Although vitamin D insufficiency is prevalent in individuals with type 2 diabetes and several studies have suggested a relationship of 25(OH)D insufficiency and peripheral neuropathy, few studies have explored an association with diabetic cardiovascular autonomic nerve fiber function. Diabetic cardiovascular autonomic nerve dysfunction is a serious and often overlooked complication where persons may suffer from orthostatic hypotension, exercise intolerance, intraoperative instability, silent myocardial ischemia, and increased risk of mortality (9–11). Diabetic peripheral neuropathy and autonomic neuropathy share similar etiologies but they may also have differences. They often track together but not always. The objective in this study was to examine the association of cardiovascular autonomic function and 25(OH)D insufficiency, defined as 25(OH)D levels <30 ng/mL, with other metabolic parameters in persons with type 2 diabetes.

METHODS

Subjects

Fifty-one participants, who volunteered to participate in this study, were evaluated at the Diabetes and Metabolic Research Center, Christiana Care Health System, Newark, DE. This study had approval of the Institutional Review Board of Christiana Care Corporation and each person gave written informed consent before taking part in the study. Participants were eligible for the study if they were ≥18 years old with type 2 diabetes mellitus. Exclusion criteria included: (a) history of a myocardial infarction, percutaneous coronary interventions, coronary artery bypass graft surgery, acute coronary syndromes, recent/ongoing atrial

fibrillation, or acute myocardial ischemia; (b) dose changes 2 months prior to enrollment for vitamin D, antihypertensive and antidiabetes medications; and (c) chronic kidney disease ≥ stage 3b. It should be noted that one person that was enrolled in the study had chronic kidney disease stage 3b and thus after exclusion of this individual the results for 50 individuals were utilized.

Cardiovascular Autonomic Function Reflex Tests

Autonomic function was performed after an overnight fast. Participants were asked to refrain from taking any prescribed or nonprescription medications, to avoid consuming tobacco products, caffeine-containing or alcoholic beverages, and to refrain from engaging in any vigorous exercise 8–10 hours before testing. Cardiovascular autonomic function was assessed by measuring RR-variation during deep breathing and the Valsalva maneuver using the ANS2000 ECG Monitor and Respiration Pacer (DE Hokanson, Inc., Bellevue, WA). In brief as these methods have been previously described (12), RR-variation is a measure of the change in heart rate that results from variation in intrathoracic pressure due to respiration (13). It is predominantly a function of the parasympathetic nervous system, although sympathetic activity may affect it (14). There are several different methods to analyze RR-variation (e.g., standard deviation, mean circular resultant (MCR), expiration/inspiration (E/I) ratio). In this study, RR-variation during deep breathing was recorded for six minutes with participants in a supine position and breathing at a rate of 5 breaths per minute achieved by having the individual follow a set of moving lights on a respiration pacer. RR-variation during deep breathing was measured by vector analysis (i.e., MCR) and by the E/I ratio of the first six breath cycles. The E/I ratio was calculated by the mean value of the longest RR-interval during expiration and the shortest RR-interval during inspiration. The MCR is resistant to effects of ectopic beats whereas the E/I ratio is affected by ectopic beats (15). In this study cohort, the E/I results for six participants were labeled as missing. Age normative values have been published for RR-variation during deep breathing quantitated by calculating the MCR (16), with lower values for the MCR and E/I ratio associated with greater autonomic dysfunction.

Heart rate response to the Valsalva maneuver was also determined in this study. The Valsalva maneuver, a more generalized test of cardiovascular autonomic nerve function, assesses baroreceptor sensitivity, cardiac function, sympathetic and vagal pathways, and vascular responsiveness (17). To perform this test, participants expire into the mouthpiece of a manometer, maintaining a pressure of 40 mmHg for 15 seconds. The Valsalva ratio was defined as the longest RR-interval following the maneuver to the shortest RR-interval during the maneuver. The results for the Valsalva maneuver were incomplete for six participants.

Clinical measurements

Weight and height were measured using a stadiometer. Body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2). Blood pressure was monitored electronically in the supine posture using an oscillometric automatic recorder.

Blood analytes

Blood was drawn for the following parameters at the end of the study visit after completion of the cardiovascular autonomic function tests. Levels of 25(OH)D (reference range >29 ng/mL), insulin (reference range 2.6–24.9 mcIU/mL), C-peptide (reference range 1.1–4.4 ng/mL), and parathyroid hormone (reference range 15–65 pg/mL) were determined by an electrochemiluminescence immunoassay while glucose (reference range <100 mg/dL) measurements were performed using an enzymatic method. Serum creatinine (reference range 0.50–1.30 mg/dL) levels were determined by an enzymatic colorimetric assay. Insulin resistance was calculated using the homeostasis model assessment for insulin resistance (HOMA-IR) online calculator downloaded from http://www.dtu.ox.ac.uk (18). HbA1c (reference range 4.0–6.0%) was measured by high performance liquid chromatography (HPLC) using a Tosoh G7 automated HPLC analyzer (Tosoh Bioscience, Inc., South San Francisco, CA). Calcium (reference range 8.4–10.3 mg/dL) levels were determined using the Vitros Ca slide method on the Vitros 5,1 FS chemistry system (Ortho-Clinical Diagnostics, Rochester, New York). Leptin and total adiponectin levels were measured by radioimmunoassay (Millipore Corporation, Billerica, MA).

Statistical analyses

Comparisons of demographic and metabolic parameters between the sufficient (i.e., 25(OH)D levels ≥30 ng/mL) and insufficient (i.e., 25(OH)D levels <30 ng/mL) groups were made with unpaired t-tests for continuous data and contingency table (chi-square) analysis for categorical variables. Correlation coefficients were used to evaluate associations with 25(OH)D. Analysis of covariance (ANCOVA), controlling for age, was used to assess differences between the 25(OH)D sufficient and insufficient groups with regard to tests of autonomic function. Stepwise linear regression analyses, where the dependent variables were measures of autonomic function, were performed to assess for independent associations of 25(OH)D insufficiency, participant demographics, and metabolic parameters. Normality was tested and if violated, a natural logarithmic transformation or nonparametric test was used.

RESULTS

Table 1 provides participants' physical characteristics and metabolic parameters. Individuals with low 25(OH)D levels were younger, more insulin resistant, had a higher BMI, and lower adiponectin levels.

Significant correlations with 25(OH)D levels included BMI ($r=-0.44$, $p<0.01$); total adiponectin ($r=0.28$, $p<0.05$); HOMA-IR ($r=-0.47$, $p<0.01$); and calcium ($r=0.39$, $p<0.01$). The concentration of 25(OH)D was examined both as a dichotomous and continuous variable. Results were similar so the continuous correlation values were reported here. An exception was dichotomous 25(OH)D with age ($r=-0.31$, $p<0.05$).

The effect of 25(OH)D insufficiency on measures of autonomic function is shown in Table 2. Results of the ANCOVA, after controlling for age, showed that 25(OH)D insufficiency was significantly associated with a lower MCR and E/I ratio (p's <0.01). The effect size

reported in this study is partial eta-squared ($_p\eta^2$) and can be interpreted similar to R^2. Our results indicate that after adjusting for age, 25(OH)D insufficiency accounted for approximately 20% of the variability in MCR and the E/I ratio. The analyses in Table 2 were repeated after excluding four participants which appeared to have secondary hyperparathyroidism due to 25(OH)D. Exclusion of these individuals did not affect the results (data not shown).

Stepwise linear regression selection procedures were performed regressing the MCR and E/I ratio on potential independent variables which included: age, gender, BMI, HOMA-IR, HbA1c, leptin, total adiponectin, parathyroid hormone, calcium, serum creatinine, and 25(OH)D insufficiency. The same model was obtained for both the MCR and E/I ratio, where age and 25(OH)D insufficiency were selected as significant determinants of parasympathetic function. Because age was a potential moderator, the interaction of age×25(OH)D insufficiency was also included. The robustness of including the interaction term in the model as a potential independent variable was tested by rerunning the stepwise procedure. The stepwise procedure returned a final model that included the main effects of age, 25(OH)D insufficiency and their interaction, for both the MCR and E/I ratio (Table 3). Forward and backward selection procedures also resulted in the same three independent variables, age, 25(OH)D insufficiency, and their interaction, for both measures. These results suggest that for younger individuals with type 2 diabetes, 25(OH)D insufficiency is more strongly associated with a reduction in RR-variation during deep breathing than for older individuals (Figure 1 A and B). Thus, individuals with 25(OH)D insufficiency had more parasympathetic dysfunction than would be predicted by age alone. With the MCR as the dependent variable, the $F(3,46)=14.79$, $p<0.001$, model $R^2=0.491$, and $_{adjusted}R^2=0.458$. With the E/I ratio as the dependent variable, the $F(3,40)=11.14$, $p<0.001$, model $R^2=0.455$, and $_{adjusted}R^2=0.414$.

DISCUSSION

In this study, we investigated whether cardiovascular autonomic function is associated with 25(OH)D insufficiency and other metabolic parameters in persons with type 2 diabetes. The results of this study demonstrated that 25(OH)D insufficiency is associated with reduced parasympathetic nerve function, with the association being stronger in younger persons with type 2 diabetes than in older individuals. It is well known that with the normal process of aging, nerve function is decreased. Thus in our study, age was a more important factor when explaining nerve function in the older individuals, however, in the younger individuals, 25(OH)D insufficiency played a significant role.

This was a cross-sectional study and thus a causal link between 25(OH)D insufficiency and cardiovascular autonomic function could not be assumed. Nonetheless it is important to recognize the potential beneficial pleiotropic effects of vitamin D beyond that of being involved in bone metabolism and calcium and phosphorus homeostasis. Over the past two decades the potential association of vitamin D deficiency as a risk factor for several chronic diseases (e.g., metabolic syndrome, cancer, autoimmune diseases, cardiovascular disease) has been described (19). Insulin synthesis and secretion has been shown to be altered by vitamin D deficiency (20). In a study of 126 healthy subjects, 25(OH)D levels were found to

have a positive correlation with insulin sensitivity whereas hypovitaminosis D had a negative effect on beta cell function, with low 25(OH)D levels preventing a proper compensatory insulin response by the pancreas (21). It is well known that type 2 diabetes is characterized by insulin resistance. In this study, HOMA-IR was used to estimate the amount of insulin resistance. Our results showed a significant correlation between lower 25(OH)D levels and increased insulin resistance in this type 2 diabetes cohort. In addition, vitamin D is fat soluble and with increased BMI there is a decrease in serum vitamin D levels. This correlation was confirmed in our study.

Recent data has suggested that 25(OH)D insufficiency is found in individuals with diabetic peripheral neuropathy. This was demonstrated in studies where peripheral neuropathy was determined via objective testing (1, 3), by self-reported symptoms of peripheral neuropathy (2), in a case report of the reversal of severe pain with correction of 25(OH)D deficiency (22), and in a nonrandomized, non-blinded trial of 51 type 2 diabetic patients with 25(OH)D insufficiency and neuropathic pain where a significant reduction in pain scores after 3 months supplementation with cholecalciferol tablets (average dose, 2059 IU) was shown (23).

Another major form of neuropathy that occurs in diabetes is cardiovascular autonomic neuropathy. It is the impairment of cardiovascular autonomic control and results in abnormalities in heart rate control and vascular dynamics (10, 24). The prevalence of cardiovascular autonomic dysfunction is approximately 20% but with increasing age and duration of diabetes it may be as high as 65% (24). Cardiovascular autonomic dysfunction predicts cardiovascular risk and is a significant cause of morbidity and mortality (11, 25). As is true for peripheral neuropathy, the pathogenesis of cardiovascular autonomic dysfunction is multifactorial but several mechanisms may explain the association with vitamin D insufficiency. Inflammation has been implicated in the development of diabetic neuropathy (26), with elevated levels of acute phase proteins promoting inflammation. Vitamin D modulates the acute phase response (27). Low vitamin D levels have been linked to reduced levels of neurotrophins in animal models (22), with treatment via a vitamin D derivative shown to induce nerve growth factor (6). Reduction in neurotrophins results in vulnerability of nerve fibers to toxins (e.g., hyperglycemia) (22) but vitamin D may play a role in detoxification mechanisms (7). In this study, glycemic control, assessed via a single HbA1c, was comparable between the two groups (i.e., 25(OH)D sufficient vs. insufficient) and was not selected in the stepwise linear regression models. This does not, however, indicate that metabolic control does not play a role in the development of autonomic dysfunction. Given that one HbA1c is only reflective of short-term glycemic control, multiple results for each participant taken over time would present a truer picture of the metabolic insult that may have affected nerve function. It should also be noted that glycemic control for the sufficient and insufficient 25(OH)D groups was considered adequate. Nonetheless, individuals in this study did have HbA1c values ranging from 5.6 to 11.4%. The metabolic insult of diabetes on neural tissue is not the only effect but neurodegenerative changes caused by a reduced neural vascular supply may also be involved in the pathogenesis (4). Increased oxidative stress contributes to altered nerve metabolism and dysfunction of the microvascular (4). Antioxidative properties of vitamin D have been recently shown in type 2 diabetes (28). Thus, vitamin D may have several functional attributes that provide neuroprotection.

In this study, we did not find an association for the Valsalva ratio and 25(OH)D insufficiency. The Valsalva maneuver encompasses a complex reflex arc involving baroreceptor sensitivity, both sympathetic and parasympathetic pathways, cardiac function, and vascular responsiveness (17). It is a generalized measure of cardiovascular autonomic function that requires more autonomic impairment before abnormalities are seen (17). Thus, it is possible that 25(OH)D insufficiency had a greater effect on measures of RR-variation with deep breathing. It is also possible that since sympathetic function is more difficult to assess, the effect of 25(OH)D insufficiency on the parasympathetic system may be more easily observed.

This study has some potential limitations that deserve mention. Levels of 25(OH)D were determined via a single measurement. An average 25(OH)D level over time might better reflect a true risk. Over half of the participants were taking some form of a vitamin D supplement (e.g., multivitamin), however, the dose had not changed for 2 months prior to an individual participating in the study. Dietary sources of vitamin D were not controlled for. Vitamin D levels are affected by ultraviolet exposure but it should be noted that this study was completed in a 4 ½ month period centered around peak daylight hours from mid-April to August. Second, individuals were on concomitant medications (e.g., glucose-lowering agents, antihypertensive medications) which may have potentially masked some associations but participants did not have medication changes for 2 months prior to enrolling in the study. Lastly, there was only a small number of individuals (n=9) with 25(OH)D levels considered deficient (i.e., <20 ng/mL), this precluded any meaningful statistical comparisons.

In summary, vitamin D levels and actions are influenced by metabolic factors such as adiposity and other organ systems. In this study, we attempted to examine 25(OH)D insufficiency, multiple metabolic parameters, and their potential role in cardiovascular autonomic nerve function. Our results suggest that 25(OH)D insufficiency is associated with reduced parasympathetic nerve function particularly in younger persons with type 2 diabetes. Given the association of 25(OH)D insufficiency and cardiovascular autonomic function, evaluation of an individual’s 25(OH)D level on a routine basis may be warranted. Furthermore, there is the need for prospective clinical studies to determine if replenishment of vitamin D improves cardiovascular autonomic function in individuals with diabetes and whether supplementation with vitamin D into the sufficient range could prevent the development of cardiovascular autonomic nerve dysfunction.

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Abbreviations

25(OH)D	25-hydroxyvitamin D
BMI	body mass index
BP	blood pressure

E/I ratio	expiration/inspiration ratio
ELISA	enzyme linked immunosorbent assay
HOMA-IR	homeostasis model assessment for insulin resistance
HPLC	high performance liquid chromatography
Ln	natural logarithmic transformation
MCR	mean circular resultant
T2DM	type 2 diabetes mellitus.

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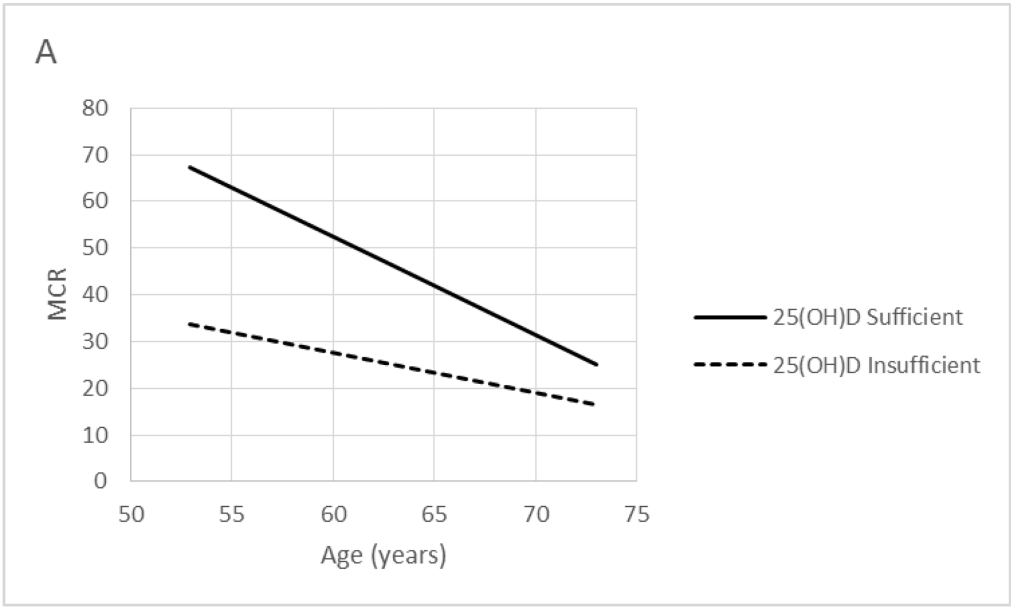

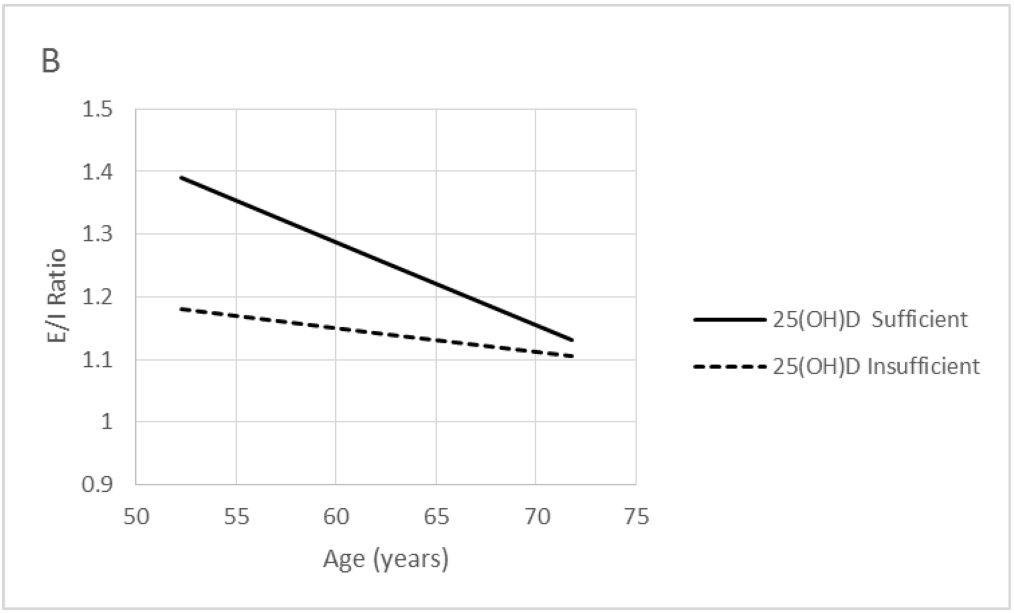

Fig. 1.

Age and measures of cardiovascular autonomic function [A] mean circular resultant (MCR) and [B] expiration/inspiration (E/I) ratio for individuals with 25-hydroxyvitamin D levels ≥30 ng/mL (i.e., 25(OH)D sufficient) versus individuals with 25-hydroxyvitamin D levels <30 ng/mL (i.e., 25(OH)D insufficient).

Table 1

Participant Demographics and Metabolic Parameters

	25(OH)D Sufficient (n=24)	25(OH)D Insufficient (n=26)	p-value
Age (years)	66 ± 9	60 ± 10	0.029
Duration of diabetes (years)	13 ± 7	12 ± 9	0.280
Male/female (n)	10/14	11/15	0.963
Systolic blood pressure (mmHg)	125 ± 13	125 ± 14	0.903
Diastolic blood pressure (mmHg)	73 ± 7	74 ± 8	0.873
Heart rate (bpm)	72 ± 15	71 ± 11	0.721
HbA1c (%)	7.4 ± 1.4	7.2 ± 1.0	0.846
Body mass index (kg/m^2)	29.9 ± 4.8	35.3 ± 4.3	<0.001
HOMA-IR	1.7 ± 0.9	2.5 ± 1.3	
Ln HOMA-IR	0.40 ± 0.51	0.77 ± 0.57	0.019
Leptin (ng/mL)	18.8 ± 13.2	26.6 ± 19.7	
Ln leptin	2.66 ± 0.80	2.99 ± 0.82	0.156
Total adiponectin (mg/L)	8.6 ± 6.9	5.4 ± 2.8	
Ln total adiponectin	1.94 ± 0.64	1.56 ± 0.51	0.024
25-hydroxyvitamin D (ng/mL)	39.4 ± 6.6	21.4 ± 5.1	<0.001
Parathyroid hormone (pg/mL)	33.2 ± 17.2	38.8 ± 13.5	0.204
Calcium (mg/dL)	9.6 ± 0.5	9.4 ± 0.3	0.049
Serum creatinine (mg/dL)	0.87 ± 0.29	0.85 ± 0.22	0.760

Data are presented as mean ± SD

Ln: natural logarithmic transformation

HOMA-IR: homeostasis model assessment for insulin resistance

25(OH)D sufficient: 25-hydroxyvitamin D levels ≥30 ng/mL

25(OH)D insufficient: 25-hydroxyvitamin D levels <30 ng/mL

Table 2

Measures of Cardiovascular Autonomic Function Adjusted for Age

Measure	25(OH)D Sufficient	25(OH)D Insufficient	p-value	$_p\eta^2$
Mean circular resultant	39.5 ± 26.3 (n=24)	27.6 ± 17.2 (n=26)	<0.01	0.248
Expiration/inspiration ratio	1.21 ± 0.17 (n=20)	1.15 ± 0.09 (n=24)		
Ln expiration/inspiration ratio	0.18 ± 0.12 (n=20)	0.14 ± 0.07 (n=24)	<0.01	0.193
Valsalva ratio	1.41 ± 0.18 (n=20)	1.46 ± 0.18 (n=24)		
Ln valsalva ratio	0.33 ± 0.12 (n=20)	0.37 ± 0.12 (n=24)	NS	0.004

Data are presented as mean ± SD

Ln: natural logarithmic transformation

NS: non-significant

25(OH)D sufficient: 25-hydroxyvitamin D levels ≥30 ng/mL

25(OH)D insufficient: 25-hydroxyvitamin D levels <30 ng/mL

$_p\eta^2$: the effect size reported in this study is the partial eta-squared which can be interpreted similar to R^2 indicating that 25(OH)D insufficiency accounted for approximately 20% of the variability for the mean circular resultant and expiration/inspiration ratio.

Table 3

Final Linear Regression Models for Measures of Cardiovascular Autonomic Function

Dependent Variable	Independent Variables	Regression Coefficient	Standard Error	p-value
MCR	Age (years)	−2.105	0.376	<0.001
	25(OH)D insufficiency	−99.781	32.264	0.003
	Age × 25(OH)D insufficiency	1.248	0.502	0.017
E/I ratio	Age (years)	−0.013	0.003	<0.001
	25(OH)D insufficiency	−0.703	0.214	0.002
	Age × 25(OH)D insufficiency	0.009	0.003	0.008

Variables not selected in the final stepwise linear regression models were: gender, body mass index, homeostasis model assessment for insulin resistance (HOMA-IR), HbA1c, leptin, total adiponectin, parathyroid hormone, calcium, and serum creatinine.

MCR: mean circular resultant

E/I ratio: expiration/inspiration ratio

25(OH)D insufficiency: 25-hydroxyvitamin D levels <30 ng/mL