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Does Vitamin D Deficiency Effect Heart Rate Variability in Low Cardiovascular Risk Population?

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Abstract

AIM: This study aimed to evaluate the cardiac autonomic dysfunction and the cardiac arrhythmia risk using heart rate variability parameters in subjects with vitamin D deficiency and low cardiovascular risk.

MATERIAL AND METHODS: One hundred five consecutive individuals, 54 patients with low vitamin D status and 51 healthy controls were enrolled in this study. The overall cardiac autonomic tone was quantified by using various heart rate variability parameters included mean RR interval, mean Heart Rate, mean of standard deviations of intervals for 24 hours (SDNN), standard deviation of averages of intervals (SDANN), mean of standard deviation of intervals for 5 minutes (SDNNI), root mean square of difference of successive intervals (rMSSD) and the proportion of intervals differing more than 50 ms (pNN50) values. The 12-lead ECG was recorded from each participant, and QT intervals were measured.

RESULTS: Baseline demographic profiles were similar between two groups. The heart rate variability parameters such as mean RR interval, mean HR, SDNN, SDANN, SDNNI, rMSSD and pNN50 (%) values were not significantly different in patients with low vitamin D status compared to control group. The electrocardiography analysis revealed only slight but significant prolongation of corrected QT (QTc) intervals in the control group.

CONCLUSION: HRV variables were not significantly altered in patients with vitamin D deficiency in low cardiovascular risk profile group. Further studies evaluating these findings in other cohorts with high cardiovascular risk are required.

Introduction

Vitamin D has a major role in a wide range of systems and organ functions including the cardiovascular system, beyond its effects on bone [1, 2]. The prevalence of vitamin D deficiency is high in up to 50% of healthy adults [3]. Vitamin D deficiency has been implicated in a variety of cardiovascular disorders, including hypertension, coronary artery disease, heart failure, and peripheral vascular disease [4, 5]. The experimental studies have shown the potential link between low vitamin D levels and the activation of the renin-angiotensin system, inflammation, peripheral insulin resistance, endothelial dysfunction, and adverse ventricular remodelling [6-10]. Recent studies revealed that vitamin D deficiency results in structural and ionic channel remodelling and autonomic dysfunction that may predispose the individuals to lethal cardiac arrhythmias and sudden cardiac death (SCD) [11-15].

Heart rate variability (HRV), the variation in the cardiac interbeat interval over time, provides a non-invasive assessment of cardiovascular autonomic functions [16]. It has been used as a predictor of sudden cardiac death or a marker of the progression of cardiovascular disease in several high-risk populations [17, 18].

There has been only one study evaluating the effects of the vitamin D deficiency on HRV with confusing results. In this study, we aimed to evaluate the cardiac autonomic dysfunction using HRV parameters and in-patient with low cardiovascular risk and vitamin D deficiency [19].

Material and Methods

A total 105 subjects, 54 patients with vitamin D deficiency and 51 healthy controls were enrolled in this study. All subjects were free of cardiovascular risk factors and haed been living in a city of western

Anatolia all through their life. Exclusion criteria were as follows: hypertension, diabetes mellitus, thyroid disorders, coronary artery disease, valvular heart disease; left ventricular dysfunction, use medications that interfere with vitamin D metabolism, primary hyperparathyroidism, hypercalciuria, malignancy, sarcoidosis, Paget's disease, malabsorption syndromes, estimated glomerular filtration rate ≤ 60 ml/min, and history of nephrolithiasis.

All subjects were recruited from Sakarya University School of Medicine (SAU) between October 2011 and September 2012. All the procedures were hby the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, which was revised in 1983. The Ethics Committee of Sakarya University Faculty of Medicine approved the study protocol.

Biochemical Examination

For blood tests, subjects were asked to fast for at least 12 h, and the blood was centrifuged at 3,000 rpm for 15 min to obtain the serum. Serum 25(OH) D was analysed using 25 OH Vitamin D reagent based on the enzyme immunoassay (IDS Ltd. Boldon UK).

Electrocardiography and Holter analysis

The 12-lead electrocardiograms (ECG) were recorded from each participant with sinus rhythm (25 mm/s rate and 1 cm/mV amplitude). Electrocardiograms were transferred to a personal computer via a scanner, magnified by Adobe Photoshop software, and then the duration of QT and RR intervals were measured. QT interval, which is the duration from the beginning of QRS complex to the end of T wave, was measured in a derivation in which T wave was clearly seen. Measured QT intervals were corrected by Bazett's Formula (QT/ $\sqrt{RR}$), and defined as corrected QT interval (QTc).

All subjects underwent 1- hour Holter monitoring while they were in a sitting position after resting for 30 minutes for HRV analyses. The measurements were taken in the morning times by single investigator blinded to the diagnosis of the participants. Holter ECGs were analysed using the Del Mar Reynolds Pathfinder Holter system. The time-domain parameters were calculated: mean of all normal RR intervals (mean RR); standard deviations of all normal-to-normal (NN) intervals, (SDNN); mean of the standard deviations of all NN intervals for all 5-minute segments of the entire recording (SDNNI); standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording (SDANN); the square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD); the number of pairs of adjacent NN RR intervals differing by more than 50 ms divided by the total number of all NN intervals (pNN50 total). EKG exclusion criteria were as follows: atrial fibrillation, recordings with non-sinus beats that were more than 1% of a total number of beats, and artefacts.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA), version 15.0 software for Windows. Descriptive statistics (frequency, mean, standard deviation, ranges) were calculated. The quantitative values between two groups were compared using a t-test, and the qualitative values were compared using the $\chi 2$ test. Correlation of variables was demonstrated using Pearson's and Spearman's correlation coefficients in normal distributed parametric and nonparametric variables, respectively. For assessment of the association of variables, linear regression and logistic regression were used for parametric and binary variables, respectively. P value of <0.05 was considered as statistically significant in all cases.

Results

Fifty-four (7 male, 47 female) individuals with vitamin D deficiency and 51 healthy subjects (14 male, 37 female) were included this study. Age, sex, systolic blood pressure, diastolic blood pressure, mean heart rate, body mass index were not significantly different between two groups. Serum values of 25(OH) D, calcium, parathormone, creatinine, TSH, FT4 and glucose were not different between the two groups (Table 1).

Table 1: Baseline Demographic and clinical characteristics

	Healty controls (n = 51)	Patient with vitamin D deficiency (n = 54)	p-value
Age (years)	28.8 ± 6.48	27.8 ± 5.54	0.37
Gender (M/F)	14/37	7/47	0.053
SBP	115.9 ± 12.5	116.4 ± 10.8	0.33
DBP	73.9 ± 5.5	73,8 ± 6.7	0.39
BMI	24.22 ± 3.2	24.13 ± 3.4	0.89
25(OH)D (nmol/l)	52.47 ± 21.7	15.28 ± 8.3	< 0.001

Values are mean ± SD; M, male; F, female; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Electrocardiogram and heart rate variability analysis revealed that mean RR, mean HR, SDNN, SDANN, SDNNI, RMSDD, and PNN50 in time domain parameters did not differ significantly between groups. When the QT intervals were compared, only a slight but significant proloangation of QTc intervals were detected in the control group. However, there was no significant difference between two groups in the QT intervals. Table 2 summarises the HRV and QT parameters in subjects with vitamin D deficiency and the control group.

Table 2: Heart rate variability parameters and QT analysis in patients with vitamin D deficiency and healthy controls

	Healthy Controls (n = 51)	Patient with Vitamin D Deficiency (n = 54)	p-value
Mean heart rate (beats/min)	89 ± 10.7	88.7 ± 12.1	0.90
Mean RR	694 ± 93.8	698 ± 100	0.86
SDNN (ms)	70.8 ± 21.5	66.6 ± 20.4	0.31
SDANN (ms)	45.1 ± 16.6	38,5 ± 21.4	0.37
SDNNI (ms)	54.4 ± 17.3	52.3 ± 15.1	0.50
rMSDD (ms)	25.4 ± 11.3	25.8 ± 11.1	0.86
pNN50 (%)	7.06 ± 8.6	6.54 ± 7.5	0.52
QT (ms)	369 ± 33.6	359 ± 27.1	0.07
QTc (ms)	408 ± 28.3	395 ± 25	0.013

SDNN, standard deviations of all NN intervals; SDNNI, mean of the standard deviations of all NN intervals for all 5-minute segments of the entire recording; SDANN, standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording; RMSSD, the square root of the mean of the sum of the squares of differences between adjacent NN intervals; pNN50, the number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN interval.

Correlation analysis for HRV parameters in vitamin D deficiency group is shown in Table 3.

Table 3: Correlation coefficients for heart rate variability parameters in vitamin D deficiency group

Standardised coefficients	Beta	t	p-value
SDNN (ms)	0.101	0.32	0.74
SDANN (ms)	-0.119	-0.60	0.54
SDNNI (ms)	-0.201	-0.86	0.38
rMSDD (ms)	0.259	1.34	0.18
pNN50 (%)	-0.125	-0.77	0.44
QT (ms)	0.074	0.79	0.42
QTc (ms)	-0.135	-1.48	0.14

Abbreviations; see Table 2.

Discussion

This study showed that low vitamin D status is not associated with diminished HRV parameters in a low cardiovascular risk group. A probable explanation for the lacking association is that our study focuses on younger individuals who were free of any cardiovascular disease and risk factors. Furthermore, low vitamin D status alone has not any potential to initiate lethal arrhythmias, especially ventricular fibrillation as assessed by HRV and QT.

Our results are contrary the study of YJ TAK et al., in which they have studied HRV in a population with more advanced age and high cardiovascular risk. In their study, they have included a very high-risk group into the study as compared to our study group. We did not find any significant correlation in the HRV and QT data between the vitamin D deficiency and control groups [19]. HRV shows the effects of sympathetic and parasympathetic on the sinus node. HRV parameters evaluate the different types of autonomic nerve system effects on the heart with sinus rhythm. RMSSD and HF show variations in parasympathetic effects and LF is an indicator of sympathetic activity regulation on the sinus node. SDNN and LF show the influenced of both adrenergic and cholinergic activities on the sinus node. Any changes in all HRV parameters affect SDNN and SDNN is decreased in left ventricle systolic dysfunction [20]. SDANN, SDNNI, rMSDD and pNN50 are the other HRV parameters that show cardiac autonomic functions and evaluate the sympathetic and parasympathetic tones on cardiac functions [21]. Vitamin D has direct effects on myocytes. Vitamin D also affects cardiac contractility indirectly by calcium metabolism and directly via vitamin D receptors [12]. Our hypothesis mainly depends on the seasonal changes in arrhythmia related deaths in winter times and vitamin is a sunlight defendant [22, 23]. So, we have chosen the HRV analyses for evaluation of the subclinical disturbances that poses the vitamin deficient people to malign cardiac arrhythmias.

Structural and ionic channel remodelling due to low vitamin D serum levels may prolong the repolarization interval [12]. These changes have been shown to cause altered myocardial calcium, prolongation of the repolarization interval and cardiac action potential over time [11-14]. Furthermore, low vitamin D levels also induce oxidative stress, vasoconstriction and cardiac hypertrophy. All of these mechanisms may also increase myocardial susceptibility to fatal cardiac arrhythmias and eventually lead to SCD [13, 22, 25]. Previous studies showed that seasonal variations in SCD rates are high during winter and are lowest in the summer months [23, 24]. The synthesis of vitamin D is also dependent on the intensity of daylight exposure with peak values in the summer and lowest values in winter [26, 27]. iAlso, prior studies have demonstrated seasonal variation in autonomic tone that may be induced by the intensity of daylight exposure and D vitamin status [28].

A recent study evaluated the association between SCD and the combination of low vitamin D status and parathyroid hormone (PTH) excess in participants who were free of clinical cardiovascular disease at baseline. However, the combination of vitamin D deficiency and high PTH concentrations did not increase the risk of SCD to 2.5 times, while individual risk factors, low vitamin D status nor high PTH levels were related with SCD events [13]. These associations have not been found in populations free of cardiovascular disease. Another strength of our study was a measurement of vitamin D levels only at a single point in time. However, we found no association between vitamin D deficiency and cardiac autonomic dysfunction using HRV which suggests that the effects of vitamin D deficiency on the cardiovascular system may not be immediate.

Limitations: Most important limitation of our study is the small sample size. Another issue is the absence of 24 or 48-hour Holter ECG monitoring and absence of follow-up for developing adverse events.

In conclusion, we found that there was no relationship between HRV variables and the vitamin D deficiency in subjects without cardiovascular risk factors. Vitamin D deficiency does not alter cardiac autonomic functions as assessed by HRV. Further studies are needed for evaluation of these findings in other cohorts with cardiovascular risk factors.

References

1. Peterlik M, Cross HS. Vitamin D and calcium deficits predispose for multiple chronic diseases. Eur J Clin Invest. 2005;35:290–304. https://doi.org/10.1111/j.1365-2362.2005.01487.x PMid:15860041

2. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et. al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008;117:503–11. https://doi.org/10.1161/CIRCULATIONAHA.107.706127 PMid:18180395 PMCid:PMC2726624

3. Holick M F. Vitamin D deficiency. N Engl J Med. 2007;357:266–81. https://doi.org/10.1056/NEJMra070553 PMid:17634462

4. Martins D, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, et al. The prevalence of cardiovascular risk factors and the serum levels of vitamin D in the United States: data from the NHANES III. Arch Intern Med. 2007;167:1159–65. https://doi.org/10.1001/archinte.167.11.1159 PMid:17563024

5. Gaddipati VC, Bailey BA, Kuriacose R, Copeland RJ, Manning T, Peiris AN. The relationship of vitamin D status to cardiovascular risk factors and amputation risk in veterans with peripheral arterial disease. J Am Med Dir Assoc. 2011;12:58–61. https://doi.org/10.1016/j.jamda.2010.02.006 PMid:21194661

6. Xiang W, Kong J, Chen S, Cao LP, Qiao G, Zheng W, et.al. Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. Am J Physiol Endocrinol Metab. 2005; 288:125–132. https://doi.org/10.1152/ajpendo.00224.2004 PMid:15367398

7. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxy vitamin D is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest. 2002; 110:229-38. https://doi.org/10.1172/JCI0215219

8. Riachy R, Vandewalle B, Moerman E, Belaich S, Lukowiak B, Gmyr V, Muharram G, et al. 1,25- Dihydroxyvitamin D3 protects human pancreatic islets against cytokine-induced apoptosis via down-regulation of the Fas receptor. Apoptosis. 2006;11(2):151–9. https://doi.org/10.1007/s10495-006-3558-z PMid:16502254

9. Mitsuhashi T, Morris Jr RC, Ives HE. 1,25-dihydroxyvitamin D3 modulates growth of vascular smooth muscle cells. J Clin Invest 1991;87:1889–95. https://doi.org/10.1172/JCI115213 PMid:1645744 PMCid:PMC296939

10. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2006;83:754–9. PMid:16600924

11. Kim HW, Park CW, Shin YS, Kim YS, Shin SJ, Choi EJ, et.al. Calcitriol regresses cardiac hypertrophy and qt dispersion in secondary hyperparathyroidism on hemodialysis. Nephron Clin Pract. 2006;102:21– 9. https://doi.org/10.1159/000088295 PMid:16166802

12. Tishkoff DX, Nibbelink KA, Holmberg KH, Dandu L, Simpson RU. Functional vitamin D receptor (VDR) in the t-tubules of cardiac myocytes: VDR knockout cardiomyocyte contractility. Endocrinology. 2008;149:558–64. https://doi.org/10.1210/en.2007-0805 PMid:17974622 PMCid:PMC2219302

13. Deo R, Katz R, Shlipak MG, Sotoodehnia N, Psaty BM, Sarnak MJ, et. al. Vitamin D, parathyroid hormone, and sudden cardiac death: results from the Cardiovascular Health Study. Hypertension. 2011;58(6):1021-8. https://doi.org/10.1161/HYPERTENSIONAHA.111.179135 PMid:22068871 PMCid:PMC3337033

14. Mann MC, Exner DV, Hemmelgarn BR, Sola DY, Turin TC, Ellis L, et al. Vitamin D levels are associated with cardiac autonomic activity in healty humans. Nutrients. 2013;5:2114-27. https://doi.org/10.3390/nu5062114 PMid:23752493 PMCid:PMC3725496

15. Drechsler C, Pilz S, Obermayer-Pietsch B, Verduijn M, Tomaschitz A, Krane V, et.al. Vitamin D deficiency is associated with sudden cardiac death, combined cardiovascular events, and mortality in haemodialysis patients. Eur Heart J. 2010;31:2253–61. https://doi.org/10.1093/eurheartj/ehq246 PMid:20688781 PMCid:PMC2938469

16. John C A, Thomas BJ, Breithardt G, Cerutti S, Cohen RJ, Coumel P, et al. Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Heart rate variability. Eur Heart J. 1996;17:354-81. https://doi.org/10.1093/oxfordjournals.eurheartj.a014868

17. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, et.al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation. 1996;94(11):2850-5. https://doi.org/10.1161/01.CIR.94.11.2850 PMid:8941112

18. Kleiger RE, Stein PK, Bigger JT. Heart rate variability: Measurement and clinical utility. Ann Noninvasive Electrocardiol. 2005;10:88–101. https://doi.org/10.1111/j.1542-474X.2005.10101.x PMid:15649244

19. 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): 4373-88. https://doi.org/10.3390/nu6104373 PMid:25325256 PMCid:PMC4210923

20. Koizumi K,Terui N, Kollai M. Effect of cardiac vagal and sympathetic nerve activity on heart rate in rhythmic fluctuations. J Auton Nerv Syst. 1985;12:251–9. https://doi.org/10.1016/0165-1838(85)90065-7

21. Sasaki K, Maruyama R. Consciously controlled breathing decreases the high-frequency component of heart rate variability by inhibiting cardiac parasympathetic nerve activity. Tohoku J Exp Med. 2014; 233(3): 155-63. https://doi.org/10.1620/tjem.233.155 PMid:24965685

22. Bodyak N, Ayus JC, Achinger S, Shivalingappa V, Ke Q, Chen YS, et.al. Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in dahl salt- sensitive animals. Proc Natl Acad Sci U S A. 2007;104:16810–5. https://doi.org/10.1073/pnas.0611202104 PMid:17942703 PMCid:PMC2040477

23. Beard CM, Fuster V, Elveback LR. Daily and seasonal variation in sudden cardiac death, Rochester, Minnesota, 1950–1975. Mayo Clin Proc. 1982;57:704–6. PMid:7132431

24. Peckova M, Fahrenbruch CE, Cobb LA, Hallstrom AP. Weekly and seasonal variation in the incidence of cardiac arrests. Am Heart J. 1999;137:512–5. https://doi.org/10.1016/S0002-8703(99)70507-7

25. Zittermann A, Schleithoff SS, Koerfer R., Vitamin D and vascular calcification. Curr Opin Lipidol. 2007;18:41–6. https://doi.org/10.1097/MOL.0b013e328011c6fc PMid:17218831

26. Kloner RA, Poole WK, Perritt RL. When throughout the year is coronary death most likely to occur? A 12-year population-based analysis of more than 220,000 cases. Circulation 1999;100:1630–4. https://doi.org/10.1161/01.CIR.100.15.1630 PMid:10517734

27. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab. 1988;67:373–8. https://doi.org/10.1210/jcem-67-2-373 PMid:2839537

28. Corr PB, Yamada KA, Witkowski FX, Fozzard HA, Haber E, Jennings RB, et al. Mechanisms controlling cardiac autonomic function and their relation to arrhythmogenesis. The heart and cardiovascular system. New York, NY: Raven Press, 1986:1343.