ISSN: 2643-4466

Kaya. Int Arch Intern Med 2019, 3:017
DOI: 10.23937/2643-4466/1710017
Volume 3 | Issue 2
Open Access

International Archives of Internal Medicine

RESEARCH ARTICLE

Effect of Vitamin D on Novel Ventricular Repolarization Indices

Hakan Kaya*

Department of Cardiology, Adiyaman University, Turkey

***Corresponding author:** *Hakan Kaya, Assistant Professor, Department of Cardiology, Adiyaman University, Adiyaman, Turkey, Tel: 05056379170*

Abstract

Background: Vitamin D deficiency may be the underlying cause of most health issues and diseases. There are few studies investigating the effect of low vitamin D levels on the cardiac arrhythmias. The electrocardiographic Tpeak to Tend (Tpe) interval and Tpe/QT ratio may associate with increased ventricular arrhythmias. The goal of this study was to evaluate the relationship between ventricular repolarization and vitamin D levels in apparently healthy individuals by using Tpe interval, Tpe/QT ratio and Tpe/corrected QT (cQT).

Methods: A total of 400 subjects (200 patients with vitamin D deficiency and 200 healthy volunteers) were enrolled in the study. Tpe interval, Tpe/QT ratio and Tpe/cQT ratio were evaluated from surface electrocardiography and these indices were compared between groups.

Results: No difference was observed in terms of clinical characteristics between the two groups. Tpe interval, Tpe/QT ratio and Tpe/cQT ratio were statistically significantly higher in vitamin D deficient subjects than the control subjects (87.9 ± 13.2 *vs.* 77.1 ± 4.5 ms, $p < 0.001$; 24 ± 0.03 *vs.* 0.21 ± 0.02, $p < 0.001$; 0.22 ± 0.02 *vs.* 0.19 ± 0.02, $p < 0.001$; respectively). Moreover, significant negative co-relation was observed between Tpe interval, Tpe/QT ratio, Tpe/cQT ratio and vitamin D levels ($r = -0.388$, $p < 0.001$; $r = -0.364$, $p < 0.001$; $r = -0.354$, $p < 0.001$; respectively).

Conclusion: Tpe interval, Tpe/QT ratio and Tpe/cQT ratio were increased in vitamin D deficient subjects and this increase was negatively correlated with vitamin D levels. Low vitamin D levels may increase the risk of ventricular arrhythmia in apparently healthy individuals.

Keywords

Tpe interval, Tpe/QT ratio, Ventricular arrhythmia, Vitamin D

Abbreviations

CVD: Cardiovascular Diseases; SCD: Sudden Cardiac Death; VA: Ventricular Arrhythmia; ECG: Electrocardiography; Tpe: Electrocardiographic Tpeak to Tend Interval; cQT: Electrocardiographic Corrected QT Interval; AF: Atrial Fibrillation; HRV: Heart Rate Variability

Introduction

Vitamin D receptors are ubiquitously found in several tissues/cells such as the endothelium and myocytes. Previous studies showed an association between vitamin D deficiency and cardiovascular diseases (CVD). Vitamin D has been shown to contribute to cardiovascular complications [1]. It is reported that vitamin D deficient subjects can be at risk for hypertension, diabetes, hyperlipidemia, peripheral artery disease and cardiovascular complications such as left ventricular hypertrophy, myocardial infarction and arrhythmia [2-5]. This mechanism may help to explain why low vitamin D levels are associated with CVD.

In the literature, especially the relationship between vitamin D deficiency and atrial fibrillation has been investigated. However, little data is available about the effect of low vitamin D levels on ventricular arrhythmia (VA). It is reported that vitamin D deficiency leads to ionic channel remodelling and autonomic dysfunction that may give rise to lethal cardiac arrhythmias and sudden cardiac death (SCD) [6-10]. Current evidences have shown that Tpe interval and Tpe/QT can be used as a parameter of ventricular repolarization [11-12]. Tpe interval and Tpe/QT ratio may be associated with increased VA and SCD [12,13].

The aim of this study was to evaluate the effect of low vitamin D levels on novel ventricular repolarization indices: Tpe interval and Tpe/QT ratio.

Materials and Methods

Study design and study population

This prospective study was done in a university hospital. Four hundred subjects were enrolled in the

Citation: Kaya H (2019) Effect of Vitamin D on Novel Ventricular Repolarization Indices. Int Arch Intern Med 3:017. doi.org/10.23937/2643-4466/1710017

Accepted: July 17, 2019: **Published:** July 19, 2019

study. All subjects were selected from patients who referred to the endocrinology department and whose vitamin D levels were measured. Two hundred healthy volunteers were selected for the control group. Patient group was consisted of two hundred individuals who had vitamin D deficiency. The related data were obtained through anamnesis, physical examination, electrocardiography (ECG) and echocardiography. Approval was obtained by ethics committee and informed consent was provided for each and every subject in the study. Those who had osteoporosis, pregnancy, had left ventricular hypertrophy and dysfunction, left bundle branch block in ECG, rheumatoid heart disease, heart valvular disease, thyroid dysfunction, chronic lung disease, diabetes mellitus, primary hyperparathyroidism, malignancy, chronic kidney disease, anemia, electrolyte disturbance, smoking habit, chronic liver disease, chronic infection, atrioventricular conduction disturbance, non-sinus rhythm in ECG, systemic rheumatoid disease, and who are older than 75-years-old, under vitamin D treatment, or who had been using antidepressant, and antipsychotic or antihistaminic drugs, were excluded from the study.

Tpe interval and Tpe/QT ratio measurements

The 12-lead ECG was recorded from every subject with sinus rhythm (50 mm/s rate). To reduce errors, two cardiologists calculated Tpe interval and QT interval from surface ECG. U waves on the ECGs were exclusion criteria. QT interval was defined as the interval from the beginning of the QRS complex to the end of the T wave. QT interval was evaluated as much as possible in all of 12 electrodes. For corrected QT (cQT), measured QT intervals were corrected for heart rate using Bazett's formula [14]. Tpe interval was defined as the interval from the peak of T wave to the end of T wave. Tpe interval was measured in precordial leads. Tpe/QT and Tpe/cQT ratios were obtained from these measurements.

Vitamin D measurement

For vitamin D measurements, blood samples were collected from all patients. Then, these blood samples were centrifuged and serum 25(OH) D was analysed using 25 OH Vitamin D reagent based on the enzyme immunoassay (Beckman Coulter Inc, U.S.A.). Values were expressed as ng/ml. In our laboratory normal reference values of vitamin D is 10-80 ng/ml. All the subjects who had the values below the lowest normal value were selected as patient group.

Statistical analysis

The SPSS, v 22.0, statistical program (Chicago, USA) was used. Numerical and Categorical variables were given as mean ± SD and percentage, respectively. Comparison of the numerical variables was done by using Mann-Whitney U Test or Independent t-test between the two groups. Comparison of the categorical variables was done by using Chi-square test and Fisher's exact test. For the correlation analysis Spearman's test was used. A p value < 0.05 was considered significant.

Results

Baseline demographic and clinical characteristics of two groups are presented in Table 1. Age, gender, systolic blood pressure, diastolic blood pressure and body mass index were not statistically different (p > 0.05, for all). The levels of vitamin D were statistically higher in the control subjects than the vitamin D deficient pa-

Table 1: Baseline demographic and clinical characteristics of the study population.

	Vitamin D deficiency group (n = 200)	Control group (n = 200)	P value
Age (years)	49.09 ± 8.5	49.6 ± 6.8	0.695
Gender, male, n%	127 (63.5)	141 (70.5)	0.271
BMI (kg/m^2)	26.3 ± 2.8	25.5 ± 3.2	0.211
Systolic BP (mmHg)	126.6 ± 6.9	125.7 ± 6.4	0.459
Diastolic BP (mmHg)	71.9 ± 5.2	70.4 ± 6.7	0.181
Vitamin D (ng/ml)	7.7 ± 1.5	18.3 ± 4.6	< 0.001

BMI: Body mass index; BP: Blood pressure.

Table 2: Electrocardiographic and echocardiographic characteristics of the study population.

	Vitamin D deficiency group (n = 200)	Control group (n = 200)	P value
Heart rate (beats/min)	73.2 ± 9.6	72.9 ± 8.4	0.842
LVEF (%)	61.5 ± 2.7	60.9 ± 3.3	0.335
QT (ms)	362.3 ± 33.4	351.6 ± 24.1	0.119
cQT (ms)	395.7 ± 37.6	386.5 ± 24.3	0.185
Tpe (ms)	87.9 ± 13.2	77.1 ± 4.5	< 0.001
Tpe/QT	0.24 ± 0.03	0.21 ± 0.02	< 0.001
Tpe/cQT	0.22 ± 0.02	0.19 ± 0.02	< 0.001

LVEF: Left ventricular ejection fraction; QT: QT interval; cQT: Corrected QT interval; Tpe: Tpeak to Tend interval.

tients (18.3 ± 4.6 *vs.* 7.7 ± 1.5 ng/ml; p < 0.001). The echocardiographic and ECG data is shown in Table 2. Heart rate and left ventricular ejection fraction were similar between groups (73.2 ± 9.6 *vs.* 72.9 ± 8.4 beats/min, p = 0.842; 61.5 ± 2.7 *vs.* 60.9 ± 3.3, p = 335; respectively). QT interval and cQT interval were similar between two groups, while values of the Tpe interval were significantly higher in patient group than the control group (87.9 ± 13.2 *vs.*77.1 ± 4.5 ms; p < 0.001). Tpe/cQT and Tpe/QT ratios were statistically higher in vitamin D deficient patients than the control group (0.22 ± 0.02 *vs.* 0.19 ± 0.02; p < 0.001 and 24 ± 0.03 *vs.* 0.21 ± 0.02; p < 0.001; respectively). In addition, Tpe interval, Tpe/cQT and Tpe/QT ratios were seen to be negatively correlated with vitamin D deficiency (r = -0.388 p < 0.001; r = -0.354 p < 0.001; r= -0.364 p < 0.001; respectively) (Table 3).

Discussion

The results of this study showed that vitamin D deficiency was associated with increased Tpe interval, Tpe/QT ratio and Tpe/cQT ratio in apparently healthy individuals. Moreover, a weak but significantly negative co-relation was observed between vitamin D deficiency and these incides. This study is the first investigation to examine the association between vitamin D deficiency and ventricular arrhythmias by using novel ventricular repolarization indices which are electrocardiographic Tpe interval and Tpe/QT ratio. There are few studies about the effect of low vitamin D levels on cardiac arrhythmias in the literature. In fact, most of studies in the literature showed that vitamin D deficiency is associated with atrial fibrillation (AF). Chan, et al. reported that genetic vitamin D deficiency may cause increased AF in CVD [15]. In a meta-analysis, lack of vitamin D was shown to enhance the risk of AF [16]. Emren, et al. showed that vitamin D deficiency was associated with new onset AF post-coronary artery bypass grafting surgery [17]. The effect of low vitamin D levels on cardiac arrhythmias have been evaluated using the heart rate variability (HRV) method in previous studies. The sympathetic activity on the ventricular myocardium and variations in cardiac autonomic neural tone were investigated in the studies which were done with HRV. There are conflicting results in these studies. In one study, the relationship of low vitamin D levels with HRV was investigated and it was reported that low vitamin D levels were related with cardiac arrhythmias [18]. In another study, it was reported that there was no relationship between HRV and low vitamin D levels [19]. Deo, et al. reported that low vitamin D levels leads to oxidative stress, vasoconstriction, and cardiac hypertrophy, which may lead to VA and even SCD [8]. HRV measurements are quite different and complex. Since different time units are examined by different researchers, the comparison and evaluation of the obtained data may leads to incorrect results [20]. Tpe interval might be a useful index to predict VA and cardiovascular mortality [13,21]. Prolonged Tpe interval was associated with increased mortality in patients with acute ST-segment elevation myocardial infarction, Brugada syndrome and long QT syndrome [22]. However, the Tpe interval is affected by variations of heart rate and body weight [22]. Recently a novel index of the ventricular repolarization, the Tpe/QT ratio, has been suggested to be more sensitive for the dispersion of ventricular repolarization compared to QT dispersion, cQT dispersion, Tpe interval, and to be independent of variations in heart rate [22,23]. Moreover, Tpe/QT ratio have been evaluated in the several studies and the authors have been stated that the increase of this index may be related to VA [24-26]. Vitamin D deficiency can prolong the range of repolarization as a cause of structural and ionic channel remodeling [7]. Potassium currents play an important role in shaping action potentials. The main source of electrophysiological remodeling in ventricular hypertrophy and heart failure is the down regulation of potassium currents which are associated with prolonged QT intervals and risk of malignant VA. Tamayo, et al. reported that calcitriol, the active metabolite of vitamin D, had increased ventricular potassium currents in isolated mouse myocytes [27]. In addition vitamin D indirectly affects calcium metabolism and can lead to altered myocardial calcium and prolongation of the repolarization range [6]. In conclusion, all of these mechanisms may be the cause of increased repolarization parameters which are Tpe interval and Tpe/QT ratio. The main limitation of this study is that patients have not been followed up for a long time in terms of ventricular arrhythmia.

Table 3: Correlation coefficients for Tpe interval and Tpe/QT ratio in vitamin D deficiency group.

	Correlation co-efficient (r)	P value
Tpe	-0.388	< 0.001
Tpe/QT	-0.364	< 0.001
Tpe/cQT	-0.354	< 0.001

Tpe: Tpeak to Tend interval; QT: QT interval; cQT: Corrected QT interval.

In summary, This study showed that vitamin D deficiency was associated with increased Tpe interval, Tpe/cQT ratio and Tpe/QT ratio in apparently healthy individuals. These individuals may have an increased risk for VA. This risk in vitamin D deficient subjects can be easily predicted by measuring the Tpe interval and the Tpe/QT ratio from surface ECG. Nevertheless, there is a need for multi-centre studies in which the number of patients is to be very high and these patients are to be followed up long term for ventricular arrhythmia.

References

1. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF (2008) Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? J Am Coll Cardiol 52: 1949-1956.

2. Holick MF (2007) Vitamin D deficiency. N Eng J Med 357: 266-281.
3. Giovannucci E, Liu Y, Hollis BW, Rimm EB (2008) 25-hydroxyvitamin D and risk of myocardial infarction in men: A prospective study. Arch Intern Med 168: 1174-1180.
4. Geleijnse JM (2011) Vitamin D and the prevention of hypertension and cardiovascular diseases: A review of the current evidence. Am J Hypertens 24: 253-262.
5. McGreevy C, Williams D (2011) New insights about Vitamin D and cardiovascular disease: A narrative review. Ann Intern Med 155: 820-826.
6. Kim HW, Park CW, Shin YS, Kim YS, Shin SJ, et al. (2006) Calcitriol regresses cardiac hypertrophy and QT dispersion in secondary hyperparathyroidism on hemodialysis. Nephron Clin Pract 102: 21-29.
7. Tishkoff DX, Nibbelink KA, Holmberg KH, Dandu L, Simpson RU (2008) Functional Vitamin D receptor (VDR) in the t-tubules of cardiac myocytes: VDR knockout cardiomyocyte contractility. Endocrinology 149: 558-564.
8. Deo R, Katz R, Shlipak MG, Sotoodehnia N, Psaty BM, et al. (2011) Vitamin D, parathyroid hormone, and sudden cardiac death: Results from the cardiovascular health study. Hypertension 58: 1021-1028.
9. Mann MC, Exner DV, Hemmelgarn BR, Sola DY, Turin TC, et al. (2013) Vitamin D levels are associated with cardiac autonomic activity in healty humans. Nutrients 5: 2114-2127.
10. Drechsler C, Pilz S, Obermayer-Pietsch B, Verduijn M, Tomaschitz A, et al. (2010) Vitamin D deficiency is associated with sudden cardiac death, combined cardiovascular events, and mortality in haemodialysis patients. Eur Heart J 31: 2253-2261.
11. Kors JA, Ritsema van Eck HJ, van Herpen G (2008) The meaning of the Tp-Te interval and its diagnostic value. J Electrocardiol 41: 575-580.
12. Antzelevitch C, Sicouri S, Di Diego JM, Burashnikov A, Viskin S, et al. (2007) Does Tpeak-Tend provide an index of transmural dispersion of repolarization? Heart Rhythm 4: 1114-1116.
13. Watanabe N, Kobayashi Y, Tanno K, Miyoshi F, Asano T, et al. (2004) Transmural dispersion of repolarization and ventricular tachyarrhythmias. J Electrocardiol 37: 191-200.
14. Goldenberg I, Moss AJ, Zareba W (2006) QT interval: How to measure it and what is “normal.” J Cardiovasc Electrophysiol 17: 333-336.
15. Chan YH, Yiu KH, Hai JJ, Chan PH, Lam TH, et al. (2017) Genetically deprived Vitamin D exposure predisposes to atrial fibrillation. Europace 19: 25-31.
16. Zhang Z, Yang Y, Ng CY, Wang D, Wang J, et al. (2016) Meta-analysis of Vitamin D Deficiency and risk of atrial fibrillation. Clin Cardiol 39: 537-543.
17. Emren SV, Aldemir M, Ada F (2016) Does deficiency of Vitamin D increase new onset atrial fibrillation after coronary artery bypass grafting surgery? Heart Surg Forum 219: 180-184.
18. Tak YJ, Lee JG, Kim YJ, Lee YS, Cho BM (2014) 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 6: 4373-4388.
19. Nalbant A, Vatan MB, Varım P, Varım C, Kaya T, et al. (2017) Does Vitamin D deficiency effect heart rate variability in low cardiovascular risk population? Open Access Maced J Med Sci 5: 197-200.
20. Kayıkcıoglu M, Payzın S (2001) Heart rate variability. Turk Kardiyol Dern Ars 29: 238-245.
21. Smetana P, Schmidt A, Zabel M, Hnatkova K, Franz M, et al. (2011) Assessment of repolarization heterogeneity for prediction of mortality in cardiovascular disease: Peak to the end of the T wave interval and nondipolar repolarization components. J Electrocardiol 44: 301-308.
22. Gupta P, Patel C, Patel H, Narayanaswamy S, Malhotra B, et al. (2008) T(p-e)/QT ratio as an index of arrhythmogenesis. J Electrocardiol 41: 567-574.
23. Zhao X, Xie Z, Chu Y, Yang L, Xu W, et al. (2012) Association between Tp-e/QT ratio and prognosis in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Clin Cardiol 35: 559-564.
24. Acar G, Yorgun H, Inci MF, Akkoyun M, Bakan B, et al. (2014) Evaluation of Tp-e interval and Tp-e/QT ratio in patients with ankylosing spondylitis. Mod Rheumatol 24: 327-330.
25. Acar GR, Akkoyun M, Nacar AB, Dirnak I, Yıldırım CG, et al. (2014) Evaluation of Tp-e interval and Tp-e/QT ratio in patients with rheumatoid arthritis. Turk Kardiyol Dern Ars 42: 29-34.
26. Zehir R, Karabay CY, Kalaycı A, Akgün T, Kılıçgedik A, et al. (2015) Evaluation of Tpe interval and Tpe/QT ratio in patients with slow coronary flow. Anatol J Cardiol 15: 463-467.
27. Tamayo M, Martin-Nunes L, Val-Blasco A, Piedras MJ, Larriba MJ, et al. (2018) Calcitriol, the bioactive metabolite of Vitamin D, increases ventricular K+ currents in isolated mouse cardiomyocytes. Front Physiol 9: 1186.