The effect of 25-hydroxyvitamin D levels on QT interval duration and dispersion in type 2 diabetic patients

Demet Ozgil Yetkin[1], Belgin Kucukkaya[2], Mehtap Turhan[3], Merve Oren[4]

[1]Department of Endocrinology, Kolan International Hospital, Istanbul, Turkey

[2]Department of Internal Medicine, Bayindir Hospital, Istanbul, Turkey

[3]Department of Biochemistry, Bayindir Hospital, Istanbul, Turkey

[4]Department of Public Health, Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey

Aim To assess the relationship between corrected QT (QTc) interval and vitamin 25-hydroxyvitamin D levels (25-OHD) deficiency in type 2 diabetic patients.

Methods The study included 253 patients with type 2 diabetes and 170 age-matched controls treated between October and December 2013. QTc duration and QTc dispersion were measured on ECG recordings and 25-OHD, calcium, phosphorus, and blood glucose levels were determined.

Results Patients with diabetes had significantly longer QTc duration and QTc dispersion than controls ($P < 0.001$ and $P < 0.001$ respectively). Diabetic patients with prolonged QTc duration were older and had longer diabetes duration and higher HbA1c levels than patients with normal QTc interval. They significantly more frequently had 25-OHD deficiency ($P < 0.001$), but had similar calcium and phosphorus levels. Diabetic patients with prolonged QTc dispersion were of similar age and had similar diabetes duration and HbA1c levels as patients with normal QTc dispersion. They significantly more frequently had 25-OHD deficiency ($P = 0.010$), but had similar calcium and phosphorus levels.

Conclusion This study showed prolonged QTc duration and QTc dispersion in patients with type 2 diabetes, especially those with 25-OHD deficiency.

Correspondence to:
Demet Özgil Yetkin
Ortaklar Caddesi, Köşem Apt. no: 10/8
Mecidiyekoy, Istanbul, Turkey
demetozgil@yahoo.com

Worldwide prevalence of type 2 diabetes mellitus (T2DM) is 7.7%, and is expected to further increase. The principal cause of death in patients with T2DM are cardiovascular diseases, with the annual mortality of 5.4% (1). Cardiac mortality and morbidity rate can be reduced by disease detection at the time when overt cardiac disease is still not present. This requires novel screening strategies, one of which is QT interval analysis. QT abnormalities can predict cardiac death in several diseases, including chronic heart failure, systemic hypertension, and peripheral vascular disease (2). In diabetic patients QT abnormalities can be detected at diagnosis and are better predictors of cardiac death than autonomic function tests (3). Moreover, in diabetic patients increased QT dispersion was shown to predict cardiovascular mortality (4).

Calcium-phosphorus metabolism disorders and 25 hydroxyvitamin D (25-OHD) deficiency are known risk factors for cardiovascular events (5-7). Also, disturbances that lead to decreased 25-OHD levels have been shown to result in structural and ionic channel remodeling, which may increase the susceptibility to cardiac arrhythmias. In addition, they induce cardiac hypertrophy and fibrosis, which are known risk factors for sudden cardiac death (7,8).

Altered 25-OHD and calcium homeostasis may also play a role in the development of T2DM. Vitamin D has been shown to affect the synthesis and secretion of insulin (9) and predict the increased risk of all-cause and cardiovascular mortality in T2DM patients independent of conventional risk factors (10). However, there are limited data on the relationship between 25-OHD and QT parameters in diabetic patients. The aim of this study was to investigate the relationship between the 25-OHD deficiency and the corrected QT (QTc) interval duration and dispersion in patients with diabetes.

PATIENTS AND METHODS

The study included 253 (129 women) consecutive patients with type 2 diabetes (mean age of 59.7 years and standard deviation [SD], 6.5), followed and treated at our outpatient clinic between October and December 2013. The control group included 170 (87 women) healthy volunteers (mean age of 59.1 years and SD 5.5) who attended their routine check-ups at our clinic.

Vitamin D deficiency was defined as 25-OHD concentration of less than 30 mg/mL (11). Patients who were treated with vitamin D and calcium within one year before the study were not included. We determined partici-

pants' characteristics including age, duration of diabetes, and hypertension, medications, and presence of complications including retinopathy, nephropathy, and peripheral neuropathy. Retinopathy was diagnosed by an ophthalmologist and microalbuminuria was defined as urine albumin to creatinine ratio between 30 and 300 mg/g. Peripheral neuropathy was diagnosed on the basis of neuropathic symptoms and signs or objectively abnormal results, including insensitivity to a 10 g monofilament, abnormal vibration perception threshold, using a thensiometer, and a lack of any other and lack of other significant disease (12).

Patients with known coronary artery disease, defined as the history of myocardial infarction (MI), coronary artery bypass grafting surgery, percutaneous coronary intervention, and the presence of coronary heart disease, as documented by coronary angiography, were not included in study. Patients with chronic renal failure, macroalbuminuria, and acute illness 24 hours prior testing were also not included. None of the patients were receiving drugs that could lengthen the QT interval, such as class IA, IC, or III antiarrhtymic drugs. Patients with complete bundle branch block, atrial fibrillation, second or third degree atrio-ventricular block, or less than six measurable leads in the ECG and patients with insulin treatment were excluded. All patients were taking oral hypoglycemic agents. The study was approved by the ethics committee of the Bayindir Hospital and all patients provided written informed consent.

ECG was performed with the patients lying comfortably in supine position. Digital 12-lead ECG recordings were analyzed at an ECG paper speed of 25 mm/s using a M1171A Pagewritter 200 (Philips, Andover, MA, USA). The QT intervals for each lead were measured manually from the first deflection of the QRS complex to the point of the T wave offset, defined by the return of the terminal T wave to the isoelectric TP baseline. Each QT interval was corrected for patient's heart rate using Bazett's formula: $QTc = QT\sqrt{RR}$ (ms) (13), where QTc >440 ms was considered prolonged. QTc dispersion was calculated using the difference between the maximum and the minimum QTc in any lead. QT dispersion >80 ms was considered prolonged.

Blood samples were collected after an overnight fasting from the medial cubital vein. Serum calcium and phosphorus were measured with photometric system (Roche Cobas C501, Roche Diagnostics, Indianapolis, IN, USA). 25-OHD and hemoglobin A1c (HbA1c) were measured by turbidimetric inhibition immunoassay (Roche Cobas C51, Roche Diagnostics).

Data were analyzed by IBM Statistics for Windows, version 21.0 8 (IBM Corp., Armonk, NY, USA). Normality of the distribution was tested with Kolmogorov-Smirnov test. Continuous data were expressed as mean±SD and median with interquartile ranges when appropriate. t test and Mann-Whitney-U test, depending on the normality of distribution, were used to test the differences between the study groups. χ^2 test was used for the categorical variables. Logistic regression analyses (stepwise, forward) were used to estimate odds ratios (ORs) and the 95% confidence intervals (95% CIs). In the regression model, the QTc prolongation was entered as dependent variable, and age, duration of diabetes and vitamin D deficiency as independent variables. Post hoc analysis was performed, and the power of the study with given sample size was 0.91 (two means t test). A two-tailed P value of 0.050 was considered significant.

RESULTS

Mean duration of diabetes was 9.6±6.6 years. Mean HbA1c level was 7.1±1.1% (54 mmol/mol) and median fasting blood glucose level was 133 (IQR 111-164) mg/dL. Retinopathy was present in 85 (33.5%), neuropathy in 73 (28.8%), microalbuminuria in 75 (26.9%), and hypertension in 108 patients (42.6%) (Table 1).

There was no significant difference in calcium (P=0.670), phosphorus (P=0.090), 25-OHD levels (P=0.480), and the frequency of 25-OHD deficiency (P=0.950) between the the diabetic group and controls. 25-OHD deficiency was found in 65.2% of patients and 64.7% of controls (P=0.954). Men and women also did not significantly differ in the prevalence of 25-OHD deficiency (P=0.721), QTc duration (P=0.910), and QTc dispersion (P=0.760).

Median QTc duration in patients with diabetes was 434 ms (IQR 418-467) and in controls 423 ms (IQR 403-434) (P<0.001). A prolonged QTc interval was found in 26.8% (68 in 253) of patients and 4.1% (7 in 170) of controls (P<0.001). In diabetic group, patients with prolonged QTc interval more frequently had 25-OHD deficiency than patients with normal QTc (P<0.001). There were no significant differences between these groups in calcium and phosphorus levels (P=0.114 and P=0.752, respectively) (Table 2). In multivariate regression analysis the odds of prolonged QTc intervals increased significantly with age (P=0.008), lon-

TABLE 1. Demographic and laboratory data of patients and controls*

	Diabetes mellitus patients (N=253)	Controls (N=170)	P†
Age, years (mean ± SD)	59.7±6.5	59.1±5.5	0.518
Sex, female/male	129/124	87/83	0.735
BMI, kg/m (mean ± SD)	30.1±6.8	28.5±7.2	0.073
Fasting glucose, mg/dL (median, IQR)	133, 115.2-163.8	90.9, 85.8-93.78	<0.001
Calcium, mg/dL	9.6±0.3	9.5±0.3	0.670
Phosphorus, mg/dL	3.6±0.5	3.4±0.3	0.090
25 (OH) D deficiency, n (%)	165 (65.4)	110 (64.7)	0.954
QTc interval, ms (median, IQR)	434, 418-467	423, 403-434	<0.001
QTc dispersion, ms (median, IQR)	53.8, 41-72.5	43.2, 31.9-53.9	<0.001

*SD – standard deviation; IQR – interquartile range; 25(OH)D – 25-hydroxyvitamin D; BMI – body mass index; QTc – corrected QT interval.
†t test or Mann-Whitney U test.

TABLE 2. Laboratory data of diabetic patients according to their QTc interval*

	Prolonged QT interval (QT>440 ms) (N=68)	Normal QT interval (QT<440 ms) (N=185)	P†
Age, years (mean ± SD)	61.5±6.6	59.0±6.4	0.012
Sex, female/male	23/25	50/54	0.910
Duration of diabetes, years (median, IQR)	10, 5-17	8, 5-12	0.041
Fasting blood glucose, mg/dL (median, IQR)	136.2, 111.6-181.8	132.8, 110.3-169.2	0.195
HbA1c, % (mean ± SD)	7.4±1.19	7.05±1.09	0.011
Calcium, mg/dL (mean ± SD)	9.4±0.3	9.6±0.4	0.114
Phosphorus, mg/dL (mean ± SD)	3.7±0.7	3.6±0.4	0.752
25 (OH) D deficiency, n (%)	58 (85.2)	104 (56.2)	<0.001

*SD – standard deviation; IQR – interquartile range; 25(OH)D – 25-hydroxyvitamin D; HbA1c –hemoglobin A1c; QTc – corrected QT interval.
†t test or Mann-Whitney U test.

ger duration of diabetes ($P=0.012$), higher HbA1c levels ($P=0.034$), and vitamin D deficiency ($P=0.010$) (Table 3). The model explained 80.9% of QTc duration. The presence of microalbuminuria ($P=0.347$), neuropathy ($P=0.126$), retinopathy ($P=0.310$), and hypertension ($P=0.172$) were similar in both groups.

The median QTc dispersion was 53.8 ms (IQR 41-72.5) in patients and 43.2 ms (IQR 31.9-53.9) in controls ($P<0.001$). Prolonged QTc dispersion was detected in 20.9% of patients and 4.1% of controls ($P<0.001$). Diabetic patients with prolonged QTc dispersion were of similar age and had similar HbA1c level and diabetes duration as patients with normal QTc dispersion. However, they significantly more frequently had 25-OHD deficiency ($P=0.010$). There were no significant differences in calcium and phosphorus levels ($P=0.133$ and $P=0.217$ respectively), microalbuminuria ($P=0.173$), neuropathy and retinopathy incidence ($P=0.376$ and $P=0.832$ respectively) between these groups (Table 4).

DISCUSSION

This study showed prolonged QTc interval and QTc dispersion in type 2 diabetic patients. Prolonged QTc interval was more frequent in older patients with higher HbA1c levels, longer diabetes duration, and 25-OHD deficiency.

TABLE 3. Multivariate regression analysis for risk factors of prolonged QTc interval*

	95% confidence interval	Odds ratio	P
Age	1.03-1.25	1.14	0.008
Duration of diabetes	1.02-1.21	1.11	0.012
HbA1c	1.03-3.18	1.81	0.034
25 (OH) D deficiency	1.44-22.61	5.71	0.010

*25(OH)D – 25-hydroxyvitamin D; HbA1c – hemoglobin A1c; QTc – corrected QT interval.

This is the first study that showed the association between QTc duration, dispersion, and 25-OHD deficiency in diabetic patients.

Although the best characterized sequels of 25-OHD deficiency affect the musculoskeletal system, the discovery that most tissues and many cells in the body have a vitamin D receptor has provided a new insight into the vitamin D metabolism. It was shown that the vitamin D axis affected vascular smooth muscle cell proliferation, inflammation, vascular calcification, renin angiotensin system, and blood pressure (14,15), all of which increase the risk of coronary vascular disease coronary vascular disease (CVD) and MI. In addition, vitamin D regulates calcium and phosphorus metabolism, and abnormalities in serum calcium concentrations affect QT interval duration (16).

QTc duration and QTc dispersion are the most frequently used parameters in the electrocardiographic assessment of ventricular repolarization. They have been associated with the risk of arrhythmogenesis. They have also been shown to be prolonged in diabetic patients (17,18). The prevalence of prolonged QTc has been reported to be as high as 16% in type 1 diabetes (19) and 30.1% in T2DM (20). The prevalence of prolonged QTc interval in our cohort was 26.8% and that of prolonged QTc dispersion was 20.9%. Another study found that QT interval in general population was inversely associated with serum calcium and positively associated with serum phosphorus, but there was no association with 25-OHD (21). In our diabetic cohort, prolonged QTc interval and dispersion were associated with vitamin 25-OHD deficiency, but not with calcium and phosphorus levels. Calcium plays an important role in determining the duration of the action potential of cardiac cells. It is well known that hypocalcemia prolongs QT interval due to longer phase 2 of the cardiac action potential (16). However in our study, patients with 25-

TABLE 4. Laboratory data of the patients according to QTc dispersion*

	Prolonged QTc dispersion (QTc >80 ms) (N=53)	Normal QTc dispersion (QTc <80 ms) (N=200)	$P^†$
Age, years (mean ± SD)	60.5±6.0	59.5±6.7	0.182
Sex, female/male	18/19	56/60	0.764
Duration of diabetes, years (median, IQR)	9.5, 5-15.7	9, 5-12	0.600
Fasting blood glucose, mg/dL (median, IQR)	146.7, 109.8-183	140.7, 110.8-162.7	0.592
HbA1c (mean ± SD)	7.4±1.1	7.0±1.0	0.153
Calcium, mg/dL (mean ± SD)	9.4±0.3	9.6±0.3	0.133
Phosphorus, mg/dL (mean ± SD)	3.7±0.7	3.6±0.4	0.217
25 (OH) D deficiency, n (%)	43 (81.1)	112 (56)	0.010

*SD – standard deviation; IQR – interquartile range; 25(OH)D – 25-hydroxyvitamin D; HbA1c – hemoglobin A1c; QTc – corrected QT interval.
†t test or Mann-Whitney U test.

OHD deficiency, although they had similar calcium levels as controls, had prolonged QTc interval. We may speculate that low 25-OHD levels may have an additional effect on the pathogenesis of prolonged QTc interval in patients with diabetes.

We also observed that patients with prolonged QTc interval had longer diabetes duration and higher HbA1c. Acute hyperglycemia has been shown to increase QT interval in newly diagnosed T2DM patients (22). The mechanisms involved in this process were increased intracellular calcium concentration and the impairment of sympathovagal balance (22). Additionally, hyperglycemia has been demonstrated to increase the sympathetic activity, which is evident as increased plasma cathecholamine production (23). In our cohort, prolonged QTc interval was also associated with age, but prolonged QTc dispersion was not. Mangoni et al (24) reported similar observations in healthy participants, explaining that they might be secondary to cardiac hypertrophy and myocardial action potential prolongation.

In our study, QTc duration and dispersion were linearly related. However, 34% of patients with normal QTc dispersion had a prolonged QTc interval. It was reported that QTc interval and QTc dispersion may reflect different aspects of abnormal ventricular repolarization (3). Our cohort comprised T2DM patients and in these patients several disease processes may influence myocardial depolarization and repolarization duration. Nevertheless, we found that 25-OHD deficiency prolonged both QTc interval and QTc dispersion.

25-OHD deficiency is highly prevalent in Turkey and worldwide (25,26). Its principal causes are limited cutaneous synthesis due to inadequate sun exposure or pigmented skin and cultural practices. The prevalence of 25-OHD deficiency in Turkey in the summer season is 60% (26), while the prevalence observed in our study, conducted in winter, was 65.2% in patients and 64.7% in controls. To avoid the effect of seasonal changes this study was performed between October and December.

The main limitation of this study is the manual assessment of the QTc interval and dispersion. However, superiority of available automatic methods has not been proven (27). Also, this study included patients who are receiving oral hypoglycemic therapy and without known cardiovascular disease, who are not representative of the overall type 2 diabetic population.

Despite these limitations, this study clearly demonstrated the relationship between 25-OHD deficiency and QTc parameters in diabetic patients. Assessment of 25-OHD levels in these patients may be important for better stratification of cardiac disease risk. However, these findings need to be confirmed by additional randomized trials as well as treatment studies.

References

1 Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87:4-14. Medline:19896746 doi:10.1016/j.diabres.2009.10.007

2 Sahu P, Lim PO, Rana BS, Struthers AD. QT dispersion in medicine: electrophysiological holy grail or fool's gold. QJM. 2000;93:425-31. Medline:10874051 doi:10.1093/qjmed/93.7.425

3 Rana BS, Lim PO, Naas AA, Ogston SA, Newton RW, Jung RT, et al. QT interval abnormalities are often present at diagnosis in diabetes and are better predictors of cardiac death than ankle brachial pressure index and autonomic function tests. Heart. 2005;91:44-50. Medline:15604334 doi:10.1136/hrt.2003.017632

4 Giunti S, Gruden G, Fornengo P. Increased QT interval dispersion predicts 15 year cardiovascular mortality in type 2 diabetic subjects. Diabetes Care. 2012;35:581-3. Medline:22301117 doi:10.2337/dc11-1397

5 Mozos I, Marginean O. Links between vitamin D deficiency and cardiovascular diseases. Biomed Res Int. 2015;2015:109275. Medline:26000280 doi:10.1155/2015/109275

6 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. Medline:18180395 doi:10.1161/CIRCULATIONAHA.107.706127

7 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;58:1021-8. Medline:22068871

8 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 reninangiotensin systems. Am J Physiol Endocrinol Metab. 2005;288:E125-32. Medline:15367398 doi:10.1152/ajpendo.00224.2004

9   Palomer X, Gonzalaes-Clemente JM. BlancoVaca F. The role of vitamin D in the pathogenesis of type 2 diabetes mellitus. Diabetes Obes Metab. 2008;10:185-97. Medline:18269634 doi:10.1111/j.1463-1326.2007.00710.x

10   Joergensen C, Gall MA, Schmedes A, Tarnow L, Parwing HH, Rossing P. Vitamin D levels and mortality in type 2 diabetes. Diabetes Care. 2010;33:2238-43. Medline:20606205 doi:10.2337/dc10-0582

11   Bischoff-Ferrari HA. Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes. Adv Exp Med Biol. 2014;810:500-25. Medline:25207384

12   Singleton JR, Smith AG, Russell J, Feldman EL. Polyneuropathy with Impaired Glucose Tolerance: Implications for Diagnosis and Therapy. Curr Treat Options Neurol. 2005;7:33-42. Medline:15610705 doi:10.1007/s11940-005-0004-4

13   Bazzett HC. An analysis of time relations of electrocardiograms. Hearts. 1920;7:353-70.

14   Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25 hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med. 2008;168:1174-80. Medline:18541825 doi:10.1001/archinte.168.11.1174

15   Zittermann A, Schleithoff SS, Koerfer R. Putting cardiovascular disease and vitamin D insufficiency into prospective. Br J Nutr. 2005;94:483-92. Medline:16197570 doi:10.1079/BJN20051544

16   Eryol NK, Colak R, Ozdogru I, Tanriverdi F, Unal S, Topsakal R, et al. Effects of calcium treatment on QT interval and QT dispersion on hypoglycemia. Am J Cardiol. 2003;91:750-2. Medline:12633817 doi:10.1016/S0002-9149(02)03423-9

17   Clemente D, Pereira T, Ribeiro S. Ventricular repolarisation in diabetic patients: Characterization and clinical implications. Arq Bras Cardiol. 2012;99:1015-22. Medline:23108644 doi:10.1590/S0066-782X2012005000095

18   Arildsen H, May O, Christiansen EH, Damsgaard EM. Increased QT dispersion in patients with insulin dependent diabetes mellitus. Int J Cardiol. 1999;71:235-42. Medline:10636529 doi:10.1016/S0167-5273(99)00140-0

19   Veglio M, Borra M, Stevens LK, Fuller JH, Perin PC. The relation between QTc interval prolongation and diabetic complications. The EURODIAB IDDM Complication Study Group. Diabetologia. 1999;42:68-75. Medline:10027581 doi:10.1007/s001250051115

20   Li X, Ren H, Xu ZR, Liu YJ, Yang XP, Liu JQ. Prevalence and risk factors of prolonged QTC interval among Chinese patients with type 2 diabetes. Exp Diabetes Res. 2012;2012:234084. Medline:23319939 doi:10.1155/2012/234084

21   Zhang Y, Post WS, Dalal D, Bansal S, Blasco-Colmenares E, Jan De Beur S. Serum 25-hydroxyvitamin D, calcium, phosphorus and electrocardigraphic QT interval duration: findings from NHANES III and ARIC. J Clin Endocrinol Metab. 2011;96:1873-82. Medline:21508137 doi:10.1210/jc.2010-2969

22   Marfella R, Nappo F, De Angelis L, Paolisso G, Tagliamonte MR, Giugliano D. Hemodynamic effects of acute hyperglycemia in type 2 diabetic patients. Diabetes Care. 2000;23:658-63. Medline:10834426 doi:10.2337/diacare.23.5.658

23   Marfella R, Nappo F, De Angelis L, Siniscalchi M, Rossi F, Giugliano D. The effect of acute hyperglycemia on QTc duration in healthy man. Diabetologia. 2000;•••:571-5. Medline:10855531 doi:10.1007/s001250051345

24   Mangoni AA, Kinirons MT, Swift CG, Jackson SH. Impact of age on QT interval and QT dispersion in healthy subjects: a regression analysis. Age Ageing. 2003;32:326-31. Medline:12720621 doi:10.1093/ageing/32.3.326

25   Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc. 2006;81:353-73. Medline:16529140 doi:10.4065/81.3.353

26   Alagöl F, Shihadeh Y, Boztepe H, Tanakol R, Yarman S, Azizlerli H, et al. Sunlight exposure and vitamin D deficiency in Turkish women. J Endocrinol Invest. 2000;23:173-7. Medline:10803475 doi:10.1007/BF03343702

27   Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. J Am Coll Cardiol. 2000;36:1749. Medline:11092641 doi:10.1016/S0735-1097(00)00962-1