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CLINICAL RESEARCH

Association Between Disturbed Serum Phosphorus Levels and QT Interval Prolongation

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Introduction: QT interval prolongation is a risk factor for fatal arrhythmias and other cardiovascular complications. QT interval prolongation in patients on hemodialysis (HD) is not well understood. Hypocalcemia is a suspected, but poorly verified etiology in these patients, and the association between serum phosphorus levels and QT interval prolongation is unknown. We sought to determine the prevalence of QT interval prolongation in patients on HD and to verify the association between predialysis serum calcium (Ca) and phosphate (P) levels and QT interval prolongation.

Methods: A cross-sectional study was conducted on adult patients on maintenance HD who were enrolled in the Japanese Society for Dialysis Therapy and Renal Data Registry 2019. After assessing patient characteristics, linear regression analysis was performed with predialysis serum Ca and P levels as exposures and a rate-corrected QT (QTc) interval as the outcome.

Results: A total of 204,530 patients were analyzed with a mean QTc of 451.2 (standard deviation, 36.9) ms. After multivariable analysis, estimated change in QTc (coefficients; 95% confidence interval) per 1 mg/dl increase in serum Ca and P was −2.02 (−3.00 to −1.04) and 5.50 (3.92–7.09), respectively. In the restricted cubic spline curve, estimated change in QTc increased with lower values of serum Ca. The correlation between serum P and QTc showed a U-shaped curve.

Conclusion: Decreased serum Ca levels and decreased and increased serum P levels may be associated with QT interval prolongation in patients on maintenance HD.

Kidney Int Rep (2024) **9,** 1792–1801; https://doi.org/10.1016/j.ekir.2024.03.007
KEYWORDS: calcium; hemodialysis; phosphate; QT interval prolongation

Despite advances in cardiovascular medicine,[1] cardiac mortality among patients with end-stage renal disease remains markedly high.[2,3] This is attributable to the high prevalence and incidence of sudden cardiac arrest and/or sudden cardiac death (SCD). SCD has been reported to account for approximately 15% of deaths in Japanese patients on HD,[4,5] and for 22% to 26% of deaths in patients on HD worldwide.[6–8] The incidence rate of SCD in the HD population of the US is approximately 54 deaths per 1000 patient-years,[2] whereas in a general population-based study, the overall incidence of out-of-hospital cardiac arrest was 1.9 per 1000 patient-years.[9] Arrhythmia is one of the major causes of SCD in the general population;[10] however, the causes of SCD in patients on HD are still poorly reported and remain unknown. Because both ischemic and nonischemic cardiomyopathy are highly prevalent in patients with end-stage renal disease, this myocardial vulnerability is the ordinary state in many patients on dialysis, rendering them susceptible to fatal arrhythmias due to exposure to proarrhythmic triggers, such as prolongation of QT interval by electrolyte abnormalities,[11,12] consequently leading to SCD.[13]

Prolongation of the QT interval, which is linked to ventricular repolarization time, is a well-known cause of fatal arrhythmia in the general population.[14] It is also well known that the QT interval in patients on HD is

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Received 22 June 2023; revised 9 February 2024; accepted 4 March 2024; published online 13 March 2024

significantly longer than that in the general population. Several small observational studies[15–17] reported a mean QT of 434 to 468 ms in patients on HD, longer than the 410.2 (standard deviation, 17.8) ms in the general population.[18] In addition to strict P control, the current pattern of care of patients on HD with secondary hyperparathyroidism has been to use calcimimetics instead of vitamin D, because they are more effective. Calcimimetics are Ca-sensitive receptor (CaSR) antagonists that lower serum Ca.[19] This can result in an increase in the prevalence of hypocalcemia.[20] Hypocalcemia is a known cause of QT interval prolongation in the general population[21] and in patients on HD.[15,16,22] However, all reports on patients on dialysis to date have been small observational studies, and results have not been validated on a national basis. Furthermore, 2 of these 3 reports were made before the launch of calcimimetics, and the association between hypocalcemia and QT interval prolongation is not known. In addition to Ca, serum P is also an important therapeutic and prognostic marker in patients on HD due to the mineral bone disorder (MBD) that accompanies HD. In a large observational study of patients on HD, P was identified as an associated causative factor in sudden death.[5] However, to our knowledge, no study has examined the association between P and QT interval prolongation.

On the basis of the small amount of data to date, it is essential to investigate the association between MBD markers, Ca and P, and QT interval. We conducted a cross-sectional study to determine the association between predialysis serum Ca and P and QT interval prolongation using a Japanese nationwide database.

METHODS

Registry

All data used in this study were collected from the Japanese Society for Dialysis Therapy and Renal Data Registry 2020. The details of this survey have been reported elsewhere.[23] The Japanese Society for Dialysis Medicine initiated the prospective collection of patient information and developed a computerized registry to analyze nationwide trends in dialysis care. The survey response rate exceeds 98% each year, so the registry includes almost all patients on HD in Japan. Details of the survey are available online at the Japanese Society of Dialysis Therapy website (www.jsdt.or.jp). The study protocol was approved by the Medical Ethics Committee of the Japanese Society of Dialysis Therapy (No. 59).

Study Design and Participants

Our cross-sectional study used the Japanese Society for Dialysis Therapy and Renal Data Registry data set from 2020. Among all subjects, we excluded patients with missing QT interval, missing predialysis serum Ca or P or intact parathyroid hormone; concomitant atrial fibrillation identified on the same electrocardiogram (ECG) that measured QT interval; as well as those aged younger than 18 years; or receiving dialysis less than 3 times per week, patients on peritoneal dialysis, and patients on home HD. In addition, we excluded cases of outliers from the analysis, defined as patients with a value of >3 standard deviations from the mean in any measured variable.

Outcome

Outcome was set to QT interval as a continuous variable. QT and RR intervals were extracted from the most recent ECG and QTc was calculated using the formula of Bazzet *et al*.[24]

$$QTc = QT/\sqrt{RR}$$

Exposures

The exposure factors were serum Ca and P measured just before HD on the day beginning the week (Monday or Tuesday). Serum Ca levels were corrected in accordance with the recommendation of the Japanese Society for Dialysis Therapy, namely when serum albumin levels measured at the same time were <4 g/dl.[25,26]

$$Corrected\ serum\ Ca\ (mg/dl) = serum\ Ca\ (mg/dl)$$

$$+(4.0 - serum\ albumin\ [g/dl])$$

All blood test data, including covariates, were taken from the most recent blood draw at the time the questionnaire was administered.

Covariates

We measured the following as covariates: age, sex, body mass index, dialysis vintage, diabetes mellitus, history of cardiovascular disease, serum magnesium, Ca carbonate use, Ca lanthanum use, calcimimetic use, vitamin D analog use, iron-containing phosphorus binder use, polymer-based phosphorus binder use. All blood test data were measured just before HD on the first day of the week (Monday or Tuesday). All covariates were simultaneously extracted from exposures and questionnaires distributed to dialysis facilities.

Statistical Analysis

We descriptively analyzed normally distributed continuous variables by means (standard deviation), nonnormally distributed continuous variables by medians (quartiles), and categorical variables by numbers (proportions). Further, we created a histogram to describe the distribution of QTc.

We performed univariable and multivariable analyses using linear regression models to verify the association between exposures and outcome. We set age, sex, body mass index, dialysis vintage, diabetes mellitus, history of cardiovascular disease, serum corrected Ca, serum phosphate, serum intact parathyroid hormone, serum magnesium, and use of Ca carbonate, Ca lanthanum, calcimimetics, vitamin D analogs, iron-based phosphorus binders, and polymer-based phosphorus binders as explanatory variables used in the multivariable analysis, which were considered to be confounding factors, and modified the combination of variables for each exposure. Specifically, we excluded Ca from the analysis for exposure to Ca, and P from the analysis for exposure to P. Ca multiplied by P and sex multiplied exposures were included in the model as an interaction term. In addition, categorical analyses of exposures based on tertile groups were performed and a restricted cubic spline was drawn to verify the existence of nonlinear association.

For sensitivity analysis, we verified the association between Ca and QT interval prolongation, P and QT interval prolongation, stratified by previous cardiovascular disease and sex. Although some reports indicate no gender differences in QT interval in patients on HD,[27] sex differences in the QT interval in these populations have been reported and may be a clinically important factor.[28] We further calculated estimated Ca concentrations using a Ca estimation equation that accounted for the physiological properties of ionized Ca by correction using serum P and serum albumin levels,[29] and verified the association with QT interval. We also performed restricted cubic spline with QTc as a continuous variable using a linear regression model to confirm biological plausibility.

Missing variables, except for exposure and outcome, were complemented using the multiple imputation by chained equation,[30] in which 20 imputed datasets were created. We verified the convergence of the variables in the imputation of the 20 sets using the worst linear function. All results of logistic regression models were conducted on each of 20 datasets and combined with Rubin's rule. Analyses were assessed with 2-tailed alpha = 0.05. All statistical analyses were performed using commercial software (Stata version 17.0, Stata Corp., College Station, TX).

RESULTS

Study Subjects

As shown in Figure 1, of the 332,599 Japanese Society for Dialysis Therapy and Renal Data Registry data set 2020 subjects, 204,530 met the eligibility criteria. In Table 1, we show the baseline characteristics of the included subjects. To confirm the impact of excluding patients with a missing QTc, in Supplementary Table S1, we show baseline characteristics with or without QTc missing. In Supplementary Figure S1, we show the distribution of QTc in all subjects as a histogram.

Association Among Ca, P, and QTc Prolongation in Linear Regression Models

In univariable analysis using a linear regression model, there was a statistically significant association between lower corrected Ca and longer QTc interval, and higher P and longer QTc. In multivariable analysis, the association between P and QTc showed a change that increased about 10-fold compared to the results of the univariable analysis. In categorical analyses of exposure based on tertile groups, a nonlinear association

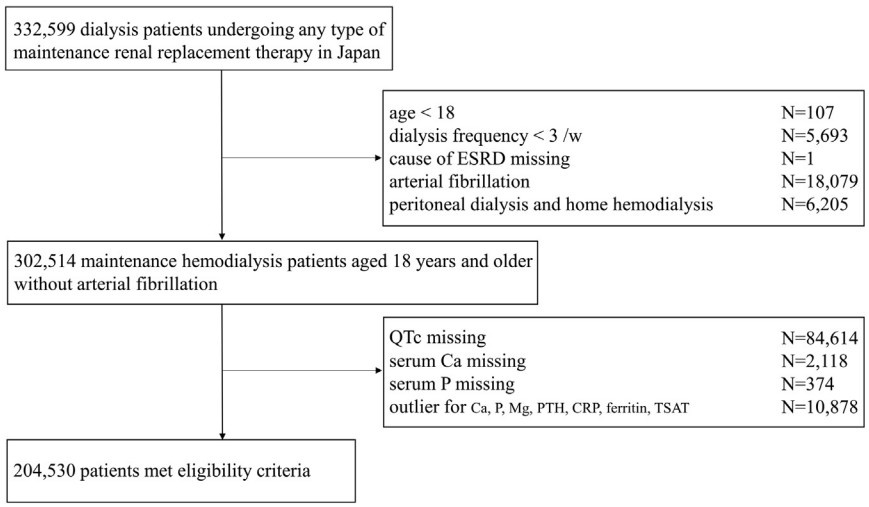

Figure 1. Study flow diagram. Of the 332,599 The Japanese Society for Dialysis Therapy and Renal Data Registry 2019 subjects, 204,530 met the inclusion criteria. Ca, calcium; CRP, C-reactive protein; ESRD, end-stage renal disease; Mg, magnesium; P, phosphate; PTH, parathyroid hormone; QTc, rate-corrected QT; TSAT, transferrin saturation.

Table 1. Baseline characteristics

Characteristics	Total (N = 204,530)	Missing, n (%)
Male, n (%)	134,133 (65.6)	0
Age (yr)	69.8 (12.4)	0
Modality, n (%)		0
HD	110,883 (54.2)	
HDF	93,647 (45.8)	
Diabetes mellitus, n (%)	103,445 (50.6)	9382 (4.6)
Cardiovascular disease, n (%)	48,680 (23.8)	48,680 (23.8)
Number of dialysis session (per wk)	3.0 (3.0–3.0)	735 (0.4)
Body mass index	22.1 (4.2)	7565 (3.7)
Dialysis vintage (mo)	68.0 (30.0–133.0)	128 (0.06)
Mean arterial pressure before dialysis (mm Hg)	103.1 (16.0)	1293 (0.6)
Heart rate before dialysis (/min)	74.1 (12.5)	3186 (1.6)
Serum urea nitrogen (mg/dl)	60.0 (15.3)	260 (0.1)
Serum albumin (g/dl)	3.5 (0.4)	982 (0.5)
Serum magnesium (mg/dl)	2.5 (0.4)	52,059 (25.5)
Corrected serum calcium (mg/dl)	9.1 (0.7)	0
Serum phosphate (mg/dl)	5.2 (1.3)	0
QTc (ms)	451.2 (36.9)	0

HD, hemodialysis; HDF, hemodiafiltration.

between P and QTc was suspected. In Table 2, we show the results of the linear regression analysis.

Association Between Ca, P, and QTc Prolongation in Restricted Cubic Spline Curve

In Figure 2a, we show the association between corrected Ca and estimated change in QTc. QTc tended to be longer with lower corrected Ca. In Figure 2b, we show the association between P and estimated change in QTc. There was a U-shaped curve association between P and QTc.

Table 2. Association between Ca, P and QTc prolongation in linear regression models

Variables	Coefficient (ms)	95% CI	P-value
Univariable analysis			
Corrected Ca (mg/dl)	−4.82	−5.07 to −4.57	<0.01
P (mg/dl)	0.58	0.46 to 1.00	<0.01
Multivariable analysis[a]			
Corrected Ca (mg/dl)	−2.02	−3.00 to −1.04	<0.01
Corrected Ca category			
First tertile (≤8.7)	0.43	−0.31 to 1.17	0.26
Second tertile (>8.7, ≤9.2)	Ref.	—	—
Third tertile (>9.2)	−0.72	−1.43 to −0.01	0.05
P (mg/dl)	5.50	3.92 to 7.09	<0.01
P category			
First tertile (≤4.6)	1.61	1.10 to 2.11	<0.01
Second tertile (>4.6, ≤5.7)	Ref.	—	—
Third tertile (>5.7)	1.91	1.36 to 2.46	<0.01

CI, confidence interval; Ca, serum calcium level; P, serum phosphate level, Ref., reference.
[a]Adjusted for age, sex, body mass index, dialysis vintage, diabetes mellitus, history of cardiovascular disease, serum calcium or phosphate level, interaction term of serum calcium and phosphate level, interaction term of sex and exposures, serum intact parathyroid hormone levels, calcium carbonate use, calcium lanthanum use, calcimimetics use, vitamin D analog use, iron-containing phosphorus binders use, and polymer-based phosphorus binders use.

Sensitivity Analysis

The results of the subgroup analysis are shown in Figures 3 and 4. In all subgroups, Ca and P showed the same association with QT interval prolongation as in the main analysis.

DISCUSSION

To our knowledge, this study is the first report to describe QTc in patients on HD using nationwide data, and further examines the association between QTc and MBD markers, serum Ca, and serum P. There are 2 main novelties in this study. The first is that a large amount of representative data showed that QTc is prolonged in patients on HD compared to the general population. Second, an unexpected U-shaped curve association between serum P and QTc has been identified, although the effect size is not so large.

Patients on HD as a Prolonged QT Interval Population

The mean QT interval in our Japanese HD population was 451 ms, and it was normally distributed, with no significant gender-related differences. In general, the upper limits of normal QT interval corrected by the Bazzet method are 450 ms for males and 460 ms for females.[31] The mean QTc in patients on HD is similar to the upper limit in males. Because in this study, there were no subjects with normal renal function as controls, it is impossible to prove that the distribution of QTc in patients on HD shifted to the longer right side. However, according to a previous study[32] that examined QT interval distribution in 3 different populations, including the general population, patients with acquired long QT syndrome, and patients with congenital long QT syndrome, the distribution of HD in this study is clearly shifted to the prolonged side compared with the general population, where the mean QTc was 406 ms, and its distribution is very similar to that seen in acquired long QT syndrome with a mean QTc of 453 ms, and shorter than that in congenital long QT syndrome with a mean QTc of 478 ms. This suggests that prolonged QTc in patients on HD is acquired, and secondary to some potential acquired factors. Coll *et al.*'s[33] attempt to investigate the association of congenital genetic factors with QT interval prolongation in patients on HD found a very weak association. Therefore, in the finding of the patients on HD with QT interval prolongation in the clinical setting, it is essential to search for potential risk factors for QT interval prolongation.

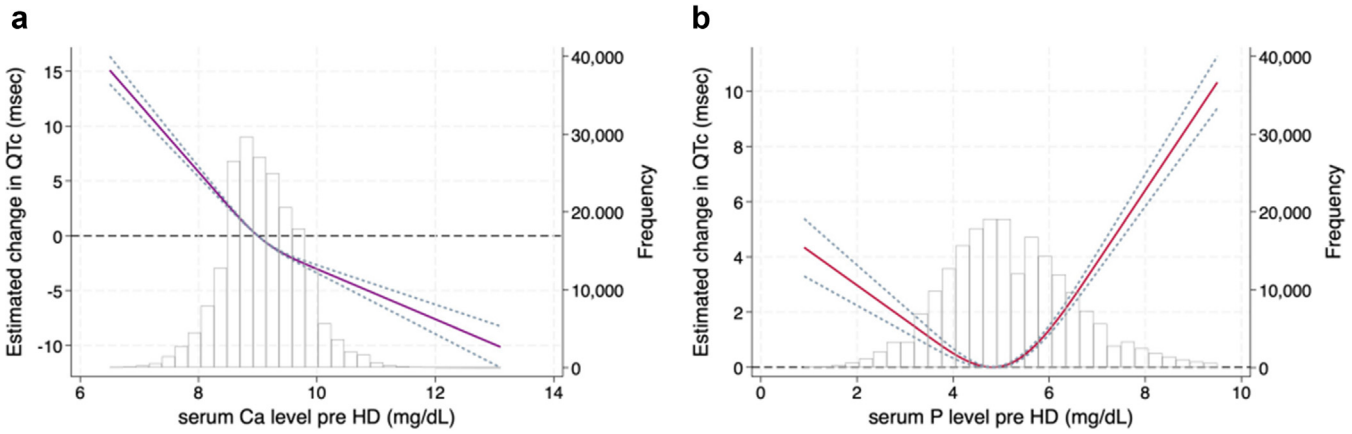

Figure 2. Restricted cubic spline showing adjusted association between QTc and serum corrected calcium and phosphate levels before hemodialysis. (a) Estimated QTc prolonged with decreased predialysis serum corrected calcium levels. (b) Estimated QTc prolonged with decreased and increased predialysis serum phosphorus levels. These models were adjusted for age, sex, body mass index, dialysis vintage, diabetes mellitus, history of cardiovascular disease, serum corrected calcium or phosphate level, interaction term of serum calcium and phosphate level, serum intact parathyroid hormone levels, calcium carbonate use, calcium lanthanum use, calcimimetics use, vitamin D analog use, iron-containing phosphorus binders use, and polymer-based phosphorus binders use. Dotted lines indicate 95% confidence intervals. Ca, calcium; HD, hemodialysis; P, phosphate; QTc, rate-corrected QT.

Known Factors Associated With QT Interval Prolongation

Vandael *et al.*'s[34] systematic review of 10 articles examining risk factors for QT interval prolongation reported the strength of each risk factor. They demonstrated that age >65 years, cardiomyopathy, and hypertension were each strong independent risk factors for QT interval prolongation. Diabetes mellitus is

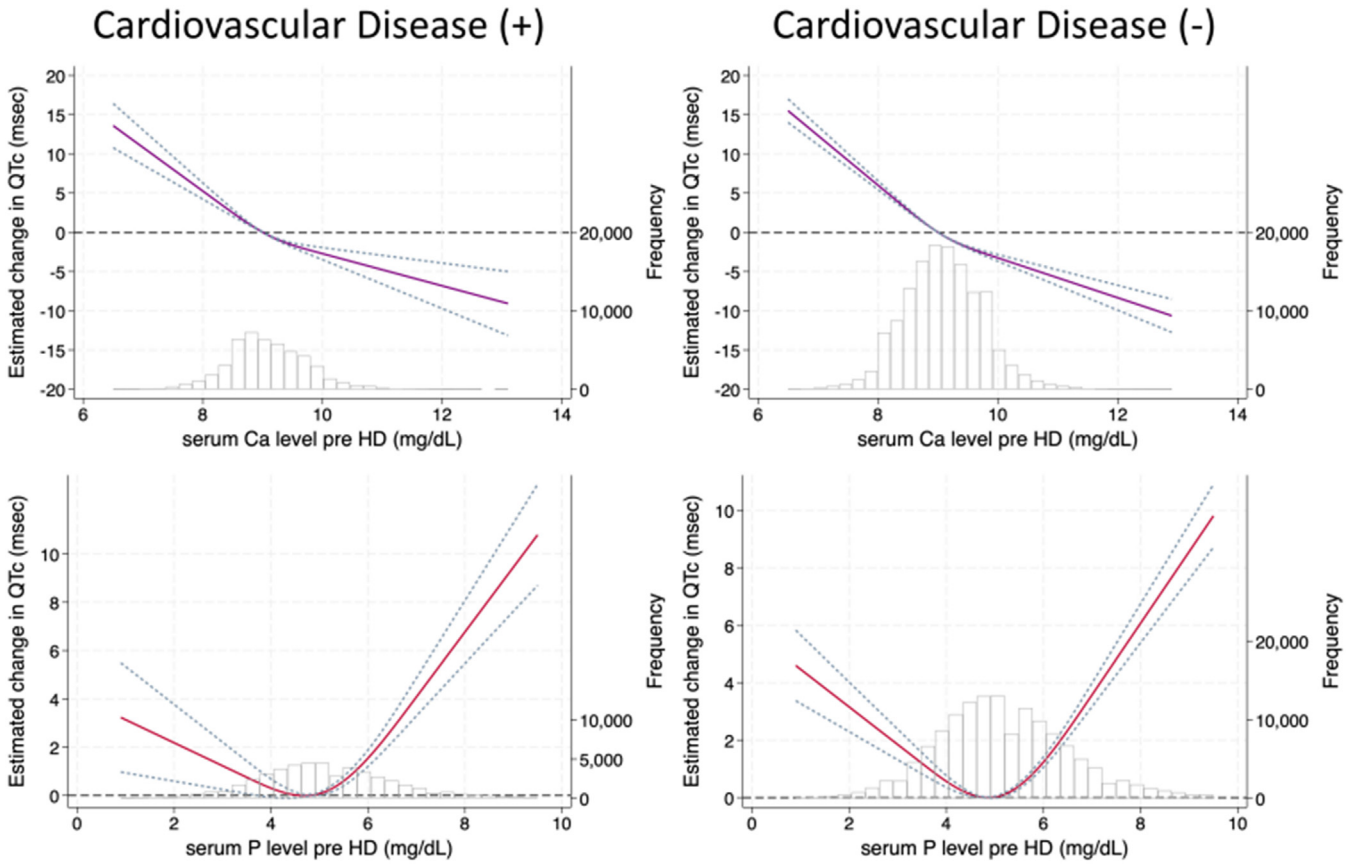

Figure 3. Subgroup analysis by presence of cardiovascular disease. In subgroup analysis divided by the presence or absence of preexisting cardiovascular disease, the association between predialysis serum corrected calcium and serum phosphorus levels and QTc did not change significantly from those in Figure 2. These models were adjusted for all adjustment variables in Figure 2 except history of cardiovascular disease. Ca, calcium; HD, hemodialysis; P, phosphate; QTc, rate-corrected QT.

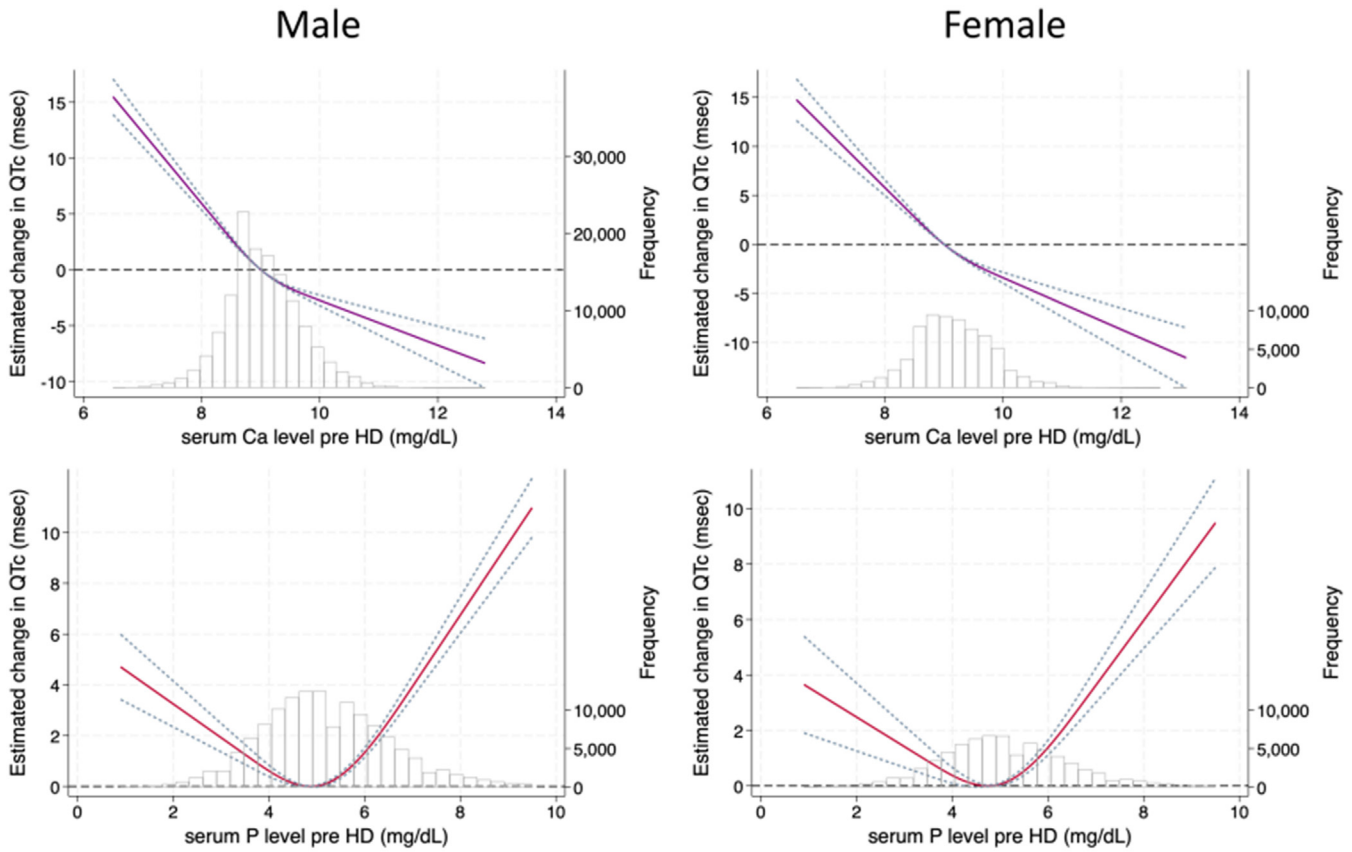

Figure 4. Subgroup analysis by sex. In subgroup analysis divided by sex, the association between predialysis serum corrected calcium and serum phosphorus levels and QTc did not change significantly from Figure 2. These models were adjusted for all adjustment variables in Figure 2 except sex. Ca, calcium; HD, hemodialysis; P, phosphate; QTc, rate-corrected QT.

listed as a moderate risk factor. In our study, the mean age was 69.6 years. Hypertension was present in 86.7%, cardiovascular disease was present in 23.8%, and diabetes mellitus was present in 50.6%. These findings indicate that the QTc's shift to the right in our patients on HD is probably due to these risk factors. The strongest risk for QT interval prolongation is reported to be the use of drugs that contribute to QT interval prolongation, such as antiarrhythmics and antidepressants. Unfortunately, in this study, information on oral medications was limited and only medication for secondary hyperparathyroidism was recorded. Not surprisingly, hypokalemia and hypocalcemia were identified as very strong and strong contributors, respectively, to QT interval prolongation. In a 2008 national survey of Japanese patients on HD without significant hypokalemia before an HD session, hypokalemia at the end of HD was found in 7% of patients.[35] This suggests that hypokalemia is not linked to QT interval prolongation. It appears reasonable to search for kidney disease-specific factors not previously known to be associated with QT interval prolongation, such as MBD markers that accelerate the progression of atherosclerosis in patients on HD.

MBD Markers and QT Interval Prolongation

MBDs are a group of end-stage renal disease-specific complications. It has been reported that inadequate management of MBD can lead to progression of cardiovascular disease and poor prognosis.[36,37]

For serum Ca, the findings of this study were quite predictable. QT interval increases sharply at Ca levels <8.5 mg/dl. No association was found with hypercalcemia. This is supported by the findings from a meta-analysis of QT intervals in patients with elevated Ca from 33 studies.[38]

Our study revealed interesting findings related to increased and decreased P levels. Although hyperphosphatemia is known to play a crucial role in the initiation and progression of vascular and valvular calcification, this is the first study to show the association between serum P levels and QT interval prolongation in a large population of Japanese patients on HD. Intriguingly, serum P levels and QTc showed a U-shaped curve. The lowest estimate QTc was observed at a predialysis serum P level of 5 mg/dl. Although their effects were not so large, both low and high P values were closely associated with prolonged QT interval. It should be kept in mind that 5 mg/dl is an appropriate

target level in guidelines for patients with HD, though it is above the upper limit of normal.

Hyperphosphatemia may be a risk factor for vascular and valvular calcification, and hypophosphatemia may be a risk factor for malnutrition, which is involved in malnutrition inflammation atherosclerosis syndrome, both of which induce ischemic and nonischemic cardiomyopathy, and consequently QT interval prolongation.[32] This is an understandable mechanism, though, in our subanalysis, the U-shaped association remained significant even after analyzing cases with and without cardiovascular complications separately. Considering that we have already confirmed that higher and lower P levels are closely associated in QT interval prolongation in patients with normocalcemia and adequate parathyroid hormone control, it is probable that P abnormalities play, at least in part, a role in prolongation of the QT interval independent of cardiomyopathy and other MBD markers, including hypocalcemia.

Alteration of the CaSR activation in cardiac cells may contribute to QT interval prolongation. The inward rectifier potassium, Ik1, channel in cardiomyocytes is known to play an important role in maintaining the stability of resting membrane potential,[39] and its expression and the expression of another inward rectifier potassium, Kir, channel can be induced by activation of CaSRs. Stimulation of cardiac CaSRs may alter Ik1-dependent repolarization and excitability and impact cardiac function. In this way, CaSR can exert membrane-stabilizing effects on cardiomyocytes, because Ik1 plays the most important role in the maintenance of a stable resting membrane potential.[40] It is reported that downregulation of Ik1 in cardiomyocytes induces QT interval prolongation in a magnesium-deficient rat model.[41] It is theoretically possible that repolarization time could be prolonged if CaSR function is modified and impaired by certain factors. Modified CaSR affects Ik1 channels in cardiomyocytes, increasing repolarization time.

An interesting mechanism by which hyperphosphatemia induces refractory hyperparathyroidism in patients on dialysis has been revealed, based on the findings from a study using isolated parathyroid tissue slices *in vitro*.[42] Higher P levels were found to attenuate CaSR activation and modify parathyroid hormone release. This suggests that incremental increases in P levels within the physiologic range for patients on HD may inhibit CaSR activity via noncompetitive antagonism. In line with these findings *in vitro*, it has been shown that hyperphosphatemia attenuates CaSR activation by way of Ca ions and by calcimimetic agents in patients on HD.[43] This suggests that hyperphosphatemia can also attenuate CaSR activation in cardiomyocytes, which could lead to prolongation of QT interval. Further *in vitro* and *in vivo* studies are needed to confirm this hypothesis.

Lower pre-HD P was also closely associated with prolonged post-HD QTc in our study. Because P plays an important role in the generation of the high-energy P bonds of adenosine triphosphate, depletion of adenosine triphosphate in myocardium may theoretically cause QT interval prolongation.[44] Indeed, fatal arrhythmias are often seen in patients with severe hypophosphatemia <1.0 mg/dl.[45] Li *et al*.[46] demonstrated that lowering adenosine triphosphate concentrations in cardiomyocytes results in a decrease in the number of slowly activating K^+ channels (Iks) and prolongation of action potential duration, which clinically appears as QT interval prolongation in the ECG. Interestingly, our present results show an increased risk of developing QT interval prolongation even with predialysis serum phosphorus levels in "the normal range." It is important to emphasize that a subset of normophosphatemic predialysis patients are hypophosphatemic after dialysis. In a 2008 Japanese Society for Dialysis Therapy and Renal Data Registry survey, 75% of patients with predialysis serum phosphorus levels between 3.0 and 3.5 mg/dl receiving HD 3 times weekly developed significant postdialysis hypophosphatemia of <2.0 mg/dl. Moreover, 92% of patients with severe postdialysis hypophosphatemia (<1 mg/dl) were found to have predialysis serum phosphorus levels <4.5 mg/dl, the upper limit of the normal range.[33] Recent investigation of the rebound increment of serum P after HD revealed that the low serum P levels increased slightly just after the session, and remained plateaued at this level for the following 3 to 4 hours, with no additional increase.[47] Although it is not clear to what extent this transient hypophosphatemia affects QT interval through adenosine triphosphate deficiency in the myocardium, it is clear that fatal arrhythmias often occur within 12 hours after an HD session.[48] We believe that hypophosphatemia after HD could be responsible for the present results. Importantly, the decrease in K levels during HD are also quickly reflected in clinical hypokalemia, and could be involved in QT interval prolongation, leading to fatal arrythmia. The effect of hypophosphatemia alone on QT interval prolongation warrants further study.

Limitations

There are 4 limitations to this study. First, because this was a cross-sectional study, the possibility of reverse causality could not be completely ruled out. However, we consider this possibility low because it is unlikely that prolonged QTc would cause fluctuation in electrolytes such as Ca and P. Further longitudinal studies are needed. Second, being an observational study,

there may be unmeasured confounding factors. However, our team believes that we have measured important confounding factors because we measured covariates after a thorough discussion of them from the planning stage of the study. Incidentally, we did not adjust for serum potassium in the multivariable analysis because we considered it a prognostic factor rather than a confounding factor, because it affects outcome but not exposures. Third, because this was a nationwide database, the measurement methods were not standardized. However, for items commonly used in HD patient management, such as the items measured in this study, the measurement methods are common to some extent, and the bias caused by the measurement methods is considered to be small enough to be acceptable. Fourth, because this study used data from a very large survey, QT interval was measured by automatic ECG measurement in terms of measurement feasibility. However, there is no consistent knowledge about the accuracy of automatic measurement of QT interval. In addition, because the reason for measuring ECG in this study is unknown, it is possible that the ECG findings may have been mixed up with emergency ECGs performed due to instability of the patient's condition. The possibility that these ECG measurement problems caused errors in the measurement of QT time cannot be ruled out. Further studies with more accurate QT interval measurements are warranted.

Conclusion

This study revealed that the QTc is often prolonged in patients on HD. Furthermore, it was suggested that decreased serum Ca levels and decreased and increased serum P levels in patients on maintenance HD may be associated with QTc prolongation.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

We thank Libby Cone, MD, MA of Dmed (dmed.co.jp <http://dmed.co.jp/>) for editing drafts of this manuscript, and the Japanese Society of Dialysis Therapy (JSDT) for providing the data. The results in the current study were derived from the analysis of data provided by the JSDT as a study by public competition. However, all interpretations and conclusions in the study are the responsibility of the authors, not the JSDT. English editing of this article was supported by the Japan Society for the Promotion of Science KAKENHI Grant Number 23K16353.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Distribution of QTc in the whole population.

Table S1. Baseline characteristics with and without QTc missing.

STROBE Statement.

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