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The QT interval in Parkinson's disease: a systematic review

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ABSTRACT

Background PD (PD) is associated with a twofold increase in the risk of death especially sudden death. A predisposing factor for cardiac sudden death is prolongation of the QT interval. This study evaluated the potential association between QT interval and PD.

Methods A systematic search was conducted of Medline and EMBASE using the search terms "PD" AND "QT interval" OR "Cardiac Repolarization" to identify articles.

Results Seven studies with persons with PD (n = 981) and control groups were identified. There was a significant difference in QT interval comparing patients with PD and persons without PD. The odds ratio showed a significant (P < 0.001) 2.6-fold (random effect) greater QTc prolongation in PD compared to control. Overall, there was a significantly longer QT in patients with PD than controls of 10.7 ± 2.8 ms. Data analysis did not show much publication bias. Focusing only on studies that related the QT interval to the severity of PD as assessed by Hoehn–Yahr classification (n = 6), there was a significant (P = 0.004) overall correlation between QT interval and the severity of PD. There was little publication bias. The data directly examining patients with PD taking any drug than might prolong QT do not support an association between these mediations and QT prolongation.

Conclusion Individuals with PD have a longer QT interval than individuals without PD. The QT interval is associated with a greater severity of PD and a greater probability of developing more severe PD. The QT interval should be considered in assessment of PD and possibly as a target for the treatment of PD.

Parkinson's disease (PD) is a condition whose prevalence increases with aging and indeed becomes very common among people after the age of 65 years.[1,2] Compared to individuals 40 to 49 years of age, the prevalence of PD is 10 fold greater in those aged 65 to 74 years, and PD prevalence is over 45 times greater for those over the age of 80 years. PD is associated with a twofold greater risk of death compared to individuals without PD.[2] Sudden death, which is usually cardiac death due to arrhythmias, is the second most common cause of death, after pneumonia in PD.[3]

One of the predisposing factors or substrates for cardiac sudden death is prolongation of cardiac repolarization which is detected on the electrocardiogram as prolongation of the QT interval.[4,5] A meta-analysis of population studies found a consistent association between prolonged QT interval and increased risk of sudden cardiac death as well as death from all cardiac causes.[5] The knowledge that genetic causes of prolonged QT interval are associated with an increased risk of fatal cardiac arrhythmias strengthens the conclusions of the meta-analysis of population studies.

Because the QT interval varies with heart rate, it is crucially important to utilize the best QT heart rate adjustment formula.[6–8] Heart rate corrected QT interval duration (QTc) increases with age.[6,7] The association between increasing age and increasing QTc [6] has similarities to the increasing prevalence of PD with increasing age (Figure 1).

The objectives of this study were three-fold. The first objective was to determine whether there is an association between longer QT intervals in PD compared to individuals of a similar age without PD. In addition, the possibility of any alteration in QT being due to drug therapy that might prolong QT was assessed. The second objective was to examine whe-

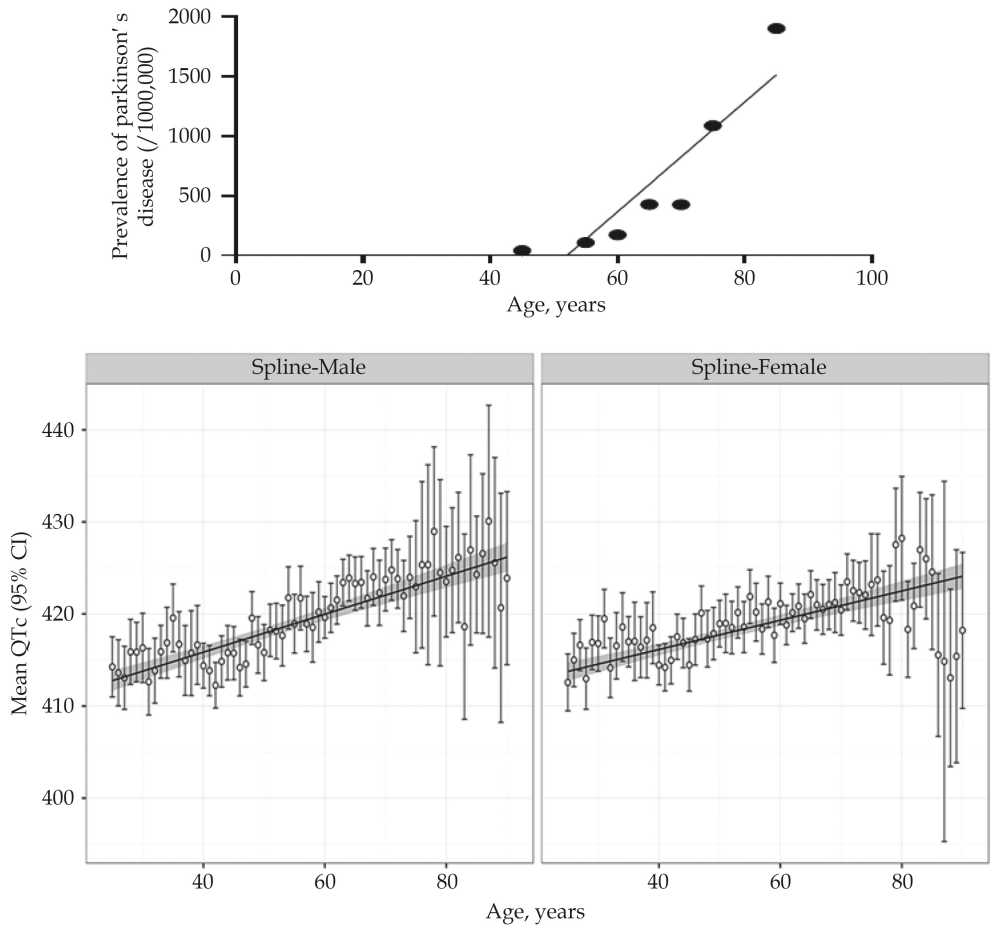

Figure 1 The prevalence of PD in according to age from a meta analysis of 47 studies from 4 geographic regions in the world[1] (upper panel). The mean spline QTc (QTcRBK), with 95% CI in different age groups from the US NHANES survery for men (left) and women (right). The linear regression (line) of age on spline QTc is plotted with the 95% CI. Lower panels are from (with permission) Rabkin, S.W, Szefer, E., Thompson, D.J.S., 2017. A New QT Interval Correction Formulae to Adjust for Increases in Heart Rate. JACC Clin. Electrophysiol. 3, 756–766. https://doi.org/10.1016/j.jacep.2016.12.005

ther the QT-heart rate adjustment formulae used in studies of PD were of the kind that was independent of the impact of heart rate on the QT interval so as to ensure the validity of any association between QT and PD. The third objective was to determine the relationship between QT interval and the severity of PD because of one of the fundamental characteristics supporting a significant relationship, rather than a simple association is the presence of a gradient of risk, in which the strength of the factor is more closely linked with a greater severity of the condition.

METHODS

There has not to our knowledge been a previous meta-analysis to examine the QT interval in PD. A systematic search was conducted of Medline and EMBASE. The search was conducted from the inception of each database through to December 15, 2023.

A search string was constructed using terms connected with Boolean operators such as "PD" AND "QT interval" or "cardiac repolarization" to identify articles reporting cardiac repolarization/QT interval in patients with PD. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was used to guide the search [9] (Figure 2). One reviewer screened article titles and abstracts for full-text review. The exclusion criteria were articles: (1) not published in English except if the English language abstract contained pertinent data for analysis; (2) involved non-human subjects; (3) non-primary research articles (reviews, editorials or letters commenting on an article); (4) pediatric age population; (5) unrelated to the investigated topic;

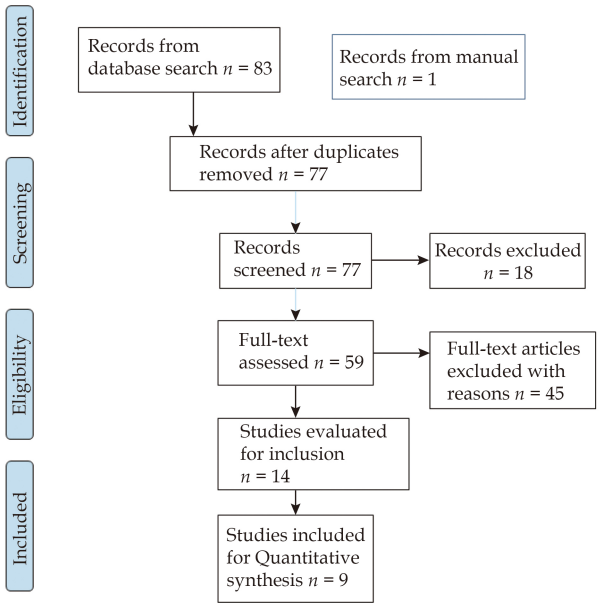

Figure 2 The literature flow of meta-analysis.

and (6) relevant data could not be extracted from the paper.

Data extraction was performed by a single reviewer. The following items were collected from each article: author, year of publication, country of origin of the study center, sample size, age, sex, definition of PD, assessment of the severity of PD, nature of the QT measurement and heart rate adjustment formulae used to correct for the impact of heart rate on the QT interval. In addition, data were collected on the impact of drugs that might potentially prolong the QT interval that were being administered to individuals with PD and their control or reference group.

There are a number of different heart rate corrected QT intervals (QTc). Those proposed by Bazett (QTcBZT), Hodges (QTcHDG), Karjalainen QTcKRJ, Fridericia (QTcFRD), Rautaharju (QTcRTH) and Framingham (QTcFRM) and others.[8] Because there was no primary patient or animal contact, there was no requirement for approval from our research ethics committee.

Statistical Analysis

Data were analyzed using forest plots depicting the standard difference of means, 95% CI, and *P*-value. The meta-analysis was performed using Comprehensive Meta-Analysis (Biostat Inc., NJ, and USA). In-study heterogeneity in the meta-analysis was tested using Q, Cochran's I^2 statistic where variance is described by SEM. The odds ratio also calculates the variance as SEM. Otherwise, data is presented as the mean and SD. Because of the wide range of sample sizes, a random effects model was chosen for data analysis. Publication bias was assessed by Funnel plots and the calculation of classic Fail safe N. The methodological approach was similar to our recent work.[10]

RESULTS

QT in Parkinson's Disease

There were seven studies with control groups that fit the criteria (Table 1). Ishizaki, *et al.*[11] examined 48 PD patients (20 males 28 females) aged 65 years and 44 controls aged 60 years, and excluded patients with heart disease. The abstract was in English and provided the important data but the paper was not in English so that details of the diagnostic criteria for PD were not available. QTc intervals were significantly longer in the PD patients than in the controls. The QTc formula employed was not available for examination. Oka, *et al.*[12] measured the QT intervals in 30 patients with PD and 30 healthy control subjects. All patients with PD met the UK PD Society Brain Bank criteria.[12] The control group was selected from persons who were considered "health" at an annual health check-up and did not have hypertension, medically significant findings, abnormal ECGs or were receiving medications.[12] QTcBZT intervals in patients with PD significantly exceeded that of healthy controls [12].

Deguchi, *et al.*[13] studied 34 patients with PD, and 30 age and gender-matched healthy controls. All patients with PD met the UK Parkinson's Disease Society Brain Bank criteria.[13] None of the patients had a history of cardiac ischemia, arrhythmia, bundle branch block pattern or significant Q waves on ECG, renal failure, chronic liver disease, a history of alcohol abuse, diabetes, hypertension, electrolyte abnormalities in serum potassium, calcium and magnesium, or were taking medication known to affect the QTc interval.[13] QTcBZT was used for analysis.

Sariahmetoglu, *et al.*[14] studied 40 persons with PD, as diagnosed by the UK PD Society Brain Bank

Table 1 QT interval in patients with PD, country of origin, diagnostic criteria and the QT interval in patients with PD receiving potentially QT prolonging medications.

Author and year	Diagnostic criteria	QTc	Country	Relation to QT prolonging drugs
Pigueras-Flores, *et al.*[15]	Movement Disorder Society Clinical Criteria	QTcBZT	Spain	No significant ($P = 0.6$) differences in QT in those receiving drugs prolonging QT vs those not on those kind of drugs.
Deguchi, *et al.*[13]	UK PD Society Brain Bank Criteria	QTcBZT	Japan	No significant ($P = 0.67$) differences in QT in those receiving drugs prolonging QT *vs* those not on those kinds of drugs.
Oka, *et al.*[12]	UK PD Society Brain Bank Criteria	QTcBZT	Japan	No significant difference in QT in patients with PD on LevoDopa or not receiving this agent.
Mochizuki, *et al.*[21]	National Institute of Neurological Disorders and Stroke diagnostic criteria for PD.	QTcBZT	Japan	Relationship not examined
Sariahmetoglu, *et al.*[14]	UK PD Society Brain Bank Criteria	QTcBZT	Turkey	Relationship not examined
Zhong, *et al.*[20]	UK PD Society Brain Bank Criteria	QTcFRD	China	Relationship not examined
Ishizaki, *et al.*[11]	Uncertain	Uncertain	Japan	Relationship not examined
Ozturk & Ozturk[16]	UK PD Society Brain Bank Criteria	QTcBZT	Turkey	Relationship not examined
Yoo, *et al.*[17]	Clinical plus PET scan	Uncertain	Korea	Relationship not examined

PD: Parkinson's disease.

criteria and 20 controls. QTcBZT was calculated. The control group consisted of volunteer who were healthy, age-matched hospital staff and their relatives with no disorders that might affect the autonomic nervous system [14].

Piqueras-Flores, *et al.*[15] evaluated 50 patients with idiopathic PD recruited from a specialized clinic and who fulfilled the diagnosis of PD according to the criteria of the Movement Disorder Society Clinical Diagnostic Criteria for PD. A control group of 50 healthy volunteers with "similar specifications" (matched control group) were also studied. The exclusion criteria were: coronary artery disease, valve disease which is previously known or was found on echocardiography, prosthetic heart valve, or cardiomyopathy.[15] QTcBZT was used for analysis. Resting heart rate was reported in only one of the studies and was reported to be the same in the PD and control group.[15]

Ozturk and Ozturk evaluated 28 persons with PD, based on United Kingdom Parkinson Disease Society Brain Bank criteria who had a mean age of 59 years, and 26 controls.[16] QTcBZT was used for analysis. The symptom progression of PD was assessed with the Modified Hoehn and Yahr Scale.

Yoo, *et al.*[17] sought to develop a machine learning model to detect PD from the 12 lead ECG. They presented their univariate data from 751 patients with idiopathic PD and 751 age and sex-matched patients without PD using a propensity score matching for covariates. The diagnosis of PD was clinical (ICD 10 code) plus a PET scan showing decreased dopamine transporter in the posterior putamen. The severity of PD was considered mild but the QT heart rate correction formula was not specified. Thus, the majority of studies utilized the same diagnostic criteria for Parkinson's specifically the UK Parkinson's Disease Society Brain Bank criteria.[12-14,16]

There is concern about the QT heart rate correction formula that was used for these studies. Most studies (five of seven studies) used the QTcBZT formula which is not as good as the other QTc formulae in the general population [6] and also in PD.[18] QTcBZT does not correct satisfactorily for the impact of heart rate on QT interval in patients with PD.[18] The potential impact of the inadequacies of QTcBZT for the association of prolonged QT in PD must remain somewhat uncertain until a study is conducted comparing a number of the better heart rate QT correction formulae in PD.

The QT interval was significantly different in patients with PD compared to controls (Figure 3). The odds ratio showed a significant ($P < 0.001$) 2.6-fold greater QTc prolongation in PD compared to control. Overall, there was a significantly longer QT in patients with PD than controls of 10.7 ± 2.8 ms. There was significant heterogeneity between studies ($Q = 32.7$, $P = 0.001$; $I^2 = 81.7$ and $\text{Tau}^2 = 0.141$) as

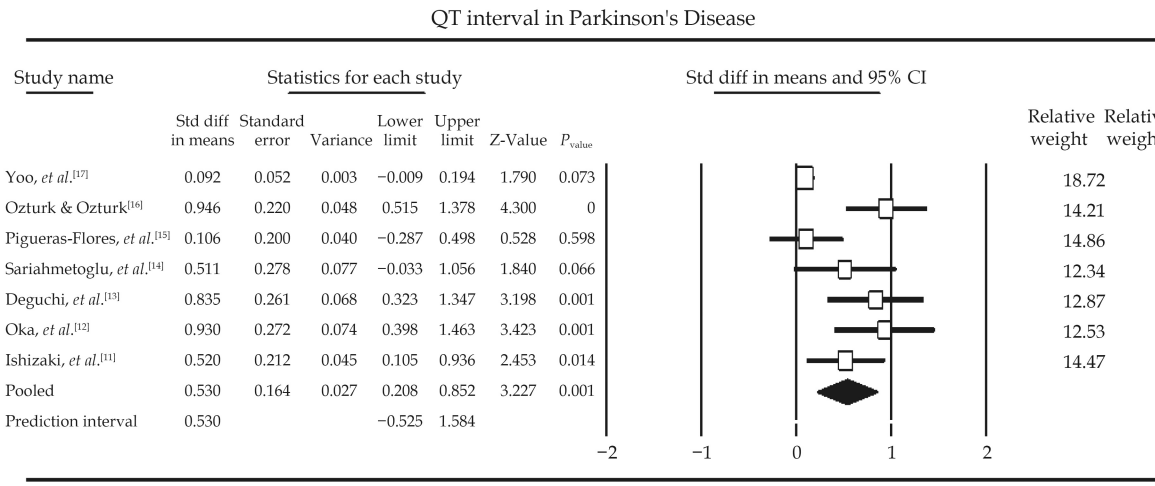

Figure 3 Forest plot for QT interval in studies that examined it, in patients with PD compared to a control group without PD. The relative weight that each study contributed to the overall effect is shown for the random effects model. PD: PD.

shown by the funnel plot which is a plot of the standard error or precision on the vertical axis as a function of effect size on the horizontal axis (Figure 4). In the absence of publication bias, studies are distributed symmetrically about the combined effect size. Data analysis did not suggest a high likelihood of publication bias. The classic Fail safe N was 74 indicating that it would take 74 (negative) studies to reverse this significant finding of a prolonged QTc in PD.

QT Interval and Severity of PD

The QT interval was directly related to the severity of PD in most but not all studies. Oka, *et al.*[12] found that in patients whose Hoehn and Yahr score was III or more, QTcBTZ was significantly greater than in patients whose score was II or less. Ishizaki, *et al.*[11] reported a significant correlation between QTc and PD severity as assessed by Hoehn and Yahr stage.

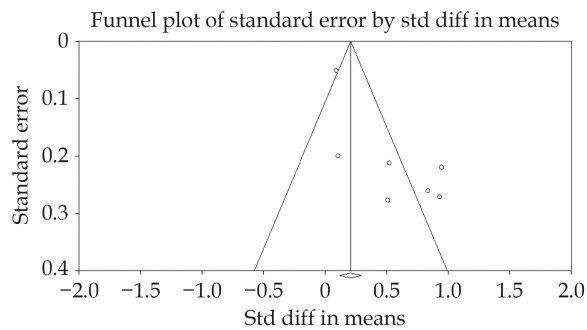

Figure 4 Funnel plot which is a measure of the study size (SE) on the vertical axis and the effect size on the horizontal axis in studies that examined QT interval, in patients with PD compared to a control group without PD. PD: PD.

Gibbons, *et al.*[19] found that QTc (QTcBZT) was associated with a significantly higher global statistical test (GST) score after 5 years of follow-up for patients with PD who were over 67 years old. Severity of PD was measured by the GST that combines into a single factor five outcome measures from (1) Modified Schwaband England activities of daily living; (2) the Parkinson's Disease Quality of Life Scale and a set of five questions from the United Parkinson Disease Rating Scale related to ambulatory capacity, the Symbol Digit Modalities test and the Modified Rankin.[19] Patients with higher GST scores had more advanced disease.[19]

Zhong, *et al.*[20] evaluated 118 PD patients and found that QTc (QTcFRD) correlated with the Hoehn–Yahr classification of the severity of PD. Deguchi, *et al* found a higher mean QTc (QTcBZT) with progressively higher level of H-Y score.[13] In contrast, Mochizuki, *et al.*[21] evaluated 156 PD patients and reported no correlation between QTcBZT and H-Y stage. Piqueras-Flores, *et al.*[15] did not correlate QTc with H-Y or PD severity.

Ozturk and Ozturk evaluated 28 persons with PD and showed a relationship between QTcBZT and the modified Hoehn and Yahr Scale.[16]

Focusing only on studies that related the QT interval to the severity of PD as assessed by Hoehn–Yahr classification yielded 6 studies. Two of the studies from the previous group were deleted and two studies (without control groups) but with PD patients, had the relationship of QT to H-Y severity

analyzed. The Hedge's g was calculated because some studies compared the mean QT in the different H-Y categories while other studies calculated a correlation statistic (*r* value). The result was a significant overall correlation between QT interval and the severity of PD (Figure 5 & Figure 6). There was heterogeneity between studies (Q = 81.6, I^2 = 93.9, P < 0.001) Tau^2= 1.158). There is little publication bias. The Fail Safe was n = 178 or one would have to locate 178 negative studies for there to be no significant (2 tail P value > 0.05) relationship between QT interval and the severity of PD. Although the data presented by Gibbons, *et al.*[19] could not be included because they did not consider the Hoehn–Yahr classification, their findings clearly support the results of this meta-analysis.[19]

There was insufficient data to make a conclusion about any relationship between QT and the duration of PD. Zhong, *et al.*[20] found that QTc (QTcFRD) correlated with disease duration. Deguchi, *et al.*[13] found a significant positive association between the duration of PD and QTc. Sariahmetoglu, *et al.*[14] did not find any significant differences in QTc intervals in patients with "early" or "advanced stage".

Separation of QT Prolonging Drugs and QTc in PD

The question has arisen whether the QT prolongation in PD is due to the underlying disease or to the drugs the patients receive for treatment of PD that might prolong the QTc. Patients with PD often are prescribed psychiatric drugs as their course of PD becomes advanced. These agents have a risk of QT prolongation.[22,23] Survey data have found a small proportion of patients with PD concomitantly using potentially QT prolonging drugs. In a survey of 192 patients with PD at one clinic, one third were prescribed QTc prolonging medication. Of these only 20 patients had prolonged QTc and two-thirds had shorter QTc after medication changes.[24] In contrast, another study reported that that while 55% of patients with PD took one or more potentially QTc-prolonging drugs, only 10% took drugs that were definitely linked to QT prolongation.[18] The data directly examining patients with PD taking any drug than might prolong QT do not support an association between these mediations and QT prolongation (Table 1).

DISCUSSION

This study contributes meaningful data leading to an improved understanding of brain-heart connections in the neurodegenerative disorder labelled PD. By pulling together available knowledge, this study concludes that individuals with PD have a longer QT interval than individuals without PD. The QT interval duration is associated with a greater severity of PD and a greater probability of subsequently developing more severe PD. Importantly there are no data that supports a significant relation between potentially QT prolonging drugs in patients with PD that might account for the longer QT interval in PD.

It is noteworthy that the association of PD with a longer QT interval was found in early studies in the field [12] as well as more recent studies.[16] Despite the long time span of the studies, the majority of studies utilized the same diagnostic criteria for Parkinson's specifically the UK Parkinson's Disease Society Brain Bank criteria.[12-14,16] It is noteworthy,

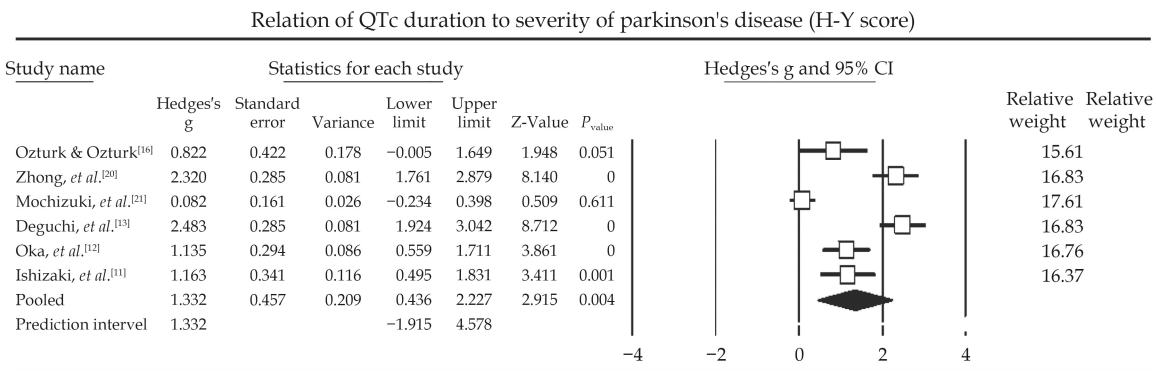

Figure 5 Forest plot for the relationship between the QT interval and severity of PD severity of PD as assessed by Hoehn–Yahr classification. The relative weight that each study contributed to the overall effect is shown for the random effects model. PD: PD.

however, that the relationship between QT prolongation and PD was stronger in studies that used the UK PD Society Brain Bank criteria for PD.

These data warrant a discussion of potential pathophysiologic explanations. PD is characterized by the clinical findings of a tremor, bradykinesia, muscle rigidity, impaired gait and posture.[25] The underlying pathophysiologic mechanism is considered to be dopaminergic neuronal loss in the substantia nigra pars compacta and depletion of dopamine in the striatum.[26] The pathways leading to the loss of dopaminergic neurones include mitochondrial damage, oxidative stress, excitotoxicity, energy failure, protein misfolding and their aggregation, impairment of protein clearance pathways, cell-autonomous mechanisms, "prion-like protein infection" and neuroinflammation.[27] Dopaminergic neuronal loss of function can be linked to QT interval prolongation. In a study of young healthy adults, iodine-123 labelled 2β-carbomethoxy-3β-(4-iodophenyl) nortropane, a radiotracer for imaging dopamine transporters in the living human brain, with single-photon emission tomography correlated with QTcBZT as well as a less common QT-heart rate correction formula (QTcKRJ).[34] In contrast, heart rate did not correlate significantly with striatal dopamine transporter binding.[34]

Exploring the consequences of PD on the heart is an exciting but still incompletely defined story which impacts on the ability to interpret the association of increased QT interval in PD. The QT interval changes may be viewed within the wider picture of the cardiac abnormalities in PD which include cardiac structural changes, heart failure and various cardiac electrophysiologic changes.[28] Focusing on electrocardiographic features, a relationship exists at several levels. From a general perspective, ECG activity has been shown to synchronize with the EEG in PD.[29] Considering only the QT interval, requires an understanding of newer putative pathophysiologic explanations for PD. PD is associated not only with a marked reduction in the catecholamine dopamine in the nigrostriatal system but also with a significant reduction in the catecholamine norepinephrine in the heart as well as a substantial loss of noradrenergic fibres in the sympathetic nervous system.[28] This observation has been attributed to the impairment in aldehyde dehydrogenase function in PD leading to the accumulation of the products of catecholaldehydes 3,4-dihydroxyphenylacetaldehyde (DOPAL) and 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL), derived from dopamine and norepinephrine (respectively), that are highly toxic especially to neurones.[28] Increased enzymatic oxidation of cytoplasmic dopamine to its aldehyde metabolite leads to a reduction in norepinephrine production, storage, and recycling in extant neurons (the so-called sick-but-not-dead neurones).[30] Oligomerizes of DOPAL to form quinone-protein adducts with α-synuclein, a major constituent in Lewy bodies, impedes vesicular storage, diminishes dopamine biosynthesis via tyrosine hydroxylase and L-aromatic-amino-acid decarboxylase including inefficient vesicular sequestration of cytoplasmic catecholamines, and attenuated neuronal reuptake via cell membrane catecholamine transporters.[30] It is possible that reduced adrenergic innervation and reduced cardiac catecholamine release might account for the increased QT in PD. Beta-adrenergic stimulation with isoproterenol produces a small decrease in QT interval.[31] Prolonged stimulation of cardiac sympathetic nerves or epinephrine administration reduces QT interval durations.[32] Thus, reduced cardiac catecholamine content in PD might prolong cardiac repolarization. The increased QT interval in PD can be linked to changes in the autonomic nervous system in PD, although there is not a great deal of robust physiologic data in this area. Gibbons, *et al*.[19] reported that in younger individuals with PD (≤ 62 years of age), QT interval was associated with baseline orthostatic fall in blood pressure suggesting a relationship between longer QTc and greater orthostatic hypotension, which is generally attributed to alterations in baro-receptor sympathetic outflow. Deguchi, *et al*.[13] found that QTc intervals were not related to orthostatic fall in blood pressure rather QT correlated with blood pressure changes with the Valsalva manoeuver. Left cardiac sympathetic denervation is associated with a transient increase in QTc which is consistent with a role of cardiac sympathetic denervation to explain part of the increased QT in patients with PD.[35] Cardiac sympathetic denervation in PD occurs independently of the movement disorder.[36] Thus, there is a discrete pathway of neuronal (sympathetic) denervation in PD

which may explain the associated increase in QT interval.

Cardiac parasympathetic dysfunction occurs in parallel with cardiac sympathetic denervation in patients with PD.[37] Again it has been suggested that cardiac autonomic dysfunction can be independent of the dopaminergic neurodegeneration responsible for motor symptoms.[37]

Another speculative possibility is based on the finding that PD-associated proteins, such as α-synuclein are present throughout the ANS.[28] Voltage-gated potassium (Kv) channels play an important role in cardiac repolarization. In primary cultured mouse microglial cells, whole-cell patch clamp recordings show that aggregated α-Synuclein protein caused upregulation of voltage-gated potassium channel Kv1.3 expression and activity of the outward Kv1.3 current.[33]

It might be suggested that the QTc interval reflects a global image of a patient's cardiovascular risk factors. This possibility is unlikely. Male sex is a CV risk factor and as shown in Figure 2 men have shorter QT intervals that women. Low HDL cholesterol is a CV risk factor and is associated with a shorter QT interval.[38] Hypertension is a complex factor as it can produce left ventricular hypertrophy which then can prolong the QT interval and QTc can be affected by antihypertensive drugs so that the true effect of hypertension on QT interval depends on the patient population.[39] In type 2 diabetes mellitus, the prevalence of QTc > 440 ms is less than 50% (44.1%) and the prevalence of high-risk QTc (≥ 500 ms) is rare (2%).[40]

There are several limitations of this study that warrant discussion. First, the number of studies examined was relatively small. The number of studies, however, represent the result of an intensive literature search and reflect the small number of studies that addressed questions about the QT interval in PD. Second, the clinical reality of caring for patients with PD, can confront patients with multiple drug therapy that may prolong the QT interval alone or in combination with other drugs that were not the concomitant therapy of individuals in the studies that were examined herein. However, the data to date do not suggest that the association of PD with QT prolongation is due to drug therapy for PD or other concomitant medication.[24] Third, a risk of bias assessment was not conducted because it is extremely difficult to obtain meaningful results in case control studies with no intervention (rendering it impossible to assess the randomization strategy and examine the nature of the intervention) and limited data on the control or reference group. Fourth, the studies did not include a subcategorization of PD based on different subtypes of PD, so it was not possible to determine whether QT prolongation occurred more commonly in any one specific PD subtype. Fifth, the studies that examined the association between the QT interval and the severity of the disease, did not consider the effect of age as a covariate. However, the severity of PD is not always a function of age. Sixth, this population meta-analysis established the correlations between greater QT interval and PD with the objective of providing data to establish an explanation for the increased risk of sudden death due to cardiac causes in PD. It is necessary to construct studies to evaluate cardiovascular mortality in patients with PD stratified by their QT interval. Considering that there are consistent associations between prolonged QT interval and increased risk of total, cardiovascular, coronary, and sudden cardiac death [5], it is most likely that such studies will confirm the relationship of QT interval to cardiac mortality in PD. A longitudinal follow-up study of patients with PD should also include other ECG features as well as cardiovascular risk factors and biochemical biomarkers of adverse cardiovascular outcomes in order to determine, in multivariate analysis, the contribution of the QT interval, using appropriate heart rate adjustment, to cardiovascular mortality in patients with PD.

In conclusion, QT interval is more prolonged in individuals with PD than in control and QT correlates with the severity of PD and the development of meaningful disability from PD. These findings suggest that clinicians should assess the QT interval in patients with PD. Considering that the linkage between the brain and cardiac autonomic system, it is worth considering the QT interval as a marker of the cardiac autonomic nervous system changes from dopaminergic neuronal loss in the brain. Taken together the association between longer QT interval and cardiac death especially sudden death plus the high prevalence of sudden death in PD, justify further research to determine whether treatment targeting

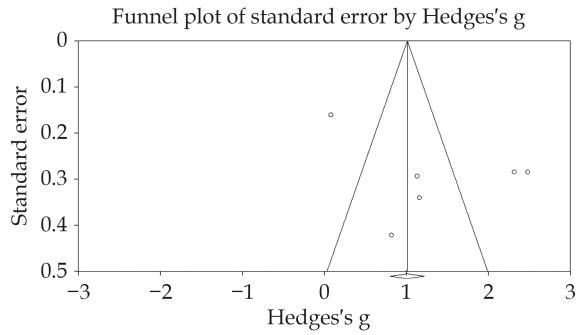

Figure 6 Funnel plot which is a measure of the study size (SE) on the vertical axis and the effect size on the horizontal axis in studies that examined relationship between the QT interval and severity of PD as assessed by Hoehn-Yahr classification. PD: PD.

QT interval would be of value in the management of patients with PD.

DECLARATIONS

Ethics Approval and Consent to Participate

Not applicable

Data Availability

Data is available from the cited literature

Declaration of Interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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AI

AI was not used in any part of this research or preparation of the manuscript

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