Incidence of prolonged QTc and severe hypoglycemia in type 1 diabetes.

The EURODIAB Prospective Complications Study.

Running title: incidence of prolonged QTC and hypoglycemia

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ABSTRACT

Objective: to assess the independent role of severe hypoglycemia on 7-year cumulative incidence of prolonged QTc in a large cohort of patients with type 1 diabetes.

Materials and Methods: People with type 1 diabetes recruited by the EURODIAB Prospective Complications Study who had normal QTc were examined at baseline and after 7 years with standardized methods (n=1415; mean age ± SD 32.1 ± 9.6 years; diabetes duration 14.2 ± 8.8 years). Hypoglycemic episodes were assessed by a questionnaire. QTc was calculated according to the Bazett's formula. In logistic regression analysis, we examined the role of severe hypoglycemia (none, 1-2 or 3 and more episodes/year) on the cumulative incidence of prolonged QTc, independently of age, sex, HbA1c, blood pressure, BMI, physical activity, distal symmetrical and autonomic neuropathy.

Results: 264/1415 (17%) patients had incident prolonged QTc. Compared to those with persistently normal QTc, a greater proportion of incident cases had 3 and more hypoglycemic episodes at baseline (16.3% vs 11.2%, p=0.03) and after 7 years (15.2% vs 9.6%, p=0.01). In logistic regression analysis, 3 or more episodes of severe hypoglycemia at baseline did not increase cumulative incidence of prolonged QTc (OR=1.34, 95% CI 0.88-2.03). By contrast, severe hypoglycemia at the follow-up examination was associated with higher incidence of QTc prolongation (OR=1.68, 1.09-2.58), which reverted to not significance after adjustment for diabetic neuropathy.

Conclusions: Severe hypoglycemia was not associated with incidence QTc prolongation in type 1 diabetic patients from the EURODIAB PCS study.

Key words: hypoglycemia, QTc, complications, surveys

Background

Prolonged corrected QT interval (QTc) reflects abnormalities of ventricular myocardial repolarization and is an independent risk marker for mortality in type 1 diabetic subjects (1). Following the results of both physiological and clinical studies, showing that both provoked and spontaneous hypoglycemia may induce QT prolongation (2-6), epidemiological studies have examined the association between severe hypoglycemia and prolonged QTc (7-9). In the cross-sectional EURODIAB IDDM Complications Study, patients who experienced frequent hypoglycemic episodes had a greater prevalence of QTc prolongation (7). Moreover, in logistic regression analyses, frequent severe hypoglycemic attacks were associated with a 27% higher likelihood of having QTc prolongation, independently of other risk factors and micro/macrovascular complications, including autonomic neuropathy (7).

However, prospective data assessing the relationship between hypoglycemia and incidence of prolonged QTc are still lacking in type 1 diabetes, and no evidence can be supported to the alternative hypotheses that prolonged QTc is causally related to repeated episodes of severe hypoglycemia or rather, both of them are linked to another common factor, such as autonomic neuropathy (10). As we previously reported on incidence and risk factors of prolonged QTc in type 1 diabetic patients from the EURODIAB Prospective Complications Study (10), we had the opportunity to examine in the 7-year prospective cohort the hypothesis that high frequency of severe hypoglycemic episodes at baseline predicts incidence of QTc prolongation.

Methods

The EURODIAB Prospective Complications Study is a clinic-based 7-year follow-up study designed to explore risk factors for diabetic complications (10-12). Full details on the design, methods, and recruitment in the EURODIAB cohort have been published elsewhere (11). The initial cohort included 3,250 persons with type 1 diabetes recruited at baseline from 31 centres in 16 European countries between 1989 and 1991. Sample selection was stratified by sex, age group, and

duration of diabetes to ensure sufficient representation in all categories. Type 1 diabetes was clinically defined as a diagnosis made at 36 years of age or lower, with a continuous need for insulin therapy within 1 year of diagnosis. The study was approved by local ethics committees, and informed consent was obtained from all subjects.

As previously described (12), of the 3,250 patients recruited at baseline, response data on severe hypoglycemic episodes were available for 3,248 subjects (99.9%). At the baseline examination, 2,202 patients (68%) declared no severe hypoglycemic attacks over the past year, 618 patients (19%) declared one to two attacks, and 428 patients (13.2%) declared three or more attacks. The latter group of patients was older, had longer diabetes duration, and had lower mean HbA_{1c} levels.

Cumulative incidence of prolonged QTc was assessed in persons who had normal QTc at baseline (n=2650) and QTc measurement at the follow-up examination (7.3 ± 0.6 years; mean ± SD). Out of the baseline cohort of 2,650, QTc data were not available at follow-up in 1,235 persons because of the following reasons: 4 local centers did not participate in the prospective study (centre drop out, n = 304), 14 patients were lost at follow up, 70 patients died during follow up, 842 subjects did not have a QTc measurement at baseline, mainly because the ECG recordings were of insufficient quality to measure a valid R-R interval, resulting in 1,415 individuals with complete incidence data. Recruited and non recruited subjects had similar age (32.6 ± 0.3 vs 32.1 ± 0.3 years, p=0.20), frequency of males (55.3% vs 53.2%, p=0.29), but slightly different values of diabetes duration (14.2 ± 0.2 years vs 15.1 ± 0.3 years, p=0.01), HbA1c (6.5 ± 0.5 % vs 6.7 ± 0.5%, p=0.01), systolic blood pressure (119.2 ± 0.4 mmHg vs 122.5 ± 0.5 mmHg, p<0.001), and plasma LDL-cholesterol (3.76 ±0.02 mmol/l vs 3.85 ± 0.03 mmol/l, p=0.04). Baseline distribution of severe hypoglycemic episodes did not differ (p=0.72) in patients included (none: 68.7%, 1-2: 19.2%, ≥3: 12.1% severe hypoglycemic episodes) and in those not included in the study (none: 69.0%, 1-2: 18.1%, ≥3: 12.9% severe hypoglycemic episodes).

Information on episodes of severe hypoglycemia in the previous 12 months was obtained from questionnaires. All patients were asked: “Over the past year, how many hypoglycemic attacks have

you had, serious enough to require the help of another person?" The questionnaires also provided information on physical activity, smoking habits, the frequency of insulin injections, and the number of daily insulin units injected per kg body weight (11).

Outcome of the study was incidence of prolonged QTc (10). RR and QT intervals were measured with a ruler on the resting ECG tracing and five consecutive beats were considered on lead V5. The QT interval was taken from the beginning of the QRS complex to the end of the down-slope of the T wave (crossing of the isoelectric line); when a U wave was present, the QT interval was measured to the nadir of the curve between the T and U waves. The QT interval corrected for the previous cardiac cycle length (QTc) was calculated according to Bazett's formula (16): $QTc= QT/(RR)^{1/2}$. Two observers unaware of data on any subject apart from identity number, measured all the intervals, and the QTc for each subject was considered as the mean value of the five calculated intervals and the mean of the reading of the two observers to minimize inter-observer variability. Intra-individual coefficient of variation of QTc interval in five ECGs performed on different days in 10 healthy subjects (5 males and 5 females) was 1.7%. A QTc of >0.44 s was considered abnormally prolonged (1, 9-10, 13).

Prevalence of hypertension, retinopathy, micro/macroalbuminuria, and cardiovascular disease (CVD) were assessed and defined as previously described (11). Distal symmetrical polyneuropathy was assessed on the basis of neuropathic symptoms and signs, including measurement of vibration perception threshold (14). Autonomic neuropathy was defined as a loss of heart rate variability with an R-R ratio <1.04 and/or postural hypotension with a fall in systolic blood pressure ≥ 20 mmHg (14). Additional measurements included fasting triglycerides, total cholesterol, HDL-cholesterol, and HbA1c. LDL-cholesterol was calculated according to the Friedewald formula. The reference range for HbA1c was 2.9–4.8%.

Data were expressed as the mean and standard deviation (SD). Variables with skewed distributions were logarithmically transformed for statistical analysis. Differences in continuous

variables between people with incidence of prolonged QTc and those with persistently normal QTc were tested with Student's t test. Pearson χ^2 test was used for differences in categorical measures.

The distribution of hypoglycemic episodes occurring in the l2 months preceding the baseline examination was strongly asymmetrical, with 972 subjects reporting no episodes, 150 one episode, 121 two and more episodes. Clinically relevant categories of severe hypoglycemic episodes (none, 1-2, ≥ 3) were considered in the analyses. In the subgroup reporting 3 and more episodes (range 3-60 episodes /year) the quartiles points were defined by 3, 4, 8 episodes/year.

As there was little variation in follow-up time among individuals, logistic regression was used to analyze the independent association of severe hypoglycemic episodes at baseline (Model 1) and follow examinations (Model 2) with the 7-year cumulative incidence of QTc prolongation (QTc >0.44 s). We included in all models variables that had previously been identified as risk factors for incident prolonged QTc in the EURODIAB cohort (age, sex, HbA1c, blood pressure, BMI, physical activity) (10). The effect of both distal symmetrical polyneuropathy and autonomic neuropathy at the follow-up examination was also assessed (Model 3 and Model 4). P value of less than 0.05 was considered to indicate statistical significance. Analyses were performed with Stata (Stata Release 10.0, Stata Corporation, College Station, Texas).

Results

After a mean of 7.3 ± 0.6 years follow-up, 264/1415 (17%) diabetic patients had incident prolonged QTc (Table 1). At the baseline examination, they had statistically significant older age, higher systolic blood pressure values and prevalence of CHD and distal symmetrical polyneuropathy than subjects with persistently normal QTc. A greater proportion of incident patients had 3 and more hypoglycemic episodes at baseline and at the second examination at 7 years of follow-up.

A subgroup of 50 patients (3.6%) reported 3 or more episodes of severe hypoglycemia at both examinations, 5.4% among incident cases and 3.2% among those with persistently normal QTc, whereas 53.8% of patients reported no severe hypoglycemic event at both examinations.

Logistic regression analysis showed that having had 3 or more severe hypoglycemic episodes at baseline was not a predictor of incident prolonged QTc (OR=1.34, 95% CI 0.88-2.03). This result was not affected by adjustment for age, sex, HbA1c, systolic pressure, BMI, and physical activity (Table 2 - Model 1). By contrast, severe hypoglycemia at 7 years examination was associated with a 68% higher risk of having incident prolonged QTc (OR 1.68, 95% CI 1.09-2.58, Model 2). After adjustment for either distal symmetrical polyneuropathy or autonomic neuropathy, ORs of severe hypoglycemia were reduces to not significant levels (Model 3 and 4). In subjects having no autonomic neuropathy, OR was 1.18 (0.63-2.20).

Discussion

This study assessed the association between severe hypoglycemia and cumulative incidence of prolonged QTc during the 7-years follow up of the EURODIAB Prospective Complications Study, one of the largest multicenter studies on type 1 diabetes. Although incident cases of prolonged QTc had significantly higher frequency of severe hypoglycemic episodes at baseline, no association was observed in logistic regression analysis, after adjustment for known risk factors of QTc prolongation. Therefore, our data do not support the hypothesis that severe hypoglycemia is a predictor of subsequent development of QTc prolongation in type 1 diabetes.

Previous data on the epidemiological relationship between hypoglycemia and QTc prolongation in type 1 diabetic patients are scarce. The cross-sectional association between hypoglycemia and QTc prolongation had been previously investigated in the EURODIAB IDDM Complications Study, and an OR for prevalent prolonged QTc of 1.27 (95% CI 1.02-1.58) was found among people having had three or more severe hypoglycemic events in the previous year compared to those having had no severe episode (7). Moreover, older age, longer diabetes duration, lower HbA1c levels, higher prevalence of hypertension, and autonomic neuropathy were independently associated with the likelihood of having the highest number of severe hypoglycemic events (12). However, no prospective study has examined the association between severe hypoglycemia and QTc

in large and representative populations of diabetic subjects. In the present prospective analysis of the EURODIAB Complications Study, we add the information that among type 1 diabetic people who had normal QTc at the baseline examination, those who developed QTc prolongation over the 7-years follow-up period had a similar baseline frequency of severe episodes compared to those with persistently normal QTc. By contrast, at the follow-up examination the subgroup that had developed incident QTc prolongation reported higher number of severe hypoglycemic episodes. However, adjustment for autonomic neuropathy affected the statistical significance of this association, suggesting that this finding was merely due to a confounding rather than a causal effect. Previous reports from the EURODIAB Prospective Complications Study showed female sex and higher values of A1C and systolic blood pressure were associated with the higher incidence of prolonged QTc, whereas physical activity and BMI within the range of 21.5–23.2 kg/m^2 were protective factors (10). As regards distal symmetrical polyneuropathy and autonomic neuropathy, neither of them were independently predictive of incident prolonged QTc, however incident cases had higher baseline prevalence of distal symmetrical polyneuropathy. Moreover, even prevalent cases of prolonged QTc had higher prevalence of distal symmetrical polyneuropathy, although limited to male sex (16). Altogether, the data from the EURODIAB studies suggest that diabetic neuropathy acts as a confounder of the association between severe hypoglycemia and prolonged QT, being associated with both of them.

Therefore, our data do not support the hypothesis that the cumulative and deleterious effects of repeated/severe hypoglycemic episodes cause long-term changes in cardiac repolarization leading to QTc prolongation. Both prolonged QTc and hypoglycemia are likely to be linked to another causal factor such as autonomic neuropathy (14-17). The relationship between hypoglycemic attacks and QTc prolongation had been extensively explored in previous physiological studies (2-5, 17-19). These works have shown that both spontaneous and provoked hypoglycemic events are associated with QTc interval prolongation. As prolonged QTc is a well-known inducer of cardiac arrhythmia, possibly leading to sudden cardiac death (20-22), these data has also provided a potential pathophysiological

link between nighttime hypoglycemia and the so-called “dead in bed syndrome” in type 1 diabetic patients (20). Our findings are not in conflict with these results, as physiological studies assessed if hypoglycemic events can trigger a transient QTc prolongation in an acute setting, while our epidemiological study has explored the potential role of repeated episodes of severe hypoglycemia as a predictor of QTc prolongation over a 7-year follow-up period and their effect may disappear after prolonged exposure because of adaptive mechanisms (2-5).

The prospective study design, the large population sample and the centralized assessment of all measurements are key strengths of our study. Though we could not re-assess all patients from the EURODIAB Complications Study, we can assume that this did not cause systematic bias in the follow-up data. Loss-follow-up was mainly due to either center drop out or insufficient quality of ECG recordings to measure a valid R-R interval rather than by selective loss of subjects. Moreover, variables such as age, sex and baseline distribution of severe hypoglycemic episodes did not differ in patients who were included and not in the study. Differences in systolic blood pressure, LDL-cholesterol and HbA1c among the two subgroups, although statistically significant, were of limited clinical value. Therefore, selection bias is unlikely to have affected the relationship between hypoglycemia and incidence of QTc prolongation. Second, data on serum electrolytes and drugs, which are known to interfere with cardiac repolarization and to affect QTc interval were not available in the EURODIAB study. However, patients recruited in the study were relatively young and hence the percentage of patients with either electrolyte disturbances or taking drugs potentially interfering with the QT interval was likely to be small. Third, we cannot exclude the possibility that in our work the consequences of hypoglycemia were underestimated because we relied on self-reports of spontaneous hypoglycemia. However, our analyses were based on numbers of severe episodes only, which required assistance of another person, and recall bias is unlikely. Finally, as patients were re-assessed 7 years after the baseline examination rather than annually, we could not perform a time-dependent analysis of the relationship between hypoglycemia and incidence of QTc prolongation and potential random changes with time in the exposure to severe hypoglycemic events might have biased

downward our estimated ORs. Only prospective studies based on continuous both glucose and ECG monitoring would provide unbiased definitive data, but their feasibility and/or practicality is currently limited.

In conclusion, present analyses of the EURODIAB Prospective Complications Study do not support the hypothesis that severe hypoglycemia is a predictor of subsequent development of QTc prolongation in type 1 diabetes.

List of abbreviations

CVD cardiovascular diseases

CHD coronary heart disease

BMI Body mass index

OR odds ratio

Declarations

Ethics approval and consent to participate: The study was approved by local ethics committees, and informed consent was obtained from all subjects.

Consent for publication: not applicable

Availability of data and material: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contribution: CA and GB contributed to the study concept and design, researched and interpreted the data and drafted the manuscript. SG, PF, DF, SS, JF, NC, FB, GG researched data and reviewed the manuscript. GG and GB oversaw the progress of the project, contributed to the discussion and reviewed the manuscript.

G.B. is the guarantors of this work and, as such, had full access to all the data analysis.e study and

take responsibility for the integrity of the data and the accuracy of the data.

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Conflict of Interest: None

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Table 1: Baseline characteristics of 1,415 type 1 diabetic subjects of the EURODIAB cohort by QTc values at follow-up. Data are expressed as: mean ± SD or geometric mean (25th, 75th centile).

	Incident cases of QTc prolongation (*n*=264)	**Normal QTc (*n*=1151)**	**P**
Age (years)	33.9 ± 10.7	31.7 ± 9.3	0.005

Diabetes duration (years)	14.7 ± 9.7	14.1 ± 8.6	0.33
BMI (kg/m^2)	23.7 ± 2.9	23.5 ± 2.6	0.27
HbA1c (%)	6.7 ± 1.7	6.5 ± 1.9	0.25
Systolic blood pressure (mmHg)	121.5 ± 17.8	118.6 ± 15.0	0.008
Diastolic blood pressure (mmHg)	75.8 ± 11.7	74.4 ± 10.8	0.06
AER µg/min	17.3 (6.6-27.7)	15.3 (6.6-23.1)	0.18
CHD (n, %)	23 (8.7%)	64 (5.6%)	0.05
Autonomic neuropathy (n, %)	89 (36.3%)	337 (31.3%)	0.128
Distal symmetrical polyneuropathy (n, %)	102 (39.4%)	340 (30.1%)	0.004
Severe hypoglycemic events at baseline (n)			
0	181 (68.6%)	791 (68.7%)	0.03
1-2	40 (15.1%)	231 (20.1%)	
≥3	43 (16.3%)	129 (11.2%)	
Severe hypoglycemic events at the follow-up examination (n) **0**	180 (70.0%)	799 (70.8%)	0.01
1-2	38 (14.8%)	221 (19.6%)	
≥3	39 (15.2%)	109 (9.6%)	

Table 2: Logistic regression analyses assessing the independent association between severe hypoglycemic episodes and incidence of QTc prolongation (dependent variable).

	Model 1	**Model 2**	**Model 3**	**Model 4**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Severe hypoglycemic events at baseline (n)				
0	1.00			
1-2	0.80 (0.54- 1.18)			
≥3	1.35 (0.90-2.03)			
Severe hypoglycemic events at the follow-up examination (n)				
0		1.00	1.00	1.00
1-2		0.82 (0.55-1.22)	0.88 (0.51-1.18)	0.80 (0.51-1.23)
≥3		**1.68 (1.09-2.58)**	**1.51 (0.96-2.39)**	**1.63 (0.99-2.68)**

Model 1 and 2: ORs adjusted for age, sex, HbA1c, physical activity, BMI, and systolic blood pressure
Model 3: as model 1 + distal symmetrical polyneuropathy at the follow-up examination
Model 4: as model 1 + autonomic neuropathy at the follow-up examination