QTc Interval Prolongation Is Independently Associated With Severe Hypoglycemic Attacks in Type 1 Diabetes From the EURODIAB IDDM Complications Study

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OBJECTIVE—Our aim was to assess whether severe hypoglycemic attacks were cross-sectionally associated with abnormalities of the QTc interval in type 1 diabetic patients.

RESEARCH DESIGN AND METHODS—The study included 3,248 type 1 diabetic patients from the EURODIAB IDDM Complications Study. Severe hypoglycemia was defined as an attack serious enough to require the help of another person. A corrected QTc interval (QTc) >0.44 s was considered abnormally prolonged.

RESULTS—Nineteen percent of patients declared one to two attacks, and 13.2% of patients had three or more attacks. Prevalence of QTc prolongation was greater in patients who experienced three or more hypoglycemic attacks. Logistic regression analysis showed that the frequency of severe hypoglycemia was independently associated with QTc prolongation, even after adjustment for diabetes complications, including autonomic neuropathy (odds ratio 1.27, 95% CI 1.02–1.58).

CONCLUSIONS—We have provided evidence that severe hypoglycemic attacks are independently associated with a prolonged QTc interval in type 1 diabetic patients from the EURODIAB IDDM Complications Study.

I ntensive glucose control increases the risk of severe hypoglycemia, and in the Diabetes Control and Complications Trial severe hypoglycemic episodes requiring assistance affected approximately one third of the intensively treated patients (1). Prolonged corrected QTc interval (QTc) reflects abnormalities of ventricular myocardial repolarization and is an independent marker of increased mortality in patients with type 1 diabetes (2).

Physiologic and clinical studies have shown that provoked and spontaneous hypoglycemia induces QT lengthening (3,4). In the EURODIAB cohort, hypoglycemia was independently associated with autonomic neuropathy (5), which is common in patients with type 1 diabetes with prolonged QTc (6); however, the relationship between hypoglycemia and QTc prolongation was not explored. The aim of the current study was to assess whether severe hypoglycemic attacks were cross-sectionally associated with QTc abnormalities in this cohort.

RESEARCH DESIGN AND METHODS—The EURODIAB IDDM Complications Study is a clinic-based study designed to explore risk factors for diabetes complications (7,8). The local ethics committees approved this study at each center, and all persons provided written informed consent.

Definitions of severe hypoglycemia were based on information obtained from a questionnaire completed by recruited subjects. 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 questionnaire also provided information on physical activity, smoking habits, frequency of insulin injections, and number of daily insulin units injected per kilogram of body weight (5,7).

Hypertension, retinopathy, microalbuminuria, macroalbuminuria, and cardiovascular disease (CVD) were assessed and defined as previously described (7,8). Glomerular filtration rate (GFR) was estimated using the four-component abbreviated equation from the Modification of Diet in Renal Disease study (9). Subjects with an estimated GFR <60 mL/min/1.73 m^2 were defined as having chronic kidney disease.

Distal symmetrical polyneuropathy (DSP) was assessed on the basis of neuropathic symptoms and signs, including measurement of vibration perception threshold (10). Autonomic neuropathy was defined as a loss of heart rate variability with an R-R ratio <1.04 or postural hypotension with a decrease in systolic blood pressure of ≥20 mmHg (10,11).

RR and QT intervals were measured blindly by two observers on the resting electrocardiogram tracing, using five consecutive beats on lead V5. The QTc for the previous cardiac cycle length was calculated

according to Bazett's equation (12). QTc >0.44 s was considered abnormally prolonged. RR and QT intervals were also measured for three consecutive cardiac cycles on the six thoracic leads. The dispersion of QTc was calculated using the difference between the maximal and the minimal QTc (QTd) in any thoracic leads. A QTd >0.080 s was considered abnormally increased (10).

Data were expressed as the mean and SD. Variables with skewed distributions were logarithmically transformed for statistical analysis. Group differences were tested by ANOVA or Pearson χ^2 test, as appropriate. All variables were included in a logistic regression analysis and retained in the final model if they added significantly to the likelihood of models or to the estimated coefficients of predictors, as assessed using the −2 log likelihood ratio test. The analysis was hypothesis-oriented and did not use stepwise selection of variables (13). P value of less than 0.05 was considered to indicate statistical significance. Analyses were performed with Stata (Stata Release 10.0, StataCorp LP, College Station, TX).

RESULTS—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 (H0), 618 patients (19%) declared one to two attacks (group H1-2), and 428 patients (13.2%) declared three or more attacks (H3). As previously reported (7), the latter group of patients was older, had longer diabetes duration, and had lower mean HbA$_{1c}$ levels.

Estimated GFR values were lower in patients declaring hypoglycemic episodes (H0: 120.1 ± 53.6; [H1-2]: 113.9 ± 30.1; H3: 106.7 ± 34.3; P = 0.02). Prevalence of hypertension (H0: 22.7%; [H1-2]: 25.7%; H3: 30.8%; P = 0.001), CVD (H0: 9.4%; [H1-2]: 8.4%; H3: 13.2%; P = 0.02), nonproliferative/proliferative retinopathy (H0: 44.7%; [H1-2]: 46.3%; H3: 54.6%; P = 0.007), DSP (H0: 34.3%; [H1–2]: 36.9%; H3: 44.6%; P < 0.0001), and QTc prolongation (H0: 14.8%; [H1-2]: 16.9%; H3: 19.3%; P = 0.05) was greater in patients who experienced three or more hypoglycemic attacks. No significant differences were observed in the prevalence of prolonged QTd (H0: 6.3%; [group H1-2]: 7.3%; H3: 8.5%; P = 0.27).

Logistic regression analysis showed that the frequency of severe hypoglycemia was associated with longer diabetes duration, lower HbA$_{1c}$, chronic renal disease, and QTc prolongation independently of confounders, as shown in Table 1 (Model 1). The relation between prolonged QTc and frequency of severe hypoglycemia was independent of diabetic macro/microvascular complications. Indeed, as shown in Table 1 (Models 2–6), the association remained significant even after further adjustment for CVD (odds ratio [OR] 1.27 [95% CI 1.01–1.58]), diabetic nephropathy (1.27 [1.03–1.58]), diabetic retinopathy (1.38 [1.08–1.78]), DSP (1.27 [1.01–1.58]), and autonomic neuropathy (1.27 [95% CI 1.02–1.58]).

CONCLUSIONS—Previous small physiologic and clinical studies have reported that provoked/spontaneous hypoglycemia can induce QT prolongation (3,4). However, this issue has never been explored in large series, and our data provide the first evidence of an independent association between hypoglycemia and QTc prolongation in a large epidemiologic study on type 1 diabetes. This finding is of clinical relevance because in type 1 diabetes, the so-called dead in bed syndrome has been related to nocturnal hypoglycemia leading to QT prolongation followed by ventricular tachyarrhythmia (3,14).

Autonomic neuropathy itself can be associated with QTc lengthening (5), and a recent study has found QTc prolongation to be common in adolescents with type 1 diabetes with early autonomic dysfunction (15). Furthermore, in the EURODIAB cohort, autonomic neuropathy was independently associated with severe hypoglycemia (5). Nonetheless, the relationship between prolonged QTc and hypoglycemia was

Table 1—*Odds ratio for severe hypoglycemic attacks in the EURODIAB IDDM Complications Study*

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Duration (years)						
1–7	1.00	1.00	1.00	1.00	1.00	1.00
8–14	1.77 (1.39–2.26)	1.79 (1.40–2.28)	1.79 (1.40–2.29)	1.85 (1.40–2.45)	1.72 (1.35–2.20)	1.80 (1.40–2.32)
15–24	2.01 (1.58–2.56)	2.03 (1.59–2.59)	2.02 (1.58–2.58)	2.15 (1.59–2.90)	1.95 (1.53–2.49)	1.95 (1.52–2.50)
≥25	2.65 (2.07–3.38)	2.66 (2.08–3.40)	2.67 (2.08–3.43)	2.81 (2.04–3.88)	2.47 (1.91–3-17)	2.48 (1.93–3.20)
HbA$_{1c}$ (%)						
<5.4	1.00	1.00	1.00	1.00	1.00	1.00
5.4–6.4	0.67 (0.55–0.83)	0.67 (0.55–0.83)	0.67 (0.54–0.83)	0.69 (0.54–0.87)	0.67 (0.54–0.83)	0.67 (0.54–0.83)
6.5–7.7	0.60 (0.48–0.74)	0.60 (0.48–0.74)	0.60 (0.48–0.75)	0.56 (0.43–0.71)	0.58 (0.47–0.72)	0.61 (0.49–0.76)
≥7.8	0.42 (0.33–0.52)	0.41 (0.33–0.52)	0.41 (0.33–0.52)	0.34 (0.26–0.45)	0.40 (0.32–0.51)	0.41 (0.32–0.52)
Estimated GFR (mL/min/1.73 m^2)						
<60	1.00	1.00	1.00	1.00	1.00	1.00
60–89	0.74 (0.47–1.17)	0.79 (0.49–1.25)	0.78 (0.48–1.25)	0.78 (0.45–1.35)	0.76 (0.48–1.21)	0.79 (0.49–1.26)
90+	0.62 (0.40–0.95)	0.66 (0.43–1.03)	0.64 (0.40–1.02)	0.62 (0.37–1.06)	0.63 (0.41–0.97)	0.64 (0.41–1.00)
QTc (s)						
≤0.44	1.00	1.00	1.00	1.00	1.00	1.00
>0.44	1.29 (1.04–1.59)	1.27 (1.03–1.58)	1.27 (1.03–1.58)	1.38 (1.08–1.78)	1.27 (1.03–1.58)	1.27 (1.02–1.58)

Model 1: adjusted for age, lipids, physical activity, insulin dosage, BMI, waist/hip ratio, alcohol consumption, use of contraceptive, social class, years of education. Model 2: Model 1 + CVD. Model 3: Model 1 + diabetic nephropathy. Model 4: Model 1 + diabetic retinopathy. Model 5: Model 1 + DSP. Model 6: Model 1 + autonomic neuropathy.

not mediated by autonomic neuropathy in the current study.

The lack of serum electrolyte measures in the EURODIAB study may limit the interpretation of results. However, the sample of patients is relatively young; therefore, the percentage of patients with electrolyte disturbances or taking drugs potentially interfering with QT duration is likely to be small and to have little impact on our findings. On the other hand, lowering of serum potassium is known to augment the arrhythmogenic effect of QT prolongation and may expose patients with type 1 diabetes with frequent severe hypoglycemic episodes and prolonged QTc to a higher risk of ventricular tachyarrhythmia and sudden death. Our results are based on self-reports of severe hypoglycemia; however, any potential misclassification was randomly distributed; thus, it is unlikely to affect observed significant associations.

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