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Full Length Research Paper

The effect of insulin therapy and plasma glucose levels on corrected QT intervals in patients with type 2 diabetes

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This study aims is to investigate the effect of medium-term insulin therapy (3 months) and plasma glucose levels on corrected QT intervals (QTc) in patients with type 2 diabetes. The subjects were 17 patients with type 2 diabetes who had poor glycemic control and were changed to insulin therapy from sulfonylurea or diet therapy alone. QTc, fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), serum potassium and body weight were measured at baseline and after 3 months of insulin therapy. A significant increase of QTc (0.406 ± 0.027 to 0.421 ± 0.025 s, P =0.0025) and a significant decrease in HbA1c (10.9 ± 1.9 to 7.9 ± 1.7%, P =0.0002) were found after 3 months of insulin therapy. QTc showed no correlation with FPG, HbA1c or body weight before insulin therapy and the change in QTc was not correlated with the change in FPG, HbA1c or body weight from before to after insulin therapy. In this study, insulin therapy for 3 months caused a significant increase of QTc in patients with type 2 diabetes. However, given the small size of the trial, further studies with larger number of patients are needed.

Key words: QTc, type 2 diabetes, insulin therapy.

INTRODUCTION

The corrected QT intervals (QTc) on an electrocardiogram (ECG) are prolonged in patients with diabetes complicated by diabetic autonomic neuropathy (Kahn et al., 1987; Chambers et al., 1990) and the prolongation is associated with mortality in such patients (Sawicki et al., 1996). QTc prolongation may also be related to circulating insulin levels and insulin resistance (Dekker et al., 1996; Festa et al., 1999; Kazumi et al., 1999) or obesity (El-Gamal et al., 1995). A recent report also demonstrated that experimental acute insulin therapy can prolong QTc (Gastaldelli et al., 2000). In contrast, it has also been reported that acute hyperglycemia produced by the glucose clamp method can induce QTc prolongation in healthy subjects and patients with type 1 diabetes (Gan et al., 2009). However, it is unclear how improvement of glycemic control by newly initiated insulin therapy influences QTc over a period of a few months, although one study showed that insulin therapy reduced QTc at 4-month follow-up in patients with type 2 diabetes (Schnell et al., 2004). Main purpose of this study is to investigate the effect of insulin therapy and plasma glucose levels on QTc in patients with type 2 diabetes. Our study showed that insulin therapy for 3 months caused a significant increase of QTc in patients with type 2 diabetes, despite the improvement of glycemic control.

PATIENTS AND METHODS

Patients

The effect of newly initiated insulin therapy on QTc was investigated in 17 patients with type 2 diabetes (9 men and 8 women) who had poor glycemic control and were changed to insulin therapy from sulfonylurea or diet therapy alone. There was no washout period of

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Abbreviations: QTc, corrected QT interval, **FPG,** fasting plasma glucose, **HbA1c,** hemoglobin A1c.

Table 1. Clinical characteristics of the non-diabetic and diabetic Japanese subjects.

Characteristics	Non-diabetes	Diabetes (Before insulin)	Diabetes (After insulin)	P	P^a
No. (male/female)	30 (14/16)	17 (9/8)	—	—	—
Age (year)	60.2 ± 4.9	58.4 ± 10.6	—	0.9128	—
Duration of diabetes (year)	—	13.1 ± 8.7	—	—	—
QTc (s)	0.388 ± 0.026	0.406 ± 0.027	0.421 ± 0.025	0.0327*	0.0025*
FPG (mg/dL)	90.1 ± 6.81	83.0 ± 49.8	149.9 ± 61.6	0.0001*	0.1598
HbA1c (%)	4.9 ± 0.3	10.9 ± 1.9	7.9 ± 1.7	0.0001*	0.0002*
BMI (kg/m^2)	21.7 ± 1.9	23.6 ± 5.1	—	0.5348	—
Body weight (kg)	—	61.6 ± 16.2	62.8 ± 16.8	—	0.1391
Diabetic therapy					
SU	—	12	—	—	—
(SU1/SU2/SU3/SU4)	—	1/3/3/5	—	—	—
Diet alone	—	5	—	—	—
Antihypertensive drugs	—	7	—	—	—
(Ca /Ca+ARB)	—	5/2	—	—	—

Data are expressed as mean ± standard deviation (SD). Comparison in variables between two groups was made by use of an unpaired *t* test. P: p value of Non-diabetes vs. Diabetes (before insulin), P^a: p value of Diabetes (before insulin) vs. Diabetes (after insulin), P <0.05 are defined as statistical significance (*). FPG: fasting plasma glucose, $HbA1_C$: hemoglobin $A1_C$, BMI: body mass index; Insulin: insulin therapy, SU: sulfonylurea, α-GI: α glucosidase inhibitor; SU1:SU alone, SU2: SU and α-GI, SU3: SU and metformin, SU4: SU, metformin and α-GI; Antihypertensive drugs: Ca: calcium channel blocker, ARB: angiotensin-II receptor blocker.

sulfonylurea before initiating insulin therapy. These patients were prospectively and consecutively enrolled in the study from October 2005 to February 2006. The clinical characteristics of the patients are summarized in Table 1. Patients with evidence of liver dysfunction, infectious disease or autoimmune disease, autonomic disorder other than diabetes mellitus, hypothyroidism, renal failure, and cardiac failure were excluded from the study. Patients treated with drugs which may influence QTc such as β blockers, anti-arrythmic drugs, and diuretics were also excluded. No patients showed apparent ketoacidosis evaluated by urine tests. QTc measurements were also performed in 30 healthy controls.

METHODS

QTc measurement: An ECG for QT measurement was recorded in the morning before breakfast after a 10 h overnight fast on the same day that blood and urine tests were performed. During the recording, the subjects were at rest in a supine position and were instructed to maintain a respiratory rate of >9 breaths/min to decrease the effect of respiratory sinus arrhythmia. No patient had an increased QRS duration. The QT interval was measured automatically using an ECG instrument FX-7412 (Fukuda Denshi Limited, Tokyo, Japan). In previous studies (Takebayashi et al., 2002; 2004), we have measured QTc manually, but technical difficulties with this approach caused us to use the automatic method in the current study. The QT interval was determined as the mean of 12 leads for each beat and QTc was calculated using Bazett's formula: $QTc = QT / RR^{1/2}$ (Bazett, 1920). The QTc for each patient was defined as the mean QTc over 100 consecutive beats. To prevent over- or underestimation of the QT interval by Bazett's formula (Puddu et al., 1988), only individuals with a normal pulse rate (60 to 100 beats/min) in resting state were enrolled in the study.

Blood tests

After collection, the blood was rapidly centrifuged at 1500 rpm for 5 min to separate serum and plasma from clot-containing blood cells. These samples were stored at -70°C until analysis. Plasma glucose, HbA_{1C}, and serum lipid concentrations were measured as described previously (Takebayashi et al., 2004). Serum potassium concentration was measured by the dilution method by ion selective equipment using automated analyzer of electrolyte (JCA-BM2256, JOEL Ltd., Tokyo, Japan).

Insulin therapy

Insulin therapy was initiated at a dose equal to approximately the body weight of the patient (kg) × 0.2 units, and then the dose was adjusted based on the degree of glycemic control. Blood tests were performed at the start of insulin therapy and after 12 weeks; in each case before breakfast after at least a 10 h period of overnight fasting. No change in administration of any drug occurred for any patient during the 12-week study period.

Regarding antihypertensive drugs, 5 patients received amlodipine (5 mg/day) and 2 patients received amlodipine (5 mg/day) and olmesartan (20 mg/day). Patients who received other anti-hypertensive drugs were not included in this study.

In this study, QTc prolongation was defined as "prolongation" from baseline QTc (= before initiation of insulin therapy) even if the

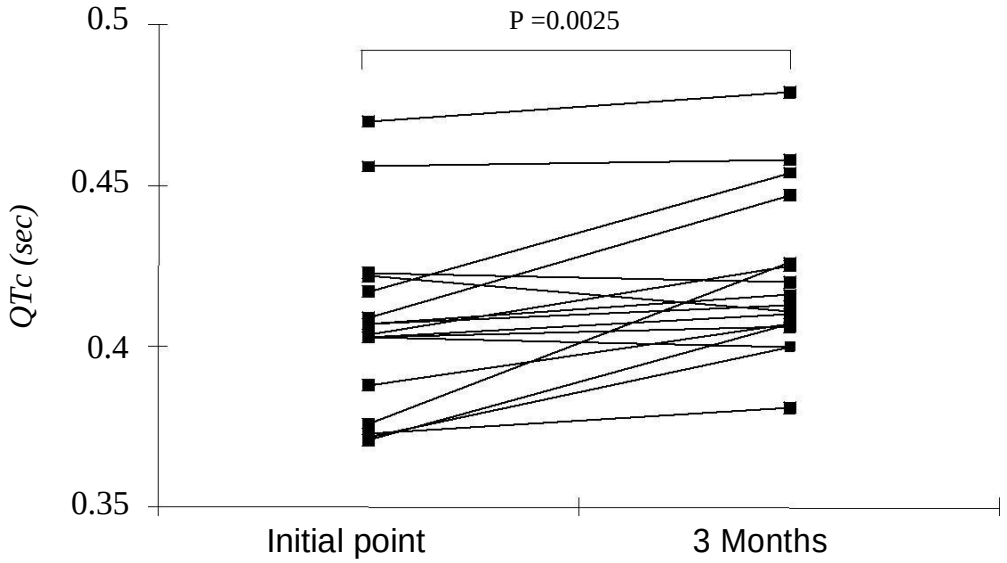

Figure 1. Effect of 3 months-insulin therapy on corrected QT intervals in patients with type 2 diabetes.

QTc after insulin therapy was still within normal range (QTc ≦ 0.43 s in men and ≦ 0.45 s in women) defined by the most recent European regulatory guidelines (Straus et al., 2006).

Ethical considerations

*All subjects gave informed consent to inclusion in the study, which was performed according to the guidelines in the declaration of*Helsinki.

Statistical methods

All data are presented as means ± standard deviation (SD). The significance of a correlation between two variables was determined by simple regression analysis. Comparison of two time points for an individual was performed using a paired t test. A P value of less than 0.05 was considered to indicate statistical significance in all analyses.

RESULTS

The mean QTc values in the 30 healthy controls and the mean baseline QTc values in the 17 patients with type 2 diabetes were 0.398 ± 0.026 and 0.406 ± 0.027 s, respectively, with no significant difference between these groups (P =0.3277). The QTc showed significant prolongation to 0.421 ± 0.025 s (P =0.0025) after 3 months of insulin therapy in the patients (Figure 1), and there was a significant difference in the mean QTc after treatment compared to the QTc in the healthy controls (P =0.0052).

A tendency for a decrease in FPG (183.0 ± 49.8 to 149.9 ± 61.6 mg/dL, P =0.1598) and a significant decrease in $HbA1_C$ (10.9 ± 1.9 to 7.9 ± 1.7%, P =0.0002) were also detected after the 3 months of insulin therapy. There were no significant changes in body weight (61.6 ± 16.2 to 62.8 ± 16.8 kg, P =0.1391), potassium (4.2 ± 0.4 to 4.1 ± 0.4 mEq/L, P =0.2342), SBP (130.4 ± 11.1 to 126.2 ± 14.1 mmHg, P =0.2979) or DBP (74.1 ± 12.3 to 71.3 ± 7.7 mmHg, P =0.3335) after insulin therapy.

There was no correlation of QTc with FPG (R =0.3521, P =0.1657), HbA1c (R =0.0457, P =0.8619) or body weight (R =0.0723, P =0.7827) at the start of insulin therapy. Similarly, the change in QTc from before to after insulin therapy showed no correlation with the change in FPG (R =-0.2432, P =0.3469), $HbA1_C$ (R =-0.1856, P =0.4686) or body weight (R =0.1309, P =0.6166) from before to after therapy.

There was also no correlation between QTc and the serum potassium concentration at the start of insulin therapy (R =0.1656, P =0.5558). However, a tendency for a negative correlation was observed between the changes in QTc and serum potassium from before to after insulin therapy (R =-0.3753, P =0.1377).

Mean insulin dose after the 3 months of insulin therapy was 19.8 ± 10.0 U/day. There were no patients showing polymorphic ventricular fibrillation on ECG after the 3 month of insulin therapy.

DISCUSSION

In the current study, we investigated the medium-term effect of insulin therapy for 3 months on QTc in patients with type 2 diabetes. Insulin therapy significantly increased QTc compared with that at baseline, and the QTc after therapy was significantly longer than that in healthy subjects. The QTc in the diabetic patients at baseline did not differ significantly compared with the QTc

in healthy subjects. We speculate that this was due to the small number of patients in this study, since we have previously shown significant QTc prolongation in diabetic patients compared with QTc in healthy subjects (Takebayashi et al., 2004), supporting previous study (Borra and Gea, 2001).

It has been shown that experimental acute insulin therapy prolongs QTc (Gastaldelli et al., 2000) and we have previously found significant QTc prolongation in patients with type 2 diabetes patients treated with insulin therapy compared with those treated with dietary modification alone in a cross-sectional study (Takebayashi et al., 2002). In addition, Sakabe et al. reported that among type 2 diabetic patients with post myocardial infarction treated with insulin, sulfonylurea, or diet alone, corrected QT dispersion was significantly greater in the insulin group (Sakabe et al., 2008). A significant positive correlation between QTc and plasma insulin levels has also been shown (Kazumi et al., 1999). Our current results appear to support these findings. In contrast, it is also reported that acute hyperglycemia can cause QTc prolongation (Gan et al., 2009), although there are reports showing that hypoglycemia also causes QTc prolongation (Christensen et al., 2010 a, b). Importantly, QTc was prolonged in the current study despite the large reduction in HbA1c (by approximately 3%) after 3 months of insulin therapy. Furthermore, QTc was not correlated with FPG or HbA1c at baseline and the changes in these parameters from before to after insulin therapy also showed no significant correlation. This appears to show that plasma glucose level did not cause prolonged QTc. Therefore, the role of glucose level in the clinical pathogenesis of prolonged QTc was not fully evident at least in this study. Taken together, we speculate that medium-term (but not acute) insulin therapy prolongs QTc independently of glycemic control.

Interestingly, in the recently published ACCORD study (Gerstein et al., 2008), patients who received intensive glucose lowering therapy (a higher percentage of insulin therapy and a higher dose of insulin) had greater mortality than those who received conventional therapy. The increased mortality with intensive therapy appeared to be explained by the higher incidence of severe hypoglycemia in these patients. However, it may be of interest to examine the influence of intensive insulin therapy on QTc, because QTc prolongation is associated with mortality in patients with diabetes (Sawichki et al., 1996).

The detailed mechanism of induction of QTc prolongation by insulin is unknown, but an influence of the serum potassium concentration on acute insulin effects has been suggested (Gastaldelli et al., 2000). In this study, there was no correlation between QTc and serum potassium at start of insulin therapy. We speculate that this negative result was due to small number of patients at least partially. However, we found a tendency for a negative correlation between the changes in QTc and serum potassium levels from before to after insulin therapy, in support of this proposed mechanism (Gastaldelli et al., 2000). However, this association was not always strong and other mechanisms may also be involved such as the change of other ions (including calcium ion) concentrations. Furthermore, ion channel gene SNPs in individual patients may have influenced QTc as reported by Gouas et al. (2007).

In the current study, the BMI of this study, which may influence QTc (El-Gamal et al., 1995), was not significantly increased compared to control group. This may be due to the fact that patients in this study were all Japanese. It is reported that Japanese type 2 diabetic patients' BMI are almost 23 kg/m^2 in large number of study (Sone et al., 2002), which corresponded to those in this study.

The study has some limitations. First, the number of patients was small and we did not perform power calculation for sample size before initiating the study. In addition, we did not use a control group of diabetic patients for comparison with the insulin-treated patients. It would have been interesting to investigate the effects on QTc of treatment with thiazolidinediones or metformin, which can decrease circulating insulin levels while decreasing plasma glucose based on improved insulin resistance. Second, administration of sulfonylureas was suspended after initiation of insulin therapy, but we were unable to use washout periods for these drugs for ethical reasons. Third, according to the most recent European regulatory guidelines (Straus et al., 2006), QTc $\leqq$0.43 s and $\leqq$0.45 s in men and women is respectively considered as normal. Therefore, the QTc in this study was still within normal range even after the insulin therapy. Because the patients in this study at baseline had relatively low QTc, it may also be important to evaluate the effect of insulin therapy on QTc in patients' population with higher QTc (borderline QTc; that is 0.450 $\geqq$QTc $\geqq$ 0.431 s in men and 0.470$\geqq$QTc $\geqq$0.451 s in women). Forth, it would have been interesting to see and compare the effect of initiation of insulin therapy on QTc not in only type 2 diabetes but also in type 1 diabetes. In addition, it would have been important to compare the effect of insulin treatment duration on QTc. Furthermore, plasma insulin levels should have been measured. Finally, because it is well documental fact that hypocalcemia prolongs QTc, serum calcium levels should have been measured to assess the association between these levels and insulin therapy. Within these limitations, we conclude that 3-month insulin therapy causes a significant QTc prolongation in patients with type 2 diabetes. A more detailed analysis is required to establish the basis of the effect of insulin on QTc.

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