The influence of different glucose tolerance on QTc interval: a population-based study

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Original investigation

Abstract

Background

Corrected QT (QTc) interval has been reported to be associated with type 2 diabetes. This study aimed to explore the relationship between different glucose tolerance and QTc interval among middle-aged and older Chinese individuals.

Methods

We conducted a cross-sectional analysis that included 9898 subjects (3194 men and 6704 women) in a Chinese population. Glucose tolerance was studied during OGTT. Insulin, blood pressure, HbA1c, serum lipids, hepatic transaminases and waist-to-hip ratio were assessed.The QTc interval was derived from ECG recordings, and the subjects were stratified based on different glucose tolerance.

Results

QTc interval levels were increased significantly in the subjects with abnormal glucose metabolism compared with the normal glucose regulation group. Multiple regression analyses QTc interval was significantly associated with fasting plasma glucose, 2-h OGTT plasma glucose and HbA1c. The odds ratios of prolonged QTc was 1.396 for IFG/IGT (95% CI: 0.126-1.730), 1.342 for type 2 diabetes (95% CI: 0.142-1.577) after all the potential confounders were adjusted.

Conclusions

IGR and diabetes are associated with prolonged QTc interval among middle-aged and older Chinese individuals. Abnormal glucose regulation can be used to monitor QTc interval in the population.

Background

The risk of sudden death is increased in patients with diabetes mellitus and impaired glucose tolerance[1, 2]. Abnormal cardiac autonomic nervous system function is one of the most significant complications of diabetes[3].The QT interval is defined as the total time required for ventricular myocardial depolarization and repolarization[4]. Corrected QT (QTc) is very important for the prediction, risk assessment and treatment of ventricular arrhythmias[2].The relation between a prolonged QTc interval and an increased risk of sudden death has been traditionally explored in familial long QT syndrome sudden cot death, and congestive heart failure, as well as in adults with diabetes mellitus[2, 5–8]

Although several researches describe the relationship between QTc interval prolongation, diabetic complications, and an increased mortality rate in adults[5, 9–11], the influence of abnormal glucose metabolism on QTc interval has not been fully clarified. Previous studies have confirmed that the prevalence of prolonged QTc interval is increased in people with type 1 and type 2 diabetes as compared to non-diabetics, and the abnormalities in cardiac repolarisation may be caused by complications of diabetes rather than diabetes in itself[5, 10, 12, 13]. Most

recently, Kurnaz E et al. found that QTc prolongation is already existent in a significant proportion of children and adolescents with newly diagnosed type 1diabetes[14].

However, up to recently, only few studies have reported conflicting data on the relationship between QTc interval and glucose metabolism regulation, especially the status of impaired glucose regulation (IGR) [5, 6, 10, 12]. In this study, we aimed to investigate the influence of different glucose tolerance on QTc interval in a cross-sectional study of Chinese individuals aged 40–70 years.

Methods

Study population

The present study is one part of the risk evaluation of cancers in Chinese diabetic individuals, i.e., the longitudinal study (REACTION) which was a population-based cross-sectional study among middle-aged and elderly Chinese individuals in 25 communities across mainland China. The studied individuals aged 40 to 70 years old. The details of the study design have been described beforehand [15, 16]. All participants came from the Chongming District in Shanghai, China. A total of 9930 suitable subjects were recruited. After the exclusion of 1940 individuals with self-reported coronary heart disease, or taking medicine affecting heart rhythm, 7990 subjects (2489 men and 5501 women) were found to be suitable for the current analysis. Written informed consent was gained from all of the participants. Approval was given by the Institutional Review Board of Xinhua Hospital affiliated with Shanghai Jiaotong University School of Medicine.

Data collection

A standardized questionnaire was used by trained physicians to collect the baseline data. The measurements of weight, height, waist circumference, hip circumference and blood pressure have been described previously. Smoking (yes/no) and alcohol drinking (yes/no) were estimated with an interview preceding the physical examination. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

A 12-lead ECG was recorded at a paper speed of 50 mm/s on a six-channel recorder. The QT interval was measured from the beginning of the QRS complex to the end of the T-wave. The QT interval corrected for the previous cardiac R-R cycle length (QTc) was calculated according to the formula proposed previously and known as Bazett's formula: QTc = QT/(RR) 1/2[17]. QTc is the mean of QTc from five consecutive cycles in lead V5. QTc⩾440 ms was considered abnormally prolonged[18].

After overnight fasting for at least 10 hours, fasting and 2h OGTT (oral glucose tolerance test) blood samples were collected from all the participants in tubes containing EDTA and were centrifuged at 4°C and stored at −80°C till analysis. The fasting glucose, 2h OGTT plasma glucose, triglycerides, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and serum creatinine (Scr) were measured on an automatic analyzer (Hitachi 7080; Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated in the light of the equation described by Matthews et al[19].

Definitions of impaired glucose regulation and type 2 diabetes

Impaired glucose regulation was defined as impaired fasting glucose (IFG, fasting plasma glucose level ≥ 6.1 and < 7.0 mmol/l) and/or impaired glucose tolerance (IGT, 2h OGTT plasma glucose level ≥ 7.8 and < 11.1 mmol/l). Isolated IFG: fasting plasma glucose ≥ 6.1 mmol/l and < 7.0 mmol/l and a 2h OGTT plasma glucose < 7.8 mmol/l.

Isolated IGT: 2h OGTT plasma glucose ≥ 7.8 mmol/l and < 11.1 mmol/l and a fasting glucose < 6.1 mmol/l. IFG/IGT: fasting plasma glucose between 6.1 mmol/l and 6.9 mmol/l and a 2h OGTT plasma glucose 7.8 mmol/l to 11.0 mmol/l. Type 2 diabetes was diagnosed by the 1999 World Health Organization criteria (fasting plasma glucose level ≥ 7.0 mmol/l and/or a 2h OGTT plasma glucose level ≥ 11.1 mmol/l[20]. A fasting glucose level lower than 6.1 mmol/l and a 2h OGTT plasma glucose level below 7.8 mmol/l were defined as normal glucose regulation (NGR).

Statistical analysis

Data management and statistical analysis were performed with the SPSS Statistical Package (version 22.0; SPSS Inc., Chicago, IL). Normally distributed data were expressed as means ± SD, whereas variables with a skewed distribution were reported as median (inter-quartile range). Comparisons of means and proportions were performed with the t-test and χ^2 tests, respectively. Crude and partial correlation and multivariable stepwise regression analysis were used to investigate the association of QTc interval with cardiovascular and metabolic related parameters. A multiple linear regression analysis was performed to determine the associations of different glucose tolerance with QTc interval. Finally, a multivariate logistic regression model was used to evaluate the ORs and 95% CIs of different glucose tolerance for prolonged QTc. The potential confounders including age, sex, insulin, SBP, DBP, CHOL, TG, smoking, and drinking were adjusted. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of participants

The clinical characteristics of the participants stratified by glucose tolerance are summarized in Table 1. The study involved 3412 participants with NGR, 2475 with IGR and 1833 with type 2 diabetes. Among the participants with IGR, 773 (9.67 %) had isolated IFG, 1255 (15.7 %) had isolated IGT, and 717 (8.97 %) had combined IFG/IGT. The NGR and diabetes groups had, respectively, the most favorable and unfavorable metabolic profiles. Across different glucose tolerance, the subjects with higher blood glucose levels were more likely to be older, have higher waist to hip ratio, higher lipid profiles, and higher levels of blood pressure. Some liver and kidney function indicators (such as AST, ALT, GGT, SCr) between groups were different significantly. In addition, the levels of QTc interval were significantly increased in the subjects with isolated IFG, isolated IGT, combined IFG and IGT, and type 2 diabetes compared with the subjects with normal glucose regulation (416.63±24.79, 418.53±24.20,419.2±27.35, and 420.79±25.49, respectively, vs. 415.6±24.30, p < 0.05) (Fig. 1). QTc interval was positively associated with abnormal glucose metabolism.

Table 1
Clinical and laboratory characteristics according to different glucose tolerance.

Characteristics	DM	IFG+IGT	IGT	IFG	NGT	P value
N	1833	717	1255	773	3412	
Age (yr)	58.21±7.20	56.86±7.46	55.22±7.60	55.56±7.60	53.47±7.79	<0.001
Gender (M/F)	747/1086	253/464	307/948	316/457	866/2546	<0.001
QTc	420.79±25.49	419.20±27.35	418.53±24.20	416.63±24.79	415.60±24.30	<0.001
BMI (kg/m2)	25.18±3.38	25.06±3.53	24.91±10.43	24.38±3.35	23.74±3.25	<0.001
WHR	0.90±0.07	0.89±0.09	0.88±0.10	0.88±0.08	0.86±0.08	<0.001
SBP (mm Hg)	136.51±19.00	133.38±17.22	127.74±17.37	130.81±18.01	123.80±18.42	<0.001
DBP (mm Hg)	81.78±10.37	82.10±9.51	79.97±9.89	80.87±9.66	77.79±10.52	<0.001
FBG (mmol/l)	8.05±2.59	6.38±0.24	5.57±0.34	6.34±0.22	5.41±0.37	<0.001
PBS (mmol/l)	13.41±4.83	9.09±0.89	8.92±0.84	6.28±1.02	6.08±1.05	<0.001
HbA1C (%)	6.91±1.61	5.83±0.41	5.74±0.39	5.71±0.41	5.60±0.40	<0.001
Insulin(pmol/l)	8.92±3.24	8.10±3.89	7.27±3.66	7.26±3.35	6.27±3.07	<0.001
HOMA-IR	3.23±0.94	2.36±0.92	1.85±0.93	2.11±0.97	1.56±0.78	<0.001
HDL (mmol/L)	1.22±0.32	1.23±0.33	1.22±0.28	1.28±0.33	1.25±0.32	<0.001
LDL (mmol/L)	2.70±0.79	2.71±0.73	2.60±0.73	2.72±0.76	2.51±0.74	<0.001
CHO (mmol/L)	4.86±1.08	4.85±0.99	4.61±0.99	4.84±1.02	4.45±0.98	<0.001
TG (mmol/L)	2.08±1.71	2.02±1.11	1.73±0.89	1.70±0.91	1.38±0.71	<0.001
ALT (U/L)	20.86±10.07	19.04±10.31	16.99±8.80	17.28±8.04	13.97±7.55	<0.001
AST (U/L)	22.80±10.95	21.88±10.16	20.57±9.22	21.36±8.76	18.89±9.03	<0.001
GGT (U/L)	38.96±14.55	33.49±32.77	28.55±36.90	31.04±14.14	22.05±11.11	<0.001
Scr (umol/L)	68.71±17.48	68.07±19.95	64.03±12.94	67.91±14.05	63.34±12.06	<0.001
Smoking (n/total)	492/3412	161/773	156/1255	115/717	359/1833	<0.001
Drinking (n/total)	705/3412	222/773	227/1255	179/717	449/1833	<0.001
Values are mean ± SD or median (interquartile range) or number (proportion)						
p values were for the ANOVA or χ2 analyses across the five groups						

Association between QTc interval and clinical characteristics

Table 2 presents the results of correlation analyses of QTc interval with metabolic related parameters. QTc levels correlated positively with age, gender, WHR, SBP, DBP, PBS, FBS, HBA1c, insulin, HOMA-IR, LDL, CHO, TG, smoking,

drinking. After adjusting for age and gender, WHR, SBP, DBP, PBS, FBS, HA1c, insulin, HOMA-IR, CHO, TG was still positively associated with QTc interval.

Table 2
Crude and partial correlation between QTc and clinical parameters in the studied subjects

Variable	Crude r	Partial r[†]
Age (year)	0.139**	-
Gender	0.148**	-
BMI (kg/m2)	0.01	0.006
WHR	0.031*	0.039*
SBP (mmHg)	0.094**	0.085**
DBP (mmHg)	0.054**	0.081**
PBS (mmol/L)	0.091**	0.075**
FBS (mmol/L)	0.084**	0.083**
HbA1c (%)	0.074**	0.053**
Insulin (pmol/L)	0.061**	0.045**
HOMA_IR	0.068**	0.054**
HDL (mmol/L)	0.014	0.004
LDL (mmol/L)	0.046**	0.021
CHO (mmol/L)	0.068**	0.041**
TG (mmol/L)	0.062**	0.071**
Smoking	-0.106**	-0.002
Drinking	-0.083**	-0.007
*p < 0.01, **p < 0.001, †adjusted for age, gender		

Determinants of QTc levels

Table3 demonstrated variables independently associated with QTc interval. Age, gender, SBP, DBP, PBS, FBS, HBA1c, TG were independent determinants for QTc interval.

Table 3
Multiple stepwise regression analysis showing variables independently associated with QTc.

Independent variables	Standardized β	t	P value
Age	0.125	10.615	<0.001
Sex	0.192	17.004	<0.001
FBS	0.065	5.706	<0.001
PBS	0.052	4.557	<0.001
HbA1c	0.043	3.819	<0.001
SBP	0.044	3.007	0.003
DBP	0.036	2.498	0.012
TG	0.049	4.358	<0.001
The analysis also included CHO, WHR, Insulin, BMI, smoking, and drinking which were all excluded from the model.			

Associations between different glucose tolerance and QTc interval

To further explore the relationship between different glucose tolerance and QTc interval, multiple regression analyses were performed. The analyses revealed that solated IGT, combined IFG/IGT and type 2 diabetes are significantly associated with QTc interval after adjusting for all potentially confounders (age, sex, insulin, SBP, DBP, CHOL, TG, smoking, and drinking) (Table4).

Table 4
Adjusted associations with QTc according to different glucose tolerance.

	Glucose tolerance category	Standardized β	t	P value
Model 1	NGT	reference	1.042	0.298
	IFG	0.012	3.561	<0.001
	IGT	0.043	3.522	<0.001
	IFG+IGT	0.041	7.196	<0.001
	DM	0.087		
Model 2	NGT	reference	1.938	0.053
	IFG	0.027	3.043	0.002
	IGT	0.044	2.279	0.023
	IFG+IGT	0.032	5.049	<0.001
	DM	0.076		
Model 1 not adjusted.				
Model 2 adjusted for age, sex, insulin, SBP, DBP, CHOL, TG, smoking, and drinking.				

Associations between different glucose tolerance and QTc prolongation

In the present study, we consider QTc☐440 ms as abnormally prolonged. Taken NGR as reference, isolated IGT, combined IFG and IGT, and type 2 diabetes were all risk factors for prolonged QTc. OR of IGT for QTc prolongation was 1.131 (95% CI 1.059−1.356), OR of IFG+IGT for QTc prolongation was 1.396 (95% CI 1.126−1.73), and OR of T2DM for QTc prolongation was 1.34 (95% CI 1.142−1.577), respectively (P for trend < 0.001) after adjusting for age, sex, insulin, SBP, DBP, CHOL, TG, smoking, and drinking (Table5).

Table 5
Adjusted ORs and 95% CIs for prolonged QTc according to different glucose tolerance.

Glucose tolerance category	n/total	Crude OR (95%CI)	Adjusted OR (95%CI)
NGT	483/3412	1	1
IFG	121/773	1.129 (0.910-1.402)	1.110 (0.888-1.387)
IGT	216/1255	1.264* (1.061-1.506)	1.131* (1.059-1.356)
IFG+IGT	144/717	1.538** (1.251-1.890)	1.396** (1.126-1.730)
DM	361/1833	1.486** (1.279-1.727)	1.342** (1.142-1.577)
Adjusted OR: Adjusted for age, sex, lipid profiles, BMI, SBP, and DBP, smoking, and drinking.			
*p < 0.01, **p < 0.001			

Discussion

The main finding of this study is the effect of different glucose tolerance on QTc interval. QTc interval prolongation is more common in patients with isolated IGT, combined IFG and IGT, and type 2 diabetes compared to participants with NGR. Moreover, this association is independent of potential confounding covariates. Given the evidence that a prolonged QTc interval is related to adverse cardiovascular event, our results indicate that persons with IGR and diabetes may be at a high risk of arrhythmia, sudden death, and cardiovascular disease (CVD) mortality.

The QTc prolongation is reported to be an independent risk factor for coronary heart disease in type 1 and type 2 diabetes and has been described to be a prominent predictor of cardiac death even in newly diagnosed type 2 diabetes[21]. The presence of cardiovascular autonomic neuropathy (CAN) is considered to be a strong indicator of mortality. Additionally, lots of studies have demonstrated that the QTc prolongation has direct detrimental effects on the deadly arrhythmias and risk of sudden death with myocardial ischemia [6, 13]. The above studies support the role of QTc interval in predicting the risks of mortality, in this study, we demonstrated that QTc interval was prolonged in pre-diabetes and diabetes in middle-aged and elderly Chinese individuals.

Previous published articles have reported the risk factors of prolonged QTc interval among patients with diabetes included age[13], gender[5], BMI[22], hypertension[23], insulin concentration and hyperglycemia[24]. In consistent with above studies, our analysis showed age, gender, SBP, DBP, PBS, FBS, HBA1c, TG were positively correlated with QTc interval. However, after further adjusting the related confounding variables, BMI, Insulin, HOMA-IR, HDL, LDL, CHO were no longer independently related to QTc interval. In agreement with our results, the EURODIAB Prospective Complications Study demonstrated that female sex, higher values of HbA1c and systolic blood pressure were associated with the higher incidence of prolonged QTc, whereas BMI and physical activity within the range of 21.5–23.2 kg/m^2 were displayed as protective factors[25].

Persons with diabetes mellitus have increased QTc interval[26]. We evaluated the association between different glucose tolerance and prolonged QTc interval using the logistic regression model. Our results agreed with the previous findings that patients with IGR, a pre-diabetic condition, were correlated with QTc interval[25, 27]. However, surprisingly, impaired fasting glucose was not found to influence QTc interval significantly, which is not in consistent with other studies[28, 29]. The reason for this is probably because the participants in our study were from only one area and more women were recruited than man.

It was previously revealed that hyperglycemia may lead to QTc prolongation by several mechanisms including the stimulation of protein kinase C which causes reduced synthesis and release of endothelial derived nitric oxide[30]. This consequently results in a decrease in the activity of Na-K-ATPase. Perhaps the reduced nitric oxide bioavailability during hyperglycemia is responsible for decreased activity of Ca^{2}ATPase as well[31], an enzyme maintains a low concentration of Ca^{2} ions in the cell. Decreased activity of Na-K-ATPase increases the intracellular calcium concentration and extend QTc interval. There is also accumulating evidence suggests that a direct relationship between type 2 ryanodine receptor (RyR2) dysfunction in the endo/sarcoplasmic reticulum leading to altered intracellular calcium homeostasis, glucose intolerance, and impaired insulin secretion in patients with catecholaminergic polymorphic ventricular tachycardia[32]. Moreover, hyperglycemia is related to increased sympathetic activity as evident by increased plasma catecholamine concentrations[33]. Sympathetic stimulation unopposed by vagal activity may also induce ventricular electrical instability.

Impaired glucose regulation is widely considered with a relatively high risk for the future development of diabetes[34]. IGR should not be seen as an independent clinical entity but rather as a risk factor for diabetes and cardiovascular disease. Moreover, it has been well recognized that IGR is associated with hypertension, high triglycerides, low HDL cholesterol and visceral obesity. Therefore, elucidating the relationship of impaired glucose regulation and QTc interval and seeking effective management for all modifiable risk factors are of great importance.

In our study, pre-diabetes and diabetes appear to be independent risk factors for QTc interval prolongation after controlling the potential cofounders. QTc interval is notably associated with glucose metabolism indices (including FPS, PPS, HbA1c). In view of this, it is reasonable to consider whether QTc interval alone should become a novel target for clinical intervention.

The advance of the present study is that it evaluated the relationship between pre-diabetes and diabetes and QTc interval in such a large-scale population. The results of our study support the concept that postprandial glucose level elevations may have an important role in the pathogenesis of cardiovascular complications[25]. The vital role of hyperglycemia, especially postprandial, as an essential risk factor for QTc prolongation has been approved in

this study. In consistent with our results, postprandial glucose is considered to be a better predictive regarding cardiovascular mortality in comparison to fasting plasma glucose in the DECODE study [35].

Our study has some limitations. First, given the cross-sectional nature of the study design, a cause-effect relationship between abnormal glucose metabolism and QTc interval could not be verified. Further prospective studies are needed to analyze the potential pathophysiological mechanism of this correlation. Secondly, besides QTc interval, other markers of cardiac repolarization abnormalities, such as QT dispersion, were not evaluated. Thirdly, because our data were obtained from middle-aged and older subjects, and the gender proportions were unbalanced, it has yet to be seen whether our results can be generalized to younger populations or other ethnic groups. Finally, the QTc intervals were from one ECG which might not represent the true resting heart rate.

Conclusions

In summary, our findings suggested that increased risk of having abnormal glucose metabolism is intensively and independently associated with prolonged QTc interval in Chinese adults. As a conversant and accessible clinical parameter, abnormal glucose regulation can be used to monitor QTc interval in the population. Although longitudinal studies are needed, our results probably have vital public health meanings. Further research is still needed to verify whether glucose control among people with glucose intolerance may be useful in reducing QTc interval prolongation and ultimately reducing the risk of ventricular arrhythmia and sudden death.

List Of Abbreviations

QTc Corrected QT; IGR impaired glucose regulation; IFG impaired fasting glucose; IGT impaired glucose; tolerance; DM diabetes mellitus; WHR waist-to-hip ratio; BMI body mass index; SBP systolic blood pressure; DBP diastolic blood pressure; FPG fasting plasma glucose; 2hPPG 2-h post-load plasma glucose; HbA1c hemoglobin A1c; TC total cholesterol; TG triglycerides; LDL low-density lipoprotein-cholesterol; HDL high-density lipoprotein-cholesterol; IGR impaired glucose regulation; ALT alanine aminotransferase; AST aspertate aminotransferase; SCr serum creatinine.

Declarations

Ethics approval and consent to participate

Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine. The methods were carried out in accordance with the approved guidelines. Written informed consent was obtained from all participants before data collection.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

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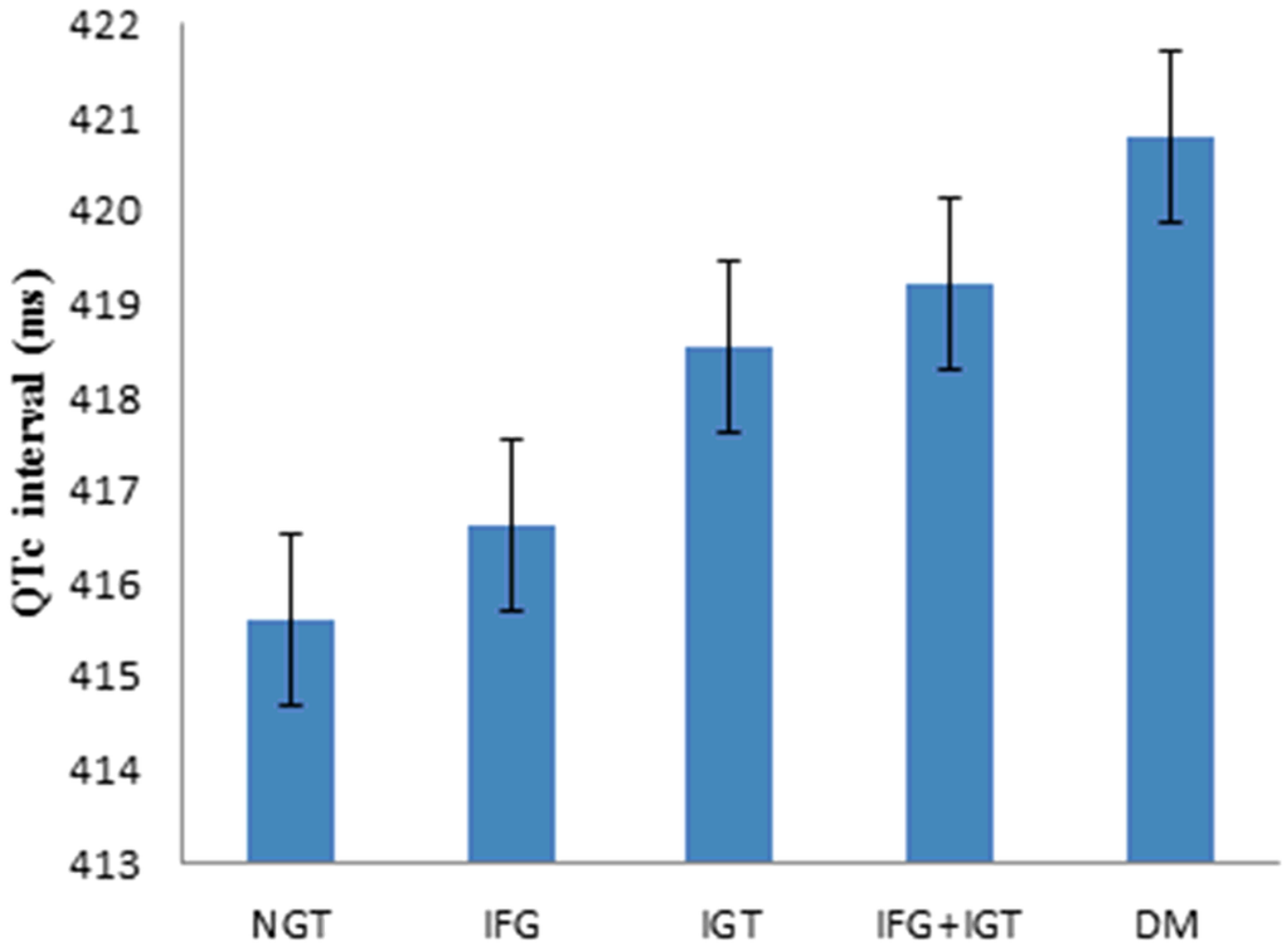
Figures

Figure 1

Adjusted means (±SEM) of QTc interval in subjects with NGR, IGR (isolated IFG, isolated IGT), combined IFG/IGT and diabetes mellitus (DM). Subjects with type 2 diabetes mellitus and IGR (isolated IFG, isolated IGT and IFG/IGT) had higher level of QTc interval than those with NGR (both $p < 0.0001$). There was no significant difference among the subgroups of IGR ($p = 0.35$) and between the IGR and type 2 diabetes mellitus groups ($p = 0.61$)