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ORIGINAL

The intriguing effects of time to glycemic goal in newly diagnosed type 2 diabetes after short-term intensive insulin therapy

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Abstract. Short-term intensive insulin therapy is effective for type 2 diabetes because it offers the potential to achieve excellent glycemic control and improve β-cell function. We observed that the time to glycemic goal (TGG) was adjustable. Original data of 138 newly diagnosed type 2 diabetic patients received intensive insulin therapy by continuous subcutaneous insulin infusion for 2-3 weeks were retrospectively collected. Subjects underwent an intravenous glucose tolerance test (IVGTT) and an oral glucose tolerance test (OGTT) pre and post treatment. The glycemic goal was achieved within 6 (4-8) days. Patients were divided into two groups by TGG above (TGG-slow) and below (TGG-fast) the median value. Patients in both groups had significantly better glycemic control. Compared with TGG-fast, TGG-slow required a few more total insulin and performed more improvement of HOMA-β and IVGTT-AUC_{Ins}, but less improvement of HOMA-IR and QUICKI. Multiple linear regression analysis revealed that TGG was always an explanatory variable for the changes (HOMA-β, IVGTT-AUC_{Ins}, HOMA-IR and QUICKI). The hypoglycemia prevalence was lower in TGG-slow (1.48% *vs*. 3.40%, $P<0.01$). Multivariate logistic regression analysis indicated that individuals in TGG-slow had a lower risk of hypoglycemia (adjusted OR, 0.700; 95% CI, 0.567-0.864; $P<0.05$). Multiple linear regression analysis confirmed that the ratio of the incremental insulin to glucose responses over the first 30 min during OGTT (ΔIns30/ΔG30), average insulin dose before achieving targets, initial insulin dose and LDL-c were independent predictors for TGG. It is intriguing to hypothesize that patients with fast time to glycemic goal benefit more in improving insulin sensitivity, but patients with slow time benefit more in improving β-cell function and reducing the risk of hypoglycemia.

Key words: Intensive insulin therapy, Type 2 diabetes, Time to glycemic goal, β-cell function, Hypoglycemia

HYPERGLYCEMIA serves as a consequence of impaired insulin release and action, meanwhile also impairs β-cell function and induces insulin resistance[1]. Glucose toxicity has been demonstrated clinically and has been investigated extensively in laboratory [2]. Short-time intensive insulin therapy can improve the underling pathophysiology in early type 2 diabetes mellitus by enabling sustained euglycemia and limiting cumulative exposure to chronic hyperglycemia [3-5]. After receiving this treatment, many patients will attain long-term glycemic remission, wherein the patients are able to maintain normal glucose levels without any antidiabetic medication.

Short-term intensive insulin therapy has been employed in the management of newly diagnosed type 2 diabetes in recent years, and this idea has been taken up by many doctors. In most published studies, intensive insulin therapy was administered by either continuous subcutaneous insulin infusion (CSII) or multiple daily injections. The treatment course was 2 to 3 weeks, few studies extended to 3 months [6]. There is no conclusive strategy how to control glucose reasonably during the course of therapy. We observed that the time to glycemic goal (TGG) was adjustable. For instance, the glycemic control goal was achieved by CSII within 6.3±3.9 days in 126 patients in the trail by Li *et al*, 2004 [7], 4.0±2.5 days in 133 patients by Weng *et al*, 2008 [8], 6.4±3.4 days in 16 patients by Hu *et al*, 2011 [9],

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3.7±1.8 days in 40 patients by Huang *et al*, 2013 [10], and 3.5±1.9 days in 104 patients by Liu *et al*, 2015 [11]. Some reports showed that the faster achievement of glycemic targets during therapy might be a predictor of sustained euglycemia [4]; nevertheless, that was just a result attached to other study purpose and only used a simple comparison regardless of confounding factors. Then TGG; "the sooner the better" or "haste makes waste"?

This study aimed to demonstrate the effects of TGG in newly diagnosed type 2 diabetic patients received intensive insulin therapy on glycemic control, β-cell function as well as the incidence of hypoglycemia.

Materials and Methods

Subjects

The original data came from the study, the impact of different course of insulin treatment on β-cell function in newly diagnosed type 2 diabetes after short-term intensive insulin therapy, registered with the Chinese Clinical Trial Registry, number ChiCTR-TRC-10001618. All 146 subjects were enrolled into study from October 2010 to April 2015. Among these patients, 8 patients were excluded (1 LADA patient, 5 T1DM patients and 2 T2DM patients who didn't reach the glycemic goal). The remaining 138 patients were under retrospective analysis. They were 46.6±8.5 years of age, with a BMI of 24.6±3.3kg/m^2 and HbA1c of 11.4±2.5%. The study was approved by the Institutional Review Board of the Sun Yat-sen Memorial Hospital affiliated to Sun Yat-sen University and all subjects had given written informed consent.

Study design

All patients were diagnosed type 2 diabetes according to WHO diagnostic criteria (1999) in department of endocrinology in our hospital and received short-term intensive insulin therapy with CSII. Patients were excluded if they had acute or severe chronic diabetic complications, severe intercurrent illness. Patients receiving antidiabetic treatment before the study or taking pharmacologic agents known to affect carbohydrate homeostasis were also excluded. The duration based on the clinical symptoms of diabetes such as polyuria, polydipsia, weight loss, etc. and the existence of diabetic microangiopathy such as diabetic retinopathy, nephropathy and neuropathy in the patients were estimated at the beginning of the study. Intensive insulin treatment by CSII was initiated using an insulin pump (MiniMed® Paradigm® 712) with insulin Lispro (Humalog). Initial insulin doses were 0.5-0.6 IU·kg^{-1}·d^{-1}. Total daily doses were divided into 50% of basal and 50% of bolus injection. The basal and boluses of insulin infusion were adjusted according to the fasting and postprandial of three meals capillary glucose levels [fasting blood glucose (FBG) and postprandial blood glucose (PBG)]. Daily insulin titration aimed to achieve the glycemic goal defined as FBG<6.1mmol/L and PBG<8.0mmol/L. Treatments were maintained for 10-14 days after achieving targets. And all patients were instructed for life style intervention. Daily blood glucose was monitored seven times per day (before and 2 hours after three meals, bedtime, and 0300 h if necessary) with a portable blood glucose meter during CSII treatment.

Measurements

At baseline fasting blood samples were obtained for measuring FBG, HbA1c, lipid profiles, liver and kidney function, etc. All Subjects underwent an intravenous glucose tolerance test (IVGTT) using 25g glucose and an oral glucose tolerance test (OGTT) using 75g glucose after an overnight fast on a different day before intensive insulin therapy. The second IVGTT was conducted in the following day at least 12 hours after insulin cessation. Patients were guided with diet and physical exercise only. The second OGTT was conducted the day after IVGTT. Blood samples for glucose and insulin were drawn both at 0, 3, 5, 7, 10 min after IVGTT and 0, 30, 60,120, 180 min after OGTT.

Measurement of plasma glucose, insulin, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), alanine aminotransferase, and creatinine was done using an autoanalyser (Beckman CX-7 Biochemical Autoanalyser, Brea, CA, USA). HbA1c was assayed by high-performance liquid chromatography (Bio-Rad, Hercules, CA, USA).

Calculations

Basic secretory function of β-cell was measured by Homeostasis Model Assessment of β-cell function (HOMA-β), HOMA-β=20×(fasting insulin [mIU/L])/(FBG[mmol/L]-3.5). The area under the curve (AUC) of insulin and acute insulin response (AIR) during IVGTT were used to evaluate the first phase insulin secretion of β-cell. The ratio of the incremental insulin to glucose responses over the first 30 min during OGTT

(ΔIns30/ΔG30) represented the early phase insulin secretion of β-cell. In addition, total β-cell secretory function was measured by the AUC of OGTT. The area under the insulin curve (IVGTT-AUC_{Ins} and OGTT-AUC_{Ins}) was calculated using trapezoidal estimation. Insulin sensitivity index was evaluated by Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI). HOMA-IR=FBG×(fasting insulin)/22.5; QUICKI=1/[logFBG+log (fasting insulin)]. The ratio between the hypoglycemia event times and the blood glucose monitoring times represented the incidence of hypoglycemia.

Statistical methods

According to the median time to reach the glycemic goal, the subjects were divided into two groups (TGG-slow and TGG-fast). To minimize the potential impact of confounding factors propensity analysis was carried out using logistic regression to create propensity scores [12]. The model was used to provide a one to-one nearest-neighbor match between the two groups of patients. The propensity analysis was established using the matching package within R Statistical Software (version 3.0.2).

Continuous variables were presented as means ± SD with the exception of skewed variables, which were presented as medians (interquartile ranges). Categorical variables were expressed as numbers (proportions). Non-normal distribution data (HOMA-β, HOMA-IR, IVGTT-AUC_{Ins}, OGTT-AUC_{Ins} and ΔIns30/ΔG30) were transformed into normal distribution data with natural logarithms. The results were compared in the propensity-matched sample. The paired *t*-tests was used to compare before and after CSII therapy in both groups, respectively. The independent samples *t*-test, the Wilcoxon rank-sum test and the chi-square test were used to compare between the two groups. Multiple linear regression models as functions of explanatory variables were identified. Univariate logistic regression analysis and multivariate logistic regression analysis were used to explore the independent effect of TGG on the incidence of hypoglycemia. A value of $P<0.05$ was considered to be statistically significant.

Results

Baseline characteristics

With CSII, the glycemic goal was achieved in 6 (4-8) days. The subjects were divided into the TGG-fast group with 6 days to target or less and the TGG-slow group with more than 6 days to target. The baseline demographic and clinical characteristics of the patients in the two groups are shown in Table 1.

Table 1 Baseline demographic and clinical characteristics in the two groups

	Before propensity matching			After propensity matching		
	TGG-fast (n=72)	TGG-slow (n=66)	*P*	TGG-fast (n=70)	TGG-slow (n=70)	*P*
Age (years)	47.0 ± 8.5	46.1 ± 8.6	0.551	47.1 ± 8.5	47.2 ± 8.4	0.976
Sex (male: female)	54:18	46:20	0.486	52:18	52:18	1.000
Duration of diabetes (months)	3 (1-12)	2.5 (0.6-9.8)	0.311	3 (1-12)	5 (1-12)	0.895
Systolic blood pressure (mmHg)	128.8 ± 14.1	132.2 ± 17.3	0.210	128.7 ± 14.2	130.6 ± 12.6	0.397
Diastolic blood pressure (mmHg)	81.7 ± 10.1	84.6 ± 9.9	0.089	81.6 ± 10.2	84.0 ± 9.8	0.158
BMI (kg/m^2)	24.4 ± 2.9	24.8 ± 3.8	0.457	24.4 ± 2.9	24.2 ± 2.7	0.759
FBG (mmol/L)	10.6 ± 3.2	12.4 ± 3.3	0.002 *	10.6 ± 3.2	10.6 ± 3.3	0.988
HbA1c (%)	11.1 ± 2.6	11.8 ± 2.2	0.109	11.1 ± 2.6	11.3 ± 2.2	0.663
TC (mmol/L)	5.6 ± 1.0	5.9 ± 1.4	0.127	5.6 ± 1.0	5.4 ± 1.2	0.295
TG (mmol/L)	1.5 (1.1-2.5)	2.1 (1.5-3.6)	0.003 *	1.5 (1.1-2.5)	1.7 (1.3-2.6)	0.253
HDL-c (mmol/L)	1.2 ± 0.3	1.2 ± 0.6	0.446	1.2 ± 0.3	1.2 ± 0.3	0.566
LDL-c (mmol/L)	3.5 ± 0.9	3.7 ± 1.1	0.425	3.6 ± 0.8	3.4 ± 1.0	0.213
Retinopathy	5 (6.9)	4 (6.1)	1.000	4 (5.7)	2 (2.9)	0.681
Nephropathy	1 (1.4)	5 (7.6)	0.104	1 (1.4)	1 (1.4)	1.000
Neuropathy	4 (5.6)	7 (10.6)	0.274	4 (5.7)	4 (5.7)	1.000
Daily insulin dosage ($IU \cdot kg^{-1} \cdot d^{-1}$)						
Initial dose	0.55 ± 0.11	0.55 ± 0.10	0.903	—	—	—
Average dose before achieving targets	0.61 ± 0.13	0.74 ± 0.16	<0.001 *	—	—	—
Average dose before CSII suspension	0.62 ± 0.15	0.76 ± 0.16	<0.001 *	—	—	—

* $P<0.01$ *vs*. TGG-fast group. Data are means ± SD, medians (interquartile ranges) or n (%). BMI, body mass index; FBG, fasting blood glucose; HbA1c, haemoglobin A1; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

Propensity score-matched patients were analyzed to adjust for any baseline differences. Before propensity score matching, there were significant differences in FBG (P=0.002) and TG (P=0.003) between the two groups. After propensity score matching, each group comprised 70 patients and there were no significant differences between the two groups for all baseline characteristics. The sum of the weighted observations still equaled to the original number of observations.

Glycemic control

The glucose excursions during the IVGTT and OGTT before and after CSII treatment are illustrated in Fig. 1A and Fig. 1B. Before the short-term intensive insulin therapy, the glycemic control was poor. After treatment, the glucose reduced obviously in the two groups (P<0.01). The data about daily insulin dosage (initial dose, average dose before achieving targets and average dose before CSII suspension) in the two groups have been shown in Table 1. Compared with TGG-fast, TGG-slow required a few more total insulin.

β-cell function and insulin resistance

β-cell function and the level of insulin resistance at baseline and after CSII treatment in the two groups are shown in Table 2. We also show the changes of β-cell function and insulin resistance indexes from the baseline after intensive insulin therapy. HOMA-β, AIR, IVGTT-AUC_{Ins}, ΔIns30/ΔG30 and OGTT-AUC_{Ins} were used for evaluating β-cell function as previously mentioned. All of these indexes were markedly improved after CSII in the two groups (P<0.01). Compared with TGG-fast, TGG-slow performed better improvement of the β-cell function. The increase of HOMA-β was 1.07±0.70 *vs*. 0.78±0.59, P<0.05. The increase of IVGTT-AUC_{Ins} was 0.51±0.46 *vs*. 0.31±0.51, P<0.05. In additional, we also found that TGG-slow had more improvement of AIR, ΔIns30/ΔG30 and OGTT-AUC_{Ins}, but no significant differences were observed. These differences may be related to the sample size and observation time. HOMA-IR and QUICKI were used for evaluating the degree of insulin resistance. Intensive treatment with CSII manifested lowered insulin resistance significantly in TGG-fast (P<0.01); however, no improvement was observed in TGG-slow (P>0.05).

Stepwise multiple linear regression analysis with DHOMA-β, DIVGTT-AUC_{Ins}, DHOMA-IR, DQUICKI (the HOMA-β, IVGTT-AUC_{Ins}, HOMA-IR, QUICKI after CSII subtracted from that before CSII) as the dependent variable respectively and TGG, sex, age, duration of diabetes, BMI, FBG, HbA1c, TC, TG, HDL-c, LDL-c, systolic blood pressure, diastolic blood pressure and average insulin dose before CSII suspension as the independent variables was conducted in order to determine the ability of the important attributes to estimate TGG in the changes of β-cell function and insulin resistance after intensive insulin therapy. We showed that TGG was always an explanatory variable for DHOMA-β (Table 3), DIVGTT-AUC_{Ins} (Table 4), DHOMA-IR (Table 5), and DQUICKI (Table 6) after adjusting for confounding covariates. The regression analysis revealed patients with the

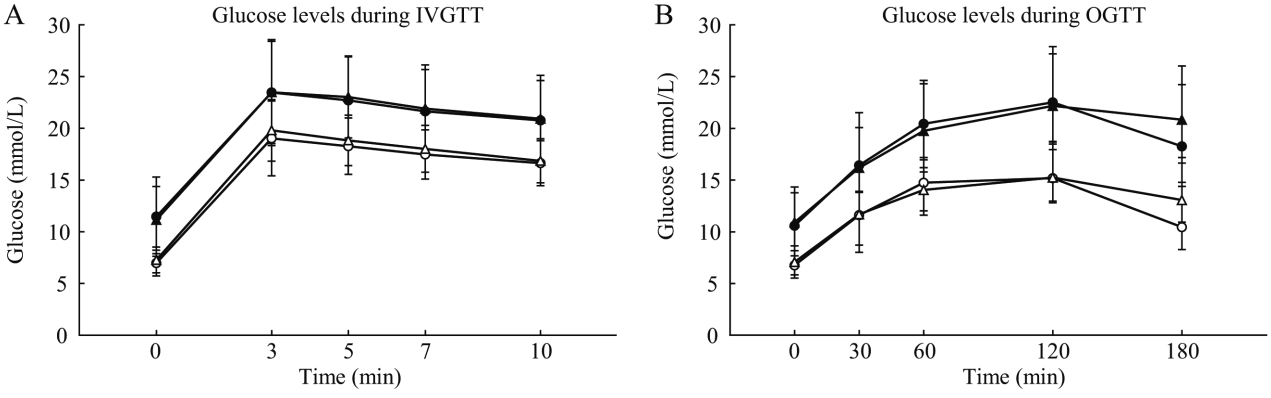

Fig.1 Means±SD for plasma glucose during the IVGTT (**A**) and OGTT (**B**) before and after intensive insulin therapy. IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test; CSII, continuous subcutaneous insulin infusion. After treatment, the glucose reduced obviously at 0, 3, 5, 7, 10 min of IVGTT and 0, 30, 60,120, 180 min of OGTT in both groups (all P<0.01). ●, TGG-fast, at baseline; ○, TGG-fast, after CSII; ▲, TGG-slow, at baseline; △,TGG-slow, after CSII.

Table 2 Islet β-cell function and insulin resistance indexes before and after intensive insulin therapy and the changes of the indexes after intensive insulin therapy in the propensity-matched sample

	TGG-fast			TGG-slow		
	baseline	After CSII	Change from baseline	baseline	After CSII	Change from baseline
Islet β-cell function index						
HOMA-β	2.64 ± 1.07	3.42 ± 0.86 *	0.78 ± 0.59	2.30 ± 0.73	3.37 ± 0.88 *	1.07 ± 0.70 §
AIR	0.28 (-0.42-1.58)	28.82 (12.14-47.98) *	26.86 (11.63-48.25)	0.56 (0.11-3.90)	27.08 (17.76-42.39) *	27.56 (16.32-41.09)
IVGTT-AUC_{Ins}	4.02 ± 0.80	4.33 ± 0.81 *	0.31 ± 0.51	3.89 ± 0.71	4.40 ± 0.60 *	0.51 ± 0.46 §
ΔIns30/ΔG30	0.12 ± 1.18	0.95 ± 0.97 *	0.83 ± 1.26	-0.61 ± 1.14	0.54 ± 0.85 *	1.16 ± 1.01
OGTT-AUC_{Ins}	3.61 ± 1.02	4.40 ± 0.65 *	0.79 ± 0.60	3.29 ± 0.87	4.11 ± 0.63 *	0.82 ± 0.57
Insulin resistance index						
HOMA-IR	0.87 ± 0.73	0.41 ± 0.72 *	-0.46 ± 0.47	0.50 ± 0.67	0.54 ± 0.57	0.04 ± 0.62 ‡
QUICKI	0.60 ± 0.12	0.68 ± 0.14 *	0.08 ± 0.09	0.66 ± 0.10	0.65 ± 0.10	0 ± 0.11 ‡

* P<0.01 *vs*. baseline; ‡ P<0.01, § P<0.05 *vs*. TGG-fast group. Change from baseline refers to the value after CSII subtract from that at baseline within-group. Data are means ± SD or medians (interquartile ranges). CSII, continuous subcutaneous insulin infusion; HOMA-β, Homeostasis Model Assessment of β-cell function; AIR, acute insulin response; IVGTT-AUC_{Ins}, AUC (area under the curve) of insulin during IVGTT (intravenous glucose tolerance test); ΔIns30/ΔG30, ratio of the incremental insulin to glucose responses over the first 30 min during OGTT (oral glucose tolerance test); OGTT-AUC_{Ins}, AUC of insulin during OGTT; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; QUICKI, Quantitative Insulin Sensitivity Check Index.

Table 3 Multiple linear regression analysis for DHOMA-β

Variable	Standardized coefficients (β)	P
(Constant)		0.002
HbA1c	0.522	<0.001
TGG	0.150	0.043

Adjusted R-squared: 0.3067, F=29.982, P<0.001. DHOMA-β, the HOMA-β after CSII subtract from that at baseline.

Table 4 Multiple linear regression analysis for DIVGTT-AUC_{Ins}

Variable	Standardized coefficients (β)	P
(Constant)		0.002
TGG	0.304	<0.001

Adjusted R-squared: 0.0854, F=13.040, P<0.001. DIVGTT-AUC_{Ins}, the IVGTT-AUC_{Ins} after CSII subtract from that at baseline.

Table 5 Multiple linear regression analysis for DHOMA-IR

Variable	Standardized coefficients (β)	P
(Constant)		0.002
TGG	0.419	<0.001
FBG	-0.321	<0.001
Diastolic blood pressure	0.214	0.006

Adjusted R-squared: 0.2866, F=18.004, P<0.001. DHOMA-IR, the HOMA-IR after CSII subtract from that at baseline.

Table 6 Multiple linear regression analysis for DQUICKI

Variable	Standardized coefficients (β)	P
(Constant)		0.021
TGG	-0.386	<0.001
FBG	0.263	<0.001
Systolic blood pressure	-0.251	<0.001
TC	0.155	0.039

Adjusted R-squared: 0.3263, F=16.862, P<0.001. DQUICKI, the QUICKI after CSII subtract from that at baseline.

slow time to reach the glycemic goal would benefit more in improving β-cell function but benefit less in improving insulin sensitivity.

Hypoglycemia

The hypoglycemia prevalence was lower in TGG-slow than TGG-fast during 2 week's CSII treatment (1.48% *vs*. 3.40%, P<0.01). Univariate logistic regression analysis indicated that individuals whose time to target was slow had a lower risk of hypoglycemia (OR, 0.815; 95% CI, 0.711-0.934; P<0.01), even after adjusting for potential confounders by multivariate analysis, including sex, age, duration of diabetes, BMI, FBG, HbA1c, TC, TG, HDL-c, LDL-c and average insulin dose before CSII suspension (adjusted OR, 0.700; 95% CI, 0.567-0.864; P<0.05).

A multiple linear regression analysis with TGG as the dependent variable

TGG was used as the dependent variable, and the independent variables were sex, age, duration of diabetes, BMI, FBG, HbA1c, TC, TG, HDL-c, LDL-c, initial insulin dose, average insulin dose before achieving targets, HOMA-β, AIR, IVGTT-AUC_{Ins}, ΔIns30/ΔG30, OGTT-AUC_{Ins}, HOMA-IR and QUICKI. We showed that ΔIns30/ΔG30, average insulin dose before achieving targets, initial insulin dose and LDL-c were independent predictors for TGG in a stepwise multiple linear regression analysis (Table 7).

Table 7 Multiple linear regression analysis for TGG

Variable	Standardized coefficients (β)	*P*
(Constant)		<0.001
ΔIns30/ΔG30	-0.273	0.004
Average insulin dose before achieving targets	0.616	<0.001
Initial insulin dose	-0.396	0.001
LDL-c	-0.210	0.021

Adjusted R-squared: 0.408, F=15.841, $P<0.001$.

Discussion

The objective of this study was to comparatively evaluate the efficacy and safety of TGG in newly diagnosed type 2 diabetic patients received intensive insulin therapy. As shown by our data (Fig. 1 and Table 2), intensive insulin therapy by CSII was effective at glycemic control and improved β-cell function and insulin sensitivity regardless of TGG. Consistent new emerging evidence suggests that hyperglycemia impairs both insulin action and insulin secretion. Hyperglycemia can leave an early imprint in cells [13]. The "metabolic memory" can appear even when glycemia is normalized. This phenomenon suggests the need for a very early aggressive treatment aiming to "normalize" the metabolic control. Short-term intensive insulin therapy resulted in both improved β-cell function and insulin resistance with rapid correction of hyperglycemia. Various types of evidence supporting the use of short-term intensive insulin therapy in patients with newly diagnosed type 2 diabetes are available [7, 8, 11, 14]. Furthermore, CSII offers insulin replacement that best mimics physiologic insulin secreting pattern, providing time and "clean" internal environment for β-cell rest and repair. So it is not surprising that glycemic control, β-cell function and insulin resistance were improved significantly by CSII in all subjects.

To date, no study has been conducted to directly assess the impact of TGG during intensive insulin therapy. More intriguingly, our results showed that TGG had a different impact on β-cell function and insulin resistance. Compared with TGG-fast, TGG-slow performed more improvement of the basic secretory function of β-cell and the first phase insulin secretion, but less improvement of insulin resistance.

The underlying mechanism is not fully understood. Intensive insulin therapy brings about a beneficial effect in relieving glucotoxicity and lipotoxicity. Some studies suggested that cellular and whole-body insulin resistance in type 2 diabetes was reversible. Chronic hyperglycemia *per se* was also able to induce and aggravate insulin resistance. Insulin-stimulated glucose transport was impaired under hyperglycaemic conditions but could be normalized following a physiological glucose concentration [15]. In our subjects, TGG-fast patients improved more insulin sensitivity by correcting hyperglycemia. Thus, the shorter the period of antecedent glucotoxicity, the more quickly the full recovery of insulin sensitivity.

However, β-cell is susceptible to acute glucose fluctuations. On the study of β-cell, studies [16, 17] found that intermittent high glucose caused a significant decrease of glucose-stimulated insulin secretion and apoptosis was also significantly increased by intermittent high glucose exposure. Similarly, Wu *et al*. [18] reported that Glucose-lowering rate influenced cardiomyocyte proliferation and apoptosis. Lowering blood glucose levels slowly was good for cardiomyocyte. These indicated the possibility of similar situation in β-cell in TGG-fast patients. Although plasma glucose concentration is controlled strictly within a narrow range after achieving targets, the plasma glucose concentration often changes markedly during the first few days, especially in TGG-fast. Lowering blood glucose level fast is harmful. This risk would offset the benefits to some extent in secretory function of β-cell. There have not been fully studies about this question so far.

Clinical iatrogenic hypoglycemia is a problem for many people with diabetes treated with insulin. In the current results, TGG-slow individuals carried a lower risk of hypoglycemia. It seems that patients will derive more safety from intensive insulin treatment with

gradual time to target in controlling blood glucose. Some researchers suggested that a gradual decrease in blood glucose might be beneficial. For patients with T2DM and CHD, an excessively fast glucose-lowering rate could impair left ventricular systolic function. LVEF increased when the glucose-lowering rate was ≤ 6 mmol·L^{-1}·d^{-1} in the T2DM group, and increased when it was ≤ 4 mmol·L^{-1}·d^{-1} in the T2DM-CHD group; Otherwise, it declined [19]. Additionally, the regulatory response of the retinal circulation to oxygen breathing was improved significantly in normoglycemia, particularly in those patients whose blood glucose level was decreased at a slower rate [20].

Compared with TGG-fast, TGG-slow patients were accompanied by higher FBG and TG level (Table 1). Both glucotoxicity and lipotoxicity contribute to the progressive loss of β-cell function. Given the role that hyperglycaemia as well as elevated plasma FFA concentrations play in the progression of diabetes [1], these findings suggested that the relatively poor patients would have slow time to reach the excellent blood glucose. In our study, the multiple linear regression analysis showed that patients with fast time to reach the glycemic goal might have better early phase insulin secretion of β-cell (ΔIns30/ΔG30), more initial insulin dose, higher LDL-c level, but less insulin dose during CSII before achieving targets (Table 7). As mentioned earlier, we recognized TGG was adjustable. The management strategy of insulin is a major clinical challenge. There is no always optimal dose of the setting of insulin initiation and titration [21]. Long period of clinical experience suggested doctors, as unmeasured factor, could adjust the TGG to some extent. While an aggressive physician may take relatively higher dose of insulin as initial therapy as the presentation of TGG-fast, a mild doctor may prefer lower dose of insulin as initial treatment as the presentation of TGG- slow.

There are some limitations in this study. First, like in the majority of retrospective investigations, the main limitation of our study is the absence of randomization. Second, all subjects were from one center of China with relatively high blood glucose (HbA1c 11.4±2.5%). The number of subjects was relatively small, such that the results might not be generalizable to other populations. Third, because of shortage of long-term observation, we cannot assess prognosis. The results need to confirm with a larger study and a better methodology before being considered as a routine clinical option.

In conclusion, this study highlights the feasibility of administering short-term intensive insulin therapy early in type 2 diabetes. Besides, we demonstrated that patients with fast time to reach the glycemic goal would benefit more in improving insulin sensitivity; patients with the slow time to target would benefit more in improving β-cell function and safety with a lower risk of hypoglycemia. These study findings arouse the understanding of the clinical and pathophysiological aspects of intensive insulin therapy.

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Disclosure

The authors declare that they have no conflicts of interest associated with this research.

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