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ORIGINAL ARTICLE

Lower mean blood glucose during short-term intensive insulin therapy is associated with long-term glycemic remission in patients with newly diagnosed type 2 diabetes: Evidence-based recommendations for standardization

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ABSTRACT

Aims/Introduction: Optimal glycemic targets during short-term intensive insulin therapy in patients with newly diagnosed type 2 diabetes are not standardized. The present study was carried out to determine the optimal glycemic targets during therapy by analyzing the impacts of glucose levels on therapeutic outcomes.

Materials and Methods: A total of 95 individuals with newly diagnosed type 2 diabetes were enrolled. Short-term intensive insulin therapy was carried out using an insulin pump to achieve and maintain glycemic targets (fasting blood glucose ≤6.0 mmol/L, 2-h postprandial blood glucose ≤7.8 mmol/L) for 14 days, with daily eight-point capillary blood glucose profiles recorded. Patients were followed up for 1 year after discharge.

Results: In most participants, the mean blood glucose and glycemic excursion parameters during the therapy were controlled within the normal range. Mean blood glucose was independently associated with amelioration of acute insulin response ($r = -0.25$, $P = 0.015$) and 1-year remission (odds ratio 0.12, 95% confidence interval 0.034–0.426), but negatively associated with more level 1 hypoglycemia ($r = -0.34$, $P = 0.001$), although major hypoglycemia was rare. Among mean blood glucose tertiles, patients in the middle (68.7%) and lower (75.0%) tertiles had a higher 1-year remission rate compared with the upper tertile (32.3%, both $P < 0.001$), whereas only the middle tertile did not have increased hypoglycemia compared with the upper tertile (8.1 ± 5.4 vs 7.2 ± 3.9 events/person, $P = 0.48$).

Conclusions: Stricter glycemic control during short-term intensive insulin therapy produced more remission despite self-manageable hypoglycemia. Based on glycemic parameters in the middle mean tertile, we propose new glycemic targets that are approximately 0.4 mmol/L lower than current the targets, as long-term benefit outweighs short-term risks.

INTRODUCTION

Early and sustained perfect glycemic control is a key challenge because of the inexorable decline of β-cell function after diagnosis, albeit various hypoglycemic agents are applied[1]. Despite newer and costlier hypoglycemic agents being utilized, the quality of blood glucose management is not accordingly improved under the current stepwise upgrading regimen for hyperglycemia management. In the USA, the proportion of patients with glycated hemoglobin (HbA1c) <7% declined and the proportion of patients with HbA1c >9% increased from 2006 to

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2013[2]. Trends are similar in China, where more complicated regimens are accompanied with even worse glycemic control, especially in patients with longer disease duration[3]. New therapies aiming at restoration of β-cell function from the beginning of diagnosis should be helpful in optimizing long-term glycemic control, reducing long-term medical costs and delaying chronic complications.

In recent years, short-term intensive insulin therapy (SIIT) has been shown to reverse β-cell dysfunction by the elimination of glucotoxicity and subsequent β-cell overload (β-cell rest effect) in newly diagnosed type 2 diabetes[4,5]. In our studies as well as those from other centers, SIIT was able to induce glycemic remission for >1 year without antihyperglycemic medicine in approximately 50% of patients with newly diagnosed type 2 diabetes, with β-cell function and insulin sensitivity remarkably ameliorated[6–9]. SIIT was therefore recommended by the current Chinese guideline as a first-line therapy for patients with newly diagnosed type 2 diabetes whose blood glucose is remarkably high[10].

The procedure of SIIT, however, still requires standardization and optimization. Heterogeneity in the execution of SIIT limits comprehensive application of this therapy. For example, SIIT was delivered with different methods (multiple daily injection or insulin pump), and lasted for various periods (from 2 weeks to >3 months) in different centers. Most importantly, the glycemic targets during SIIT are also to be unified. Therefore, guidelines that can be implemented in clinical practice that optimize benefit and reduce risk (hypoglycemia, weight gain, etc.) are required to overcome clinical inertia and facilitate patient acceptance and adherence[5].

Because β-cells are unlikely to fully recover under constant metabolic and glucotoxic distress, blood glucose should be normalized to levels at which endogenous insulin secretion is adequately suppressed to promote complete β-cell rest. As blood glucose levels around the upper limit of the normal range are sufficient to enhance insulin secretion and lead to attenuation of the acute insulin response[11,12], very strict glycemic targets should be considered on the premise of minimizing the risk of hypoglycemia, particularly clinically important episodes newly defined by the American Diabetes Association/European Association for the Study of Diabetes[13]. This hypothesis is supported by results from our previous randomized controlled trial[8], in which patients treated with SIIT had higher long-term remission rates and better β-cell recovery compared with those treated with an insulin secretagogue-based oral hypoglycemic agent regimen, which lowered blood glucose by stimulating residual β-cells.

Obviously, glycemic targets recommended by guidelines for managing chronic hyperglycemia (fasting blood glucose [FBG] <7 mmo/L, 2-h postprandial blood glucose [2hBG] <10 mmol/L, HbA1c <7%) are apparently not sufficient in the context of SIIT, as achieving HbA1c targets of 7% was unable to delay β-cell failure in the intensive treatment group of the UK Prospective Diabetes Study[14]. Near-euglycemia (FBG <6.0 mmol/L and 2hBG <8.0 mmol/L)[8,9,15,16] was set as the glycemic target during SIIT in most studies[6–9], though with some exceptions[17]. These targets are practically effective; but they are merely artificial and require further investigation.

Another major concern when applying SIIT is hypoglycemia. In large clinical trials, intensive glycemic control was always accompanied with an increased incidence of hypoglycemia[14,18,19]. Hypoglycemia is associated with glucose fluctuations, numerous adverse events and even increased mortality[20]. In previous reports, some hypoglycemic episodes were seen during SIIT[8,15]. However, to our knowledge, a detailed description of hypoglycemic events, as well as how hypoglycemia affects clinical outcomes has not been previously described, although this is important for making clinical decisions on setting glycemic targets and titrating the insulin dose.

Therefore, by investigating glycemic parameters (overall glycemic control as well as glycemic fluctuation) and hypoglycemic episodes during SIIT, we carried out the present study to analyze the impact of blood glucose levels during SIIT on clinical outcomes, hereby providing useful information on reconsidering novel glycemic targets during SIIT and its standardization.

METHODS

Participants

Data on participants were extracted from two independent randomized controlled trials (NCT00948324 and NCT01471808) carried out in the endocrinology department of The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, from June 2007 to May 2015. NCT00948324 was designed to evaluate whether short-term continuous subcutaneous insulin infusion (CSII) combined with metformin, rosiglitazone or α-lipoic acid had better outcomes compared with CSII alone, whereas NCT01471808 was carried out to compare the effect of CSII plus insulin sensitizers (pioglitazone + metformin) or sitagliptin with CSII alone. Only data of CSII alone groups in both studies were pooled for analysis to avoid the influence of other combined medicine. The recruitment criteria of the studies has been described elsewhere[15,21]. Briefly, patients who were diagnosed as type 2 diabetes according to criteria of the World Health Organization (1999)[22] were eligible if they were drug naïve, aged between 25 and 70 years, had body mass index (BMI) between 21 and 35 kg/m^2, as well as fasting plasma glucose between 7.0 and 16.7 mmol/L. Exclusion criteria were acute or severe chronic diabetic complications, severe concomitant diseases, long-term use of medications that are known to influence glycemic level (systemic glucocorticoid etc.) and positive for antibodies against glutamic acid decarboxylase. In total, 104 patients with newly diagnosed type 2 diabetes were enrolled. Nine individuals were excluded because of loss to follow up and (n = 5) or incomplete blood glucose data (n = 4). Clinical data for the remaining 95 patients were analyzed. This research was approved by the research ethics board of Sun Yat-Sen University. Signed informed consent was obtained from each participant.

Study design

The two studies from which the participants were enrolled shared exactly the same SIIT protocol and similar study design[15]. Briefly, all patients were admitted to hospital at diagnosis. After a run-in period of 2–3 days, baseline assessments were carried out and insulin lispro (Humalog, Eli Lilly and Company, Indianapolis, Indiana, USA) or insulin aspart (Novo Nordisk, Bagsværd, Denmark) was administered using an insulin pump (Medtronic Inc., Minneapolis, Minnesota, USA) with an initial total daily dose of 0.4–0.5 IU/kg. Half of the total daily dose was delivered evenly throughout 24 h as basal insulin; the other half was assigned equally before each meal. The insulin infusion regimen was titrated according to capillary blood glucose values, which were measured eight times daily (before and 2 h after three meals, at bedtime, and 3.00 AM), in order to control blood glucose within predefined targets (FBG/pre-meal blood glucose between 4.4 mmol/L and 6.0 mmol/L, and 2hBG between 4.4 mmol/L and 7.8 mmol/L). Blood glucose was maintained within these targets for an additional 14 days (maintenance phase). Afterwards, insulin was stopped after the last dose before supper, and baseline measurements were repeated the next day (at least 15 h after the cessation of insulin therapy).

During hospitalization, food intake advice was provided by nutritionists to make sure carbohydrates, proteins and fat accounted for 50–60%, 10–15% and 20–30% of total calories, as was the recommended guideline[10]. Patients were encouraged to take a 1-h walk after each meal to facilitate postprandial blood glucose control. After cessation of CSII, lifestyle modifications were recommended to be maintained. Participants were followed monthly for 3 months and every 3 months thereafter with capillary blood glucose monitoring. Glycemic remission was defined as FBG <7.0 mmol/L and 2hBG <10.0 mmol/L without any antihyperglycemic agents. Once hyperglycemia relapse was detected, fasting and postprandial plasma blood glucose were measured 1 week later. If hyperglycemia relapse was reconfirmed, standard antihyperglycemic treatment was started immediately according to current guidelines[10].

Blood sampling and measurements

Anthropometric data, such as bodyweight, height and waist circumference, were recorded before and after CSII. Venous blood was drawn for measurements of lipid profiles, fasting and postprandial plasma glucose (2 h after breakfast). An intravenous glucose tolerance test was carried out the next morning after overnight fasting as previously described[9]. Briefly, 50 mL of 50% glucose solution was administered intravenously. Serum samples were obtained before and 1, 2, 4, 6 and 10 min after glucose injection for insulin assay. Acute insulin response (AIR) was calculated as the incremental trapezoidal area during the first 10 min of the intravenous glucose tolerance test. Homeostasis model assessment was also applied for estimation of β-cell function (HOMA-β) and insulin resistance (HOMA-IR). All laboratory tests were carried out in the Central Clinical Lab of the First Affiliated Hospital of Sun Yat-Sen University.

Everyday, eight-point capillary blood glucose values during the maintenance phase (after predefined glycemic targets achieved) were recorded. Overall glucose control was evaluated by mean blood glucose (MBG), which is calculated as the arithmetic average of all eight-point glucose values. Glucose variability was evaluated with the standard deviation of blood glucose, as well as the mean amplitude of glycemic excursions (MAGE), which was calculated as the arithmetic mean of positive glycemic excursions that were greater than one standard deviation of all eight glycemic values.

Definition of hypoglycemia

Hypoglycemia episodes were reported according to the recent 2017 joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes[13]. Level 2 (major) hypoglycemia was defined as a blood glucose level of <3.0 mmol/L with or without symptoms. Episodes accompanied with cognitive impairment requiring assistance of another person for recovery was defined as level 3 (severe) hypoglycemia. Events of blood glucose with an alert value of ≤3.9 mmol/L were also reported (level 1 hypoglycemia).

Statistical analysis

Normally distributed data are presented as mean ± standard deviation values; non-normally distributed data are presented as the median (interquartile range). One-way ANOVA or Student's *t*-test was used to compare the differences of normally distributed data, whereas the Kruskal–Wallis *H*-test or Mann–Whitney test were applied for non-normally distributed data. Associations of variables were assessed with Pearson correlation (normally distributed data)/Spearman's correlation (non-normally distributed data). The χ^2-test was used for comparison of proportions. A stepwise logistic regression was applied to determine predictors of remission. Kaplan–Meier curves were plotted for time-to-event distributions. A Cox proportional hazards model was applied to estimate the hazard ratio of risk factors. All statistical procedures were accomplished with SPSS software for Windows version 19.0 (SPSS, Chicago, Illinois, USA) and software GraphPad Prism version 6.0 (GraphPad, La Jolla, California, USA).

RESULTS

Effects of SIIT on patients with newly diagnosed type 2 diabetes

The mean age of the patients was 47.4 ± 9.5 years, with a mean BMI of 25.1 ± 3.0 kg/m^2 and mean HbA1c of 11.2 ± 2.2% (99 ± 24 mmol/mol). Predefined glycemic targets (FBG/pre-meal blood glucose of 4.4–6.0 mmol/L, 2hBG 4.4–7.8 mmol/L) were achieved in 3 days (3 days). MBG, MAGE and SDBG during the maintenance phase were 5.98 ± 0.49 mmol/L, 3.23 mmol/L (1.21 mmol/L) and 1.64 ± 0.45 mmol/L, respectively. In most cases, these glycemic parameters were controlled

below the upper limit of normal reference value for the Chinese NGT population (Figure 1a)[23,24]. As shown in Table 1, after insulin therapy was stopped, blood glucose levels were significantly lower than baseline, accompanied by remarkably enhanced β-cell function (measured with AIR and HOMA-β) and improvement of insulin sensitivity (measured with HOMA-IR), which were in accordance with previous studies[8,9].

During long-term follow up, 56 patients (58.9%) had sustained optimal glycemic control for at least 1 year (remission group), whereas others did not (non-remission group). Similar to previous studies[8,9], patients in the remission group were younger in age, and had greater bodyweight reduction, better β-cell function recovery and insulin sensitivity improvement (Table 1). Compared with the non-remission group, the remission group had significantly lower blood glucose in each of the eight monitoring points when daily finger-tip blood glucose was measured during SIIT (Figure 1b). Thus, both MBG and glucose variability before and after meals (assessed by MAGE and SDBG) in the remission group were lower than those in the non-remission group (Table 1).

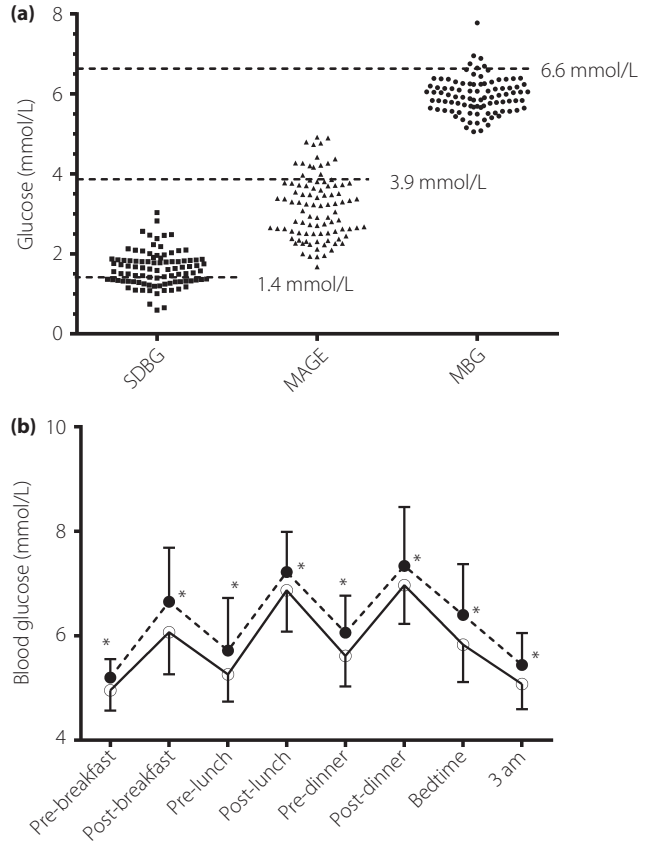

Figure 1 | Blood glucose control during maintenance phase of short-term intensive insulin therapy in patients with newly diagnosed type 2 diabetes. (a) The mean blood glucose (MBG), mean amplitude of glucose excursion (MAGE) and standard deviation of blood glucose (SDBG) of all participants during short-term intensive insulin therapy were compared with the upper limit of normal value of respective parameters in Chinese adults. (b) Glycemic profiles captured with eight-point capillary blood glucose monitoring in the remission group and non-remission group during short-term intensive insulin therapy. *$P < 0.05$ for comparison between the two groups.

Mean blood glucose, rather than glycemic fluctuation variables, was associated with better glycemic outcome after early SIIT

In order to determine possible predictors for glycemic remission, we carried out a stepwise logistic regression analysis. After adjustment for BMI, baseline AIR and HOMA-IR, both MBG (odds ratio 0.12, 95% confidence interval [CI] 0.034–0.43, $P = 0.001$) and HOMA-β before CSII (odds ratio 1.04, 95% CI 1.00–1.08, $P = 0.034$) were independently associated with 1-year remission, but none of the parameters regarding glucose excursion (MAGE, SDBG) were a predictor in the final model. MBG was negatively correlated with ΔAIR ($r = -0.25$, $P = 0.015$) and positively correlated with ΔHOMA-IR ($r = 0.21$, $P = 0.045$). No significant association was found between MBG and ΔHOMA-β, or with baseline parameters (fasting plasma glucose, postprandial plasma glucose, HbA1c, HOMA-β, HOMA-IR or AIR).

Hypoglycemia episodes during SIIT

Level 2 hypoglycemia occurred in just 36.8% of all participants (35/95). In total, 49 episodes of level 2 hypoglycemia (0.52 ± 0.80 episodes per person on average) were recorded throughout the whole SIIT procedure. All episodes of level 2 hypoglycemia were corrected with intake of carbohydrate on the participants' own without medical assistance of others, and no level 3 hypoglycemia was reported. The remission and non-remission groups had similar frequency of level 2 hypoglycemia (0.43 ± 0.68 vs 0.64 ± 0.93 episodes/person, $P = 0.20$).

On average, the frequency of level 1 hypoglycemia (blood glucose ≤3.9 mmol/L) was 8.7 ± 5.3 events per person in all participants. Approximately one-third of the events (36.1%) were asymptomatic, but detected by capillary blood glucose monitoring, whereas the rest were symptomatic. The frequency of blood glucose ≤3.9 mmol/L was negatively associated with MBG ($r = -0.34$, $P = 0.001$), but was similar between the remission and non-remission groups (8.6 ± 5.2 vs 8.8 ± 5.6 events, respectively, $P = 0.42$).

Patients in the middle MBG tertile had higher remission rate without increased risk of hypoglycemia

As lower MBG during SIIT was associated with both beneficial outcome (glycemic remission) and unfavorable events (level 1 hypoglycemia), it would be clinically helpful to search for new glycemic targets by balancing the benefits and risks. We categorized the participants into three groups according to the MBG tertiles to which the patients fell into (Table 2). The three MBG tertiles had similar baseline clinical characteristics, except

Table 1 | Effects of short-term intensive insulin therapy on clinical parameters of patients with newly diagnosed type 2 diabetes

	Overall (n = 95)	Remission group (n = 56)	Non-remission group (n = 39)	P
Age (years)	47.4 ± 9.5	45.8 ± 9.0	49.7 ± 9.9	0.049
Sex (male/female)	66/29	42/14	24/15	0.16
BMI (kg/m^2)				
Before SIIT	25.1 ± 3.0	25.4 ± 2.9	24.7 ± 3.2	0.24
After SIIT	24.8 ± 2.9**	24.9 ± 2.7**	24.6 ± 3.2	0.60
Waist circumference (cm)				
Before SIIT	91.0 ± 8.2	91.8 ± 8.6	89.7 ± 7.5	0.22
After SIIT	89.0 ± 8.5**	89.4 ± 8.7**	88.3 ± 8.2*	0.20
HbA1c, % (mmol/mol)				
Before SIIT	11.2(99) ± 2.2(24)	10.9(96) ± 2.1(23)	11.7 (104) ± 2.3(26)	0.07
After SIIT	9.4(79) ± 1.7(19)**	9.1(76) ± 1.6(17)**	9.8(84) ± 1.8(19)**	0.04
Fasting plasma glucose (mmol/L)				
Before SIIT	11.8 ± 3.1	11.3 ± 3.2	12.6 ± 2.8	0.05
After SIIT	6.8 ± 1.7**	6.1 ± 0.8**	7.7 ± 2.1**	<0.001
Postprandial glucose (mmol/L)				
Before SIIT	18.6 ± 5.9	18.0 ± 6.2	19.4 ± 5.4	0.26
After SIIT	8.8 ± 3.0**	7.6 ± 2.0**	10.7 ± 3.2**	<0.001
MBG (mmol/L)	6.0 ± 0.5	5.8 ± 0.4	6.2 ± 0.6	<0.001
SDBG (mmol/L)	1.6 ± 0.5	1.5 ± 0.4	1.8 ± 0.5	0.006
MAGE (mmol/L)	3.2 (1.2)	2.81 (1.1)	3.4 (1.4)	0.047
AIR (μU/mL·min)				
Before SIIT	−9.8 (23.4)	−9.9 (23.6)	−9.1 (19.3)	0.41
After SIIT	51.7 (58.6)**	56.3 (85.7)	29.0 (55.3)**	0.006
ΔAIR (μU·min/mL)	65.7 (74.5)	77.1 (82.9)	36.9 (43.5)	0.002
HOMA-β				
Before SIIT	17.9 (19.4)	20.1 (21.5)	12.2 (16.6)	0.005
After SIIT	44.3 (38.0)**	57.5 (47.1)**	38.2 (29.7)**	0.003
ΔHOMA-β	28.2 (29.5)	29.2 (30.4)	26.3 (28.5)	0.35
HOMA-IR				
Before SIIT	3.2 (2.3)	3.5 (2.4)	2.7 (2.8)	0.16
After SIIT	2.1 (1.5)**	1.9 (1.2)**	2.1 (1.4)*	0.07
ΔHOMA-IR	−1.0 (2.1)	−1.5 (1.9)	−0.3 (1.8)	0.002

*P < 0.05 compared with baseline. **P < 0.001 compared with baseline. AIR, acute insulin response; BMI, body mass index; HbA1c, glycated hemoglobin A1c; HOMA-β, homeostasis model assessment for β-cell function; HOMA-IR, homeostasis model assessment for insulin resistance; MAGE, mean amplitude of glycemic excursions; MBG, mean blood glucose; SDBG, standard deviation of blood glucose; SIIT, short-term intensive insulin therapy.

those in the lower MBG tertile had a lower mean age and slightly higher BMI than the other two groups.

After SIIT, the lower and middle MBG tertile groups had higher HOMA-β and better △AIR than the upper tertile (Table 2). Compared with the lower MBG tertile group, patients in the upper MBG tertile (hazard ratio 3.60, 95% CI 1.58–8.25, P = 0.002), but not those in the middle MBG tertile (hazard ratio 1.35, 95% CI 0.53–3.42, P = 0.53) had a significantly higher risk for hyperglycemia relapse. The 1-year remission rates were similar in the lower and middle MBG tertile groups (75.0 and 68.7% respectively, P = 0.78), but were lower in the upper MBG tertile group (32.3%, P < 0.001 when compared with either of the other tertiles). Furthermore, the incidence of level 1 hypoglycemia was higher in the lower MBG tertile (10.8 ± 5.9 events/person) compared with the middle and upper MBG tertile groups (8.1 ± 5.4 vs 7.2 ± 3.9 events/person respectively, P = 0.007 and 0.045 compared with the lower MBG tertile, respectively, Figure 2), with no significant difference found in the latter two groups (P = 0.48). The incidence of level 2 hypoglycemia was similar among MBG categories (0.56 ± 0.88, 0.47 ± 0.72 and 0.52 ± 0.81 episodes/person for the lower, middle and upper tertiles, respectively, P = 0.90).

DISCUSSION

Various studies, including our own, have shown that SIIT can induce remission in patients with newly diagnosed type 2 diabetes; to our knowledge, this is the first study to describe daily details of blood glucose profiles and hypoglycemia incidence during SIIT in patients with newly diagnosed type 2 diabetes

Table 2 | Clinical characteristics of mean blood glucose categories

	Lower tertile	Middle tertile	Upper tertile	*P*
MBG (mmol/L)[†‡§]	5.5 ± 0.2	6.0 ± 0.1	6.5 ± 0.5	<0.001
Age (years)	43.3 ± 8.6	50.3 ± 9.7	48.7 ± 9.1	0.007
BMI (kg/m^2)[†‡]	26.6 ± 2.9	24.8 ± 2.6	23.8 ± 2.9	<0.001
Waist circumference (cm)	93.8 ± 9.0	91.1 ± 5.79	87.9 ± 8.5	0.16
Baseline HbA1c (%)	11.0 ± 2.4	11.1 ± 2.1	11.7 ± 2.1	0.44
mmol/mol	97 ± 26	98 ± 23	103 ± 23	
FPG (mmol/L)				
Before SIIT	11.0 ± 3.1	12.2 ± 3.2	12.4 ± 2.9	0.17
After SIIT[‡§]	6.0 ± 0.9	6.5 ± 1.1	7.8 ± 2.2	<0.001
PPG (mmol/L)				
Before SIIT	17.5 ± 6.7	18.6 ± 5.1	19.6 ± 5.8	0.39
After SIIT[‡§]	7.4 ± 2.24	8.5 ± 2.5	10.9 ± 3.0	<0.001
MAGE[†‡§]	2.7 ± 0.6	3.2 ± 0.7	3.7 ± 0.8	<0.001
SDBG	0.3 ± 0.4	0.4 ± 0.5	0.3 ± 0.1	0.76
Mean FBG during SIIT (mmol/L)[†‡§]	4.8 ± 0.3	5.1 ± 0.3	5.3 ± 0.4	<0.001
Mean PBG during SIIT (mmol/L)[†‡§]	6.2 ± 0.4	6.8 ± 0.5	7.4 ± 0.7	<0.001
AIR (μU/mL·min)				
Before SIIT	−6.0 (9.6)	−11.2 (6.0)	−10.8 (17.9)	0.16
After SIIT[‡§]	65.5 (40.5)	48.6 (40.1)	23.3 (39.8)	0.006
ΔAIR (μU·min/mL)[‡§]	72.6 (32.0)	74.9 (55.7)	34.4 (43.9)	<0.001
HOMA-β				
Before SIIT	20.5 (6.5)	15.3 (20.5)	13.6 (12.8)	0.39
After SIIT[‡§]	52.0 (12.9)	54.3 (27.2)	33.5 (35.3)	0.02
ΔHOMA-β	31.3 (11.4)	29.2 (16.8)	20.4 (31.4)	0.35
HOMA-IR				
Before SIIT	3.0 (1.2)	3.3 (2.2)	3.0 (1.8)	0.49
After SIIT	1.9 (0.3)	2.1 (0.8)	2.1 (2.1)	0.92
ΔHOMA-IR	−1.4 (0.9)	−1.00 (0.5)	−0.6 (1.9)	0.07

[†]$P < 0.05$ for comparison between the lower and middle tertile. [‡]$P < 0.05$ for comparison between the lower and upper tertile. [§]$P < 0.05$ for comparison between the middle and upper tertile. AIR, acute insulin response; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HOMA-β, homeostasis model assessment for β-cell function; HOMA-IR, homeostasis model assessment for insulin resistance; MAGE, mean amplitude of glycemic excursions; MBG, mean blood glucose; PPG, postprandial glucose; SDBG, standard deviation of blood glucose; SIIT, short-term intensive insulin therapy.

treated with CSII, as well as investigating their impacts on clinical outcomes. As shown in the present study, MBG, MAGE and SDBG could be safely controlled to normal levels[23,24] in most cases by means of CSII without causing severe hypoglycemia. Thus, under frequent blood glucose monitoring, normalization of both overall glycemic levels and glucose excursion are technically feasible. In view of the benefits of SIIT shown in previous studies[6–9] and the current study, it merits consideration in select patients as a complement of the current standard care of type 2 diabetes.

A major finding of the present study was that patients with stricter overall glycemic control (lower MBG) during SIIT had better recovery in β-cell function (measured by ΔAIR), as well as higher probability of long-term glycemic remission. This fact further supports the concept that SIIT exerts its effect on β-cell recovery by reducing glucotoxicity and promoting β-cell rest. Reversibility of β-cell dysfunction by reducing β-cell overload in early type 2 diabetes has been investigated extensively and remains a challenging goal of diabetes care[25].

There are numerous possible mechanisms for recovery of insulin secretion capacity induced by SIIT. First of all, increased insulin demand and hyperglycemia could result in impairment of insulin secretion capacity and β-cell apoptosis by inducing endoplasmic reticulum stress and disturbance of unfolding protein response[26]. Endoplasmic reticulum stress can occur under mild hyperglycemia. For instance, endoplasmic reticulum stress was observed in human islets transplanted into non-diabetic mice, whose blood glucose were only slightly higher than normal levels in humans[27]. Reduction of insulin synthesis could protect β-cells against endoplasmic stress and subsequent impairment in mice models[28]. Second, β-cell dedifferentiation under chronic hyperglycemia is considered to play an important role in progressive β-cell failure in both rodent models and human patients[29,30]. After insulin therapy, dedifferentiated cells can redifferentiate to mature β-cells and lead to restoration of β-cell function in a diabetic mice model[31]. Last, but not least, clearance of hyperglycemia and modification of lifestyle in SIIT remarkably alleviated insulin resistance. SIIT has been shown to

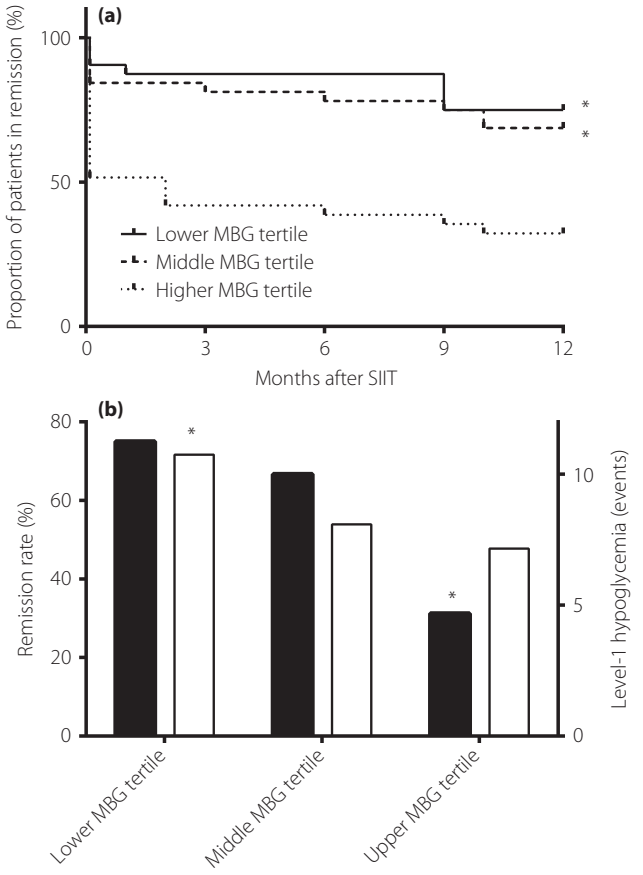

Figure 2 | Glycemic remission and incidence of level 1 hypoglycemia (blood glucose <3.9 mmol/L) during follow up in different mean blood glucose (MBG) tertiles. (a) Kaplan–Meier curve of glycemic remission showed that the upper and middle MBG tertiles had a significantly higher possibility of glycemic remission during long-term follow up. *$P < 0.05$ compared with the lower MBG tertile. (b) The 1-year remission rate and incidence of level 1 hypoglycemia among MBG tertiles. *$P < 0.05$ compared with the other two MBG tertiles.

reduce circulating free fatty acid, liver fat content and liver insulin resistance[32]. These effects might further reduce β-cell overload[21]. From this point of view, it is critical to keep blood glucose levels during SIIT close to normal levels to obtain maximal β-cell recovery. Although all participants in the present study achieved predefined glycemic targets, the long-term remission rate among MBG tertiles was heterogeneous, with a higher remission rate seen in patients with lower MBG. This fact indicates that current recommended glycemic targets should be re-evaluated.

Hypoglycemia is one of the major barriers of normalization of blood glucose in SIIT, because fear of hypoglycemia can lead to conservative insulin titration regimens and preclude optimal glycemic control. Indeed, severe hypoglycemia was associated with adverse macrovascular events, especially in those with high CV risk[18,19,33]. In contrast, the causal link between non-severe hypoglycemia and macrovascular mortality was absent. For instance, non-severe hypoglycemia was not associated with increased total mortality or cardiovascular death in the Outcomes Reduction with an Initial Glargine Intervention trial and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation studies[18,34]. The risk of severe hypoglycemia is much greater in older patients with longer duration of diabetes and severe concomitant diseases[18]. In the present study, some mild hypoglycemia events were observed, but major hypoglycemia episodes were uncommon, with no severe hypoglycemia occurring. Thus, severe hypoglycemia could be avoided when achieving near-euglycemia under the current regimen of intensive blood glucose monitoring and insulin dosing. Therefore, in newly diagnosed patients who are relatively young in age without previous cardiovascular events, the risk of hypoglycemia and related severe adverse events is very low; this should be clearly explained to patients when discussing the benefits and risks.

Optimal glycemic targets should be set by balancing beneficial effects and clinically significant hypoglycemic risk. As patients in the middle MBG tertile had a high remission rate (similar to the lower MBG tertile) without increased hypoglycemia risk (similar to the upper MBG tertile), the new glycemic targets should be set referring to the glycemic parameters in the middle MBG tertile. If we considered the 5th to 95th percentile of glycemic parameters in the middle MBG tertile as the new glycemic target ranges, MBG, FBG and 2hBG should be controlled to 5.8–6.1 mmol/L, 4.6–5.6 mmol/L and 6.0–7.6 mmol/L, respectively. Compared with current FBG and 2hBG goals, these targets were ~0.4 mmol/L lower.

Of course, it would be more convincing to carry out a randomized controlled trial in order to verify these new targets, avoiding baseline confounders that might influence both blood glucose control during SIIT and clinical outcomes. Nevertheless, as most baseline parameters in different MBG categories were similar (patients in the lower MBG tertile had higher BMI and younger age, but neither of them were associated with glycemic remission), the heterogeneity of therapeutic effects was unlikely to have resulted from baseline differences, but plausibly had a causal relationship with the difference in glycemic control during SIIT. In addition, a more intensive monitoring method, such as continuous glucose monitoring, was not applied because of the excessive cost and labor. Continuous glucose monitoring might provide more precise information on glycemic parameters for analysis, and could detect hypoglycemia earlier than capillary blood glucose testing, thus improving the safety of the treatment[35]. Finally, whether the findings of the present study can be extended to other centers in different countries also requires further research.

In conclusion, the present study showed the critical role of excellent glucose control during SIIT on reverse of β-cell dysfunction and induction of glycemic remission. In order to obtain the best benefits from SIIT, more efforts are required for establishing the best glycemic targets and standardizing the procedures of SIIT in the future.

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DISCLOSURE

The authors declare no conflict of interest.

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