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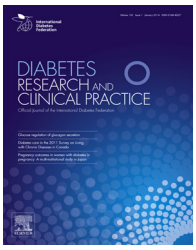

Insulin requirement profiles of short-term intensive insulin therapy in patients with newly diagnosed type 2 diabetes and its association with long-term glycemic remission

Liehua Liu, Weijian Ke, Xuesi Wan, Pengyuan Zhang, Xiaopei Cao, Wanping Deng, Yanbing Li *

Department of Endocrinology, The First Affiliated Hospital of Sun Yat-Sen University, No. 58, Zhongshan er Road, Guangzhou 510080, China

ARTICLE INFO

Article history:
Received 25 August 2014
Received in revised form
23 December 2014
Accepted 13 February 2015
Available online 21 February 2015

Keywords:
Insulin requirement
Intensive insulin therapy
Newly diagnosed type 2 diabetes
Remission

ABSTRACT

Aims: To investigate the insulin requirement profiles during short-term intensive continuous subcutaneous insulin infusion (CSII) in patients with newly diagnosed type 2 diabetes and its relationship with long-term glycemic remission.

Methods: CSII was applied in 104 patients with newly diagnosed type 2 diabetes. Daily insulin doses were titrated and recorded to achieve and maintain euglycemia for 2 weeks. Measurements of blood glucose, lipid profiles as well as intravenous glucose tolerance tests were performed before and after the therapy. Afterwards, patients were followed up for 1 year.

Results: Total daily insulin dose (TDD) was 56.6 ± 16.1 IU at the first day when euglycemia was achieved (TDD-1). Thereafter, TDD progressively decreased at a rate of 1.4 ± 1.0 IU/day to 36.2 ± 16.5 IU at the end of the therapy. TDD-1 could be estimated with body weight, FPG, triglyceride and waist circumference in a multiple linear regression model. Decrement of TDD after euglycemia was achieved (ΔTDD) was associated with reduction of HOMA-IR ($r = 0.27$, $P = 0.008$) but not with improvement in β cell function. Patients in the lower tertile of ΔTDD had a significantly higher risk of hyperglycemia relapse than those in the upper tertile within 1 year (HR 3.4, 95%CI [1.4, 8.4], $P = 0.008$).

Conclusions: There is a steady decline of TDD after euglycemia is achieved in patients with newly diagnosed type 2 diabetes treated with CSII, and ΔTDD is associated with a better long-term glycemic outcome.

1. Introduction

High prevalence of type 2 diabetes has become a major public health concern all over the world. In China, it's estimated that 11.6% of Chinese adult have diabetes, while only less than 40% achieving the glycated hemoglobin A1c (HbA1c) target of 7% [1]. Prospective research has shown that early intensive glycemic control could result in long-term micro-vascular and possible macro-vascular benefits in type 2 diabetes [2,3].

* *Corresponding author*. Tel.: +86 20 87334331; fax: +86 20 87334331.
E-mail addresses: lyb2047@163.com, easd04lyb@126.com (Y. Li).
http://dx.doi.org/10.1016/j.diabres.2015.02.011
0168-8227/

However, persistent maintenance of optimal glycemic control is one of the major challenges in the management of type 2 diabetes. As decline of β cell function is irreversible to date, the effects of anti-hyperglycemic agents may fade over time, leading to deterioration of glycemic control [4]. Elevation of blood glucose in turn accelerates the process of β cell failure via glucotoxicity. New therapeutic strategies are required to stop the vicious cycle.

Short-term intensive insulin therapy has been employed in the management of newly diagnosed type 2 diabetes in recent years. In previous studies, short-term intensive insulin therapy ameliorated β cell dysfunction, especially acute insulin response (AIR) [5–7], as well as insulin resistance measured by HOMA-IR [7,8], thereby inducing a prolonged glycemic remission of over 1 year without anti-hyperglycemic agents in more than 50% of patients [7,9]. Based on these benefits, short-term intensive insulin therapy was recommended for selective patients with newly diagnosed type 2 diabetes in Chinese guidelines [10].

However, relatively long hospitalization periods for titrating insulin dosage and frequent monitoring of blood glucose limit the application of the therapy. As the decision and subsequent titration of insulin dosage is highly reliant on the experience of the physicians, 4–6 days was usually required for achieving glycemic targets. Lack of knowledge about the insulin requirement profiles during the therapy may delay the achievement of euglycemia and, what is worse, increase the risk of hypoglycemia. Another question that remains unanswered is which factors predict glycemic remission. Several post-therapy indicators such as increment of AIR, reduction of HOMA-IR, 1,5-anhydroglucitol, fasting plasma glucose (FPG) and 2-h post-prandial blood glucose (2hPG) [7,8,11–13], have been suggested as possible indicators of remission. However, earlier and more potent predictors are still of interest. Therefore, we performed this retrospective study investigating the insulin requirement characteristics during short-term continuous subcutaneous insulin infusion (CSII) therapy in patients with newly diagnosed type 2 diabetes in order to refine the insulin titration procedure. In addition, we also examined the relationship between long-term glycemic remission and change of insulin requirement during the therapy.

2. Subjects

One hundred and four drug naïve patients with newly diagnosed type 2 diabetes were included from the CSII treated alone group in two independent randomized control trials (NCT00948324 and NCT01471808, ClinicalTrials.gov) performed in the Endocrinology department of The First Affiliated Hospital of Sun Yat-sen University from June 2007 to May 2013. Both studies shared similar recruitment criteria which have been described elsewhere [14]. Briefly, patients were diagnosed according to the World Health Organization 1999 diagnostic criteria [15]. The included patients were between 25 and 70 years old, with body mass index (BMI) between 21 and 35 kg/m^2 and fasting plasma glucose (FPG) between 7.0 and 16.7 mmol/L. Patients with acute or severe chronic complications of diabetes, severe concomitant diseases, use of medication which vastly influence glycemic levels, and positive for glutamic acid decarboxylase antibody were excluded. This research was approved by the research ethics board of Sun Yat-Sen University. Signed informed consent was obtained from each participant.

3. Materials and methods

3.1. Study design

All patients were admitted to hospital. Before treatment, there was a 2–3 day run-in period during which baseline evaluations were carried out. CSII was implemented to achieve glycemic targets (FPG between 4.4 mmol/L and 6.0 mmol/L and 2hPG between 4.4 mmol/L and 7.8 mmol/L) using insulin lispro (Humalog, Eli Lilly and Company, USA) or insulin aspart (Novo Nordisk, Bagsværd, Denmark). The initial insulin dose was delivered with a total daily dose (TDD) of 0.4–0.5 IU/kg, 50% of which was assigned as total basal dose and 50% as total pre-meal dose. Initial total basal dose was administered evenly throughout 24 h, and total pre-meal dose was divided equally before each meal. Insulin doses were adjusted according to the results of capillary blood glucose measurements, which were carried out eight times daily (before and 2 h after breakfast, lunch and supper, 11 pm, and 3 am). Everyday insulin requirement profiles were recorded. After glycemic targets were maintained for 14 days, CSII was withdrawn and baseline assessments were repeated the next day (at least 15 h after the cessation of insulin therapy). No medicine for hyperlipidemia was given during the therapy.

During hospitalization, all patients received an education program concerning diabetes self-management, which included sports advice, life style modification, and food intake guidance. Calories were calculated by a nutritionist to ensure that carbohydrates, protein and fat accounted for 50–60%, 10–15% and 20–30% of total calories, respectively, as recommended by current Chinese guideline [10]. Patients were encouraged to take a 1-h post-meal walk after each dinner. After withdrawal of CSII, all patients were followed monthly for 3 months and every 3 month thereafter with FPG and 2hPG monitored. Glycemic remission was defined as FPG < 7.0 mmol/L and 2hPG < 10.0 mmol/L without any anti-hyperglycemic agents [5,7,14]. Life-style modifications were recommended to be maintained after hospital discharge. Patients who had hyperglycemia relapse were reassessed a week later. If hyperglycemia was reconfirmed, anti-hyperglycemic agents were initiated according to current guidelines for diabetes.

3.2. Blood sampling and measurements

At baseline, demographic and anthropometric data, such as body weight, height, and waist circumference, were recorded. Venous blood was drawn for measurements of FPG, 2hPG (after breakfast), and lipid profiles. An intravenous glucose tolerance test (IVGTT) was performed on the subsequent morning in the fasting state using 50 mL of 50% glucose solution as previously described [7]. Blood samples were

obtained before and 1, 2, 4, 6, 10 min after administration of glucose to detect insulin levels. Acute insulin response (AIR) was calculated as the incremental trapezoidal area during the first 10 min of the IVGTT. Homeostasis model assessment was used to estimate β-cell function (HOMA-B) and insulin resistance (HOMA-IR) in fasting the state. All laboratory tests were performed in the Central Clinical Lab of the First Affiliated Hospital of Sun Yat-Sen University.

3.3. *Statistical analysis*

Normally distributed data are presented as mean ± SD values, and non-normally distributed data are presented as median (interquartile range). The differences of variables between groups were compared using both paired t test and independent t test (normally distributed data) or Mann–Whitney test (non-normally distributed data). The association of insulin dose and other variables are assessed with Pearson correlation (normally distributed data)/Sperman correlation (non-normally distributed data) and multiple stepwise linear regression. Time-to-event distributions were summarized with Kaplan–Meier curves. A Cox proportional-hazards model was applied to estimate the hazard ratio (HR) of the risk factors. All the statistical procedures were finished with SPSS software for Windows Version 13.0.

4. Results

4.1. *Insulin requirement profiles and their predictors during CSII*

The patients, consisting of 71 males and 33 females, were 48.3 ± 9.8 years in age, with a BMI of 25.3 ± 3.0 kg/m^2, and HbA1c of 10.9 ± 2.1% (96 ± 23 mmol/mol). Glycemic targets were achieved in 3.5 ± 1.9 days. At the first day after the glycemic targets were achieved (D1), TDD, total, basal and pre-meal dose were 56.6 ± 16.1 IU (0.82 ± 0.20 IU/kg), 25.2 ± 7.7 IU (0.37 ± 0.11 IU/kg) and 30.0 ± 10.3 IU (0.46 ± 0.17 IU/kg), respectively. Thereafter, TDD steadily decreased at a rate of 1.4 ± 1.0 IU/day (0.02 IU/kg per day), and was 36.2 ± 16.5 IU (0.53 ± 0.23 IU/kg) at the end CSII therapy (D14, $P < 0.001$ compared with that in D1). Total basal dose and total pre-meal dose were 15.4 ± 7.5 IU (0.23 ± 0.11 IU/kg, $P < 0.001$ compared with D1) and 20.7 ± 11.0 (0.30 ± 0.17 IU/kg, $P < 0.001$ compared with D1) at the end of the therapy, respectively, with a similar decline tendency as TDD (Fig. 1A). Total basal dose and total pre-meal dose were 42% and 58% of TDD, respectively at D1, and this ratio remained nearly unchanged during the therapy. At D1, basal insulin infusion rate was nearly equally distributed over 24 h, with a relatively high individual variance observed. The diurnal difference of basal insulin infusion rate

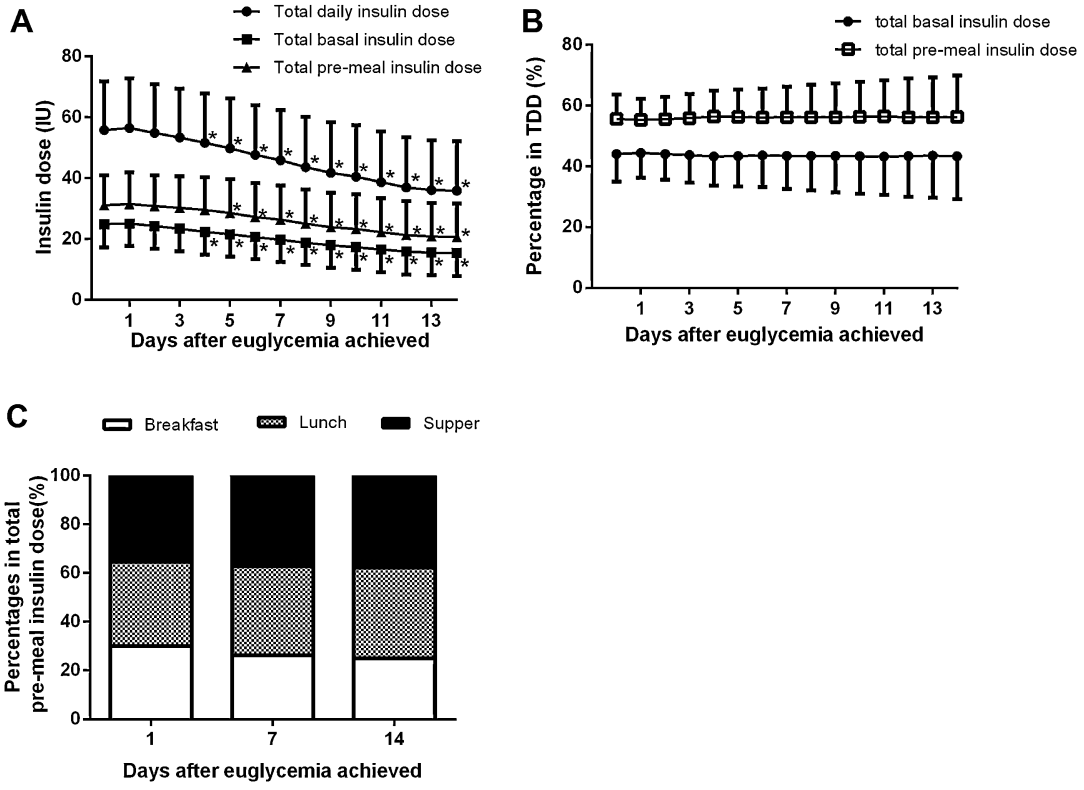

Fig. 1 – Insulin requirement profiles during CSII therapy. (A) Changes of total daily insulin dose, total basal insulin dose and total pre-meal insulin dose during CSII therapy showed a similar declined trend after euglycemia achieved. (B) The percentages of total basal insulin dose and total pre-meal insulin dose in total daily insulin dose (TDD) during CSII therapy. (C) The percentages of each pre-meal insulin doses in total pre-meal insulin dose at 1st, 7th and 14th day after euglycemia achieved.

Table 1 – Correlation of TDD-1 or ΔTDD with baseline clinical and laboratory parameters.

	ΔTDD		TDD-1	
	r	*P*	*R*	*P*
Sex	−0.17	0.09	−0.20	0.05
Age	−0.12	0.23	−0.27	0.01
Body weight (kg)	0.28	0.00	0.53	<0.001
BMI	0.25	0.01	0.42	<0.001
Waist circumference	0.23	0.02	0.49	<0.001
FPG	0.23	0.02	0.41	<0.001
2hPG	0.09	0.40	0.32	0.002
HbA1c (%)	0.23	0.02	0.22	0.02
Total cholesterol	−0.06	0.58	−0.06	0.56
Triglyceride	0.00	0.97	0.42	<0.001
LDL-c	−0.05	0.63	−0.22	0.24
HDL-c	−0.11	0.28	−0.25	0.01
AIR	−0.14	0.15	−0.31	0.001
HOMA-B	−0.11	0.26	−0.06	0.58
HOMA-IR	0.09	0.37	0.51	<0.001

BMI, Body mass index. FPG, Fasting plasma glucose. 2hPG, 2-h postprandial plasma glucose. A1C, glycated hemoglobin A1C. Spearman correlation was performed in non-normally distributed data (sex, AIR and HOMA-IR).

was only ~0.06 IU/h in D1, and slightly increased ~0.1 IU/h at D14, although the variance of basal insulin infusion rates was still minor. The pre-meal insulin doses for breakfast, lunch and supper in TDP were 30.1%, 34.4% and 35.5% of TDD in D1, respectively. During the therapy, the dose proportion for breakfast decreased gradually to 25.0% at D14, whereas those for the other two meals were similar (37.3% for lunch and 37.6% for supper) (Fig. 1B and C).

Correlation tests were performed and results are summarized in Table 1 to investigate the association of baseline parameters with TDD in D1 (TDD-1) or the decrement of TDD after euglycemia was achieved (ΔTDD), which is calculated as TDD in D1 subtracted TDD in D14. Variables with *P* value <0.05 were included in subsequent multiple linear regression tests. Patients with higher body weight, waist circumference, FPG and triglyceride at baseline tended to require more insulin to achieve euglycemia. Although TDD was higher in patient with greater BMI (BMI ≥ 25 kg/m^2, 62.3 ± 16.2 IU/d; BMI < 25 kg/m^2, 51.5 ± 13.3 IU/d, $P < 0.05$), when converted to TDD/kg, there was no difference in patients with different BMI (0.83 ± 0.2 IU/kg vs. 0.81 ± 0.2 IU/kg, $P = 0.69$). Only baseline body weight and HbA1c were independently associated with ΔTDD. Neither AIR nor HOMA-B at baseline entered the final models (Table 2).

A formula was derived from the stepwise linear regression model to calculate estimate TDD-1(eTDD-1):eTDD-1(IU) = 0.35 × body weight (kg) + 2.05 × FPG (mmol/L) + 4.24 × triglyceride(mmol/L) + 0.55 × waist circumference (cm) − 49.1 (*R* square: 0.76).

According to this formula, the calculated eTDD-1 was 56.7 ± 12.7 IU, which was highly consistent with the real TDD-1 (56.6 ± 16.1 IU, $P = 0.75$).

4.2. *ΔTDD indicates amelioration of insulin resistance and glycemic remission*

Similar to previous studies, short-term CSII therapy significantly decreased glycemic markers, ameliorated lipid profiles, improved β cell function, and reduced HOMA-IR (Table 3). ΔTDD was significantly associated with FPG after the therapy (r −0.26, $P = 0.01$, Fig. 2A), 2hPG after the therapy ($r = -0.38$, $P < 0.001$, Fig. 2B) and change of HOMA-IR (ΔHOMA-IR) ($r = -0.29$, $P = 0.004$) with age, BMI, TG and HDL-c adjusted. No significant association was found between ΔTDD and ΔAIR or ΔHOMA-B. More patients in the upper ΔTDD tertile (TDD ≥ 25.0 IU) remained in glycemic remission immediately after withdraw of CSII when compared with those in the lower tertile (ΔTDD < 13.5 IU) (91.4% vs. 65.6%, $P = 0.004$, Fig. 2C).

In total, 100 patients accomplished 1-year follow-up. The 4 discontinued subjects dropped out due to loss of contact or immigration. Of the 100 patients, 52 (52.0%) remained in glycemic remission at the end of follow-up. The characteristics of the remission group and non-remission group were summarized in Table 3. TDD in both groups were similar in the days after glycemic targets were achieved, however, it was significantly lower in the remission group 5 days after euglycemia was achieved (Fig. 2E). Therefore, ΔTDD was significantly higher in the remission group (25.3 ± 14.2 vs. 14.8 ± 13.7 IU, $P < 0.001$). The amelioration of HOMA-IR (ΔHOMA-IR) was also more obvious in remission group, however, neither improvement of AIR (ΔAIR) or HOMA-B (ΔHOMA-B) reached statistical significance, though there was a non-significant trend for ΔAIR in the remission group [41.7(60.7) vs. 71.9(88.0), $P = 0.07$]. In a Cox regression model, patients in the lower ΔTDD tertile was associated with an increased risk of hyperglycemia relapse within the 1-year follow-up compared with those in the upper tertile (long-term remission rate 31.3% and 75.0% for the lower and upper tertile, respectively, $P < 0.001$) (HR 3.4, 95%CI [1.4,8.4] adjusted for age, BMI, TG, HDL-c and HbA1c before the therapy, ΔHOMA-IR, ΔAIR, and ΔHOMA-B after the therapy (Fig. 2D).

Table 2 – Baseline predictors of total daily insulin dose at the first day when the glycemic targets achieved (TDD-1) and decrement of TDD after euglycemia achieved (ΔTDD) in stepwise multiple linear regression models.

TDD-1			ΔTDD		
Predictors	β (95% CI)	*P*	Predictors	β (95% CI)	*P*
Body weight (kg)	0.35 (0.02, 0.69)	0.04	Body weight (kg)	0.41(0.16, 0.67)	0.002
FPG (mmol/L)	2.07 (1.33, 2.77)	<0.001	HbA1c(%)	1.85 (0.38, 3.32)	0.02
Triglyceride (mmol/L)	4.24 (2.34, 6.12)	<0.001			
Waist circumference (cm)	0.55 (0.08,1.00)	0.02			

FPG, fasting plasma glucose. HbA1c, glycated hemoglobin A1C.

Table 3 – Comparison of clinical characteristics of remission group and non-remission group.

	Non-remission ($n = 47$)	Remission ($n = 53$)	P
Age (years)	49.5 ± 10.0	47.1 ± 9.6	0.21
BMI (kg/m^2)			
Before CSII	25.0 ± 3.3	25.5 ± 3.0	0.44
After CSII	24.8 ± 3.3	25.0 ± 2.8**	0.74
Waist circumference (cm)			
Before CSII	90.4 ± 7.8	90.6 ± 8.9	0.92
After CSII	88.9 ± 8.2*	88.8 ± 8.9**	0.95
HbA1 C % (mmol/mol)			
Before CSII	11.1 ± 2.0 (98 ± 21)	10.8 ± 2.2 (95 ± 24)	0.49
After CSII	9.5 ± 1.7 (80.3 ± 18.6)**	9.0 ± 1.7 (75 ± 18.6)**	0.13
Fasting plasma glucose (mmol/L)			
Before CSII	11.8 ± 3.0	11.3 ± 3.4	0.49
After CSII	7.3 ± 1.5**	6.3 ± 1.6**	0.004
2 h post prandial glucose (mmol/L)			
Before CSII	18.1 ± 5.7	17.8 ± 6.3	0.81
After CSII	10.1 ± 3.1**	7.6 ± 2.1**	0.001
Total cholesterol (mmol/L)			
Before CSII	5.8 ± 1.1	5.7 ± 1.2	0.73
After CSII	5.3 ± 1.2*	5.5 ± 1.2*	0.42
Triglyceride (mmol/L)			
Before CSII	2.0 ± 1.4	1.9 ± 1.3	0.72
After CSII	1.3 ± 0.7**	1.2 ± 0.4**	0.21
HDL-c (mmol/L)			
Before CSII	1.2 ± 0.3	1.1 ± 0.2	0.37
After CSII	1.2 ± 0.2	1.3 ± 0.3**	0.16
LDL-c (mmol/L)			
Before CSII	3.9 ± 1.1	3.9 ± 1.2	0.79
After CSII	3.6 ± 1.0*	3.8 ± 1.0	0.29
HOMA-B			
Before CSII	19.9 ± 14.4	27.9 ± 22.6	0.09
After CSII	49.7 ± 31.9**	58.4 ± 32.6**	0.09
HOMAIR			
Before CSII	3.2 (2.5)	3.6 (2.6)	0.40
After CSII	2.0 (1.6)*	1.9 (1.4)**	0.14
AIR (pmol/L min)			
Before CSII	−59.1 (149.6)	−58.5 (208.8)	0.62
After CSII	225.5 (432.2)**	372.4 (584.6)**	0.13
ΔHOMA-IR	−0.9 ± 1.7	−1.8 ± 1.9	0.008
ΔHOMA-B	30.6 ± 28.5	31.0 ± 31.2	0.98
ΔAIR	41.7 (60.7)	71.9 (88.0)	0.07
TDD-1 (IU)	56.4 ± 16.9	57.0 ± 15.4	0.87
TDD-14 (IU)	41.7 ± 17.8	31.6 ± 14.4	0.002
ΔTDD (IU)	14.8 ± 13.7	25.3 ± 14.2	<0.001

AIR, acute insulin response. TDD, total daily insulin dose. ΔTDD, decrement of TDD after euglycemia achieved. CSII, Continuous subcutaneous insulin infusion.
* $P < 0.05$ compared with baseline.
** $P < 0.001$ compared with baseline.

4.3. *Safety profiles*

During the total 2 to 3 weeks of treatment, 2 to 3 mild hypoglycemia episodes (capillary blood glucose <3.9 mmol/L and treated without the assistance of other individuals) were reported per patient. Most were reported after daytime exercise. All the episodes were rapidly corrected by reducing the insulin infusion dosage and calories intake. No severe hypoglycemia, cardiovascular events or treatment-related edema was reported.

5. Discussion

CSII has been investigated in multiple studies as a short-term intensive regimen in order to obtain a more rapid and better glycemic control in newly diagnosed type 2 diabetes patients. However, to our knowledge, there are little data concerning insulin dose titration during the therapy. Since most experiences of CSII come from treatment of type 1 diabetes and advanced type 2 diabetes, no guideline could be readily applied in newly diagnosed patients, which might result in unnecessary attempt-and-error cycles. In this study, we investigated the insulin requirement profiles in 104 newly diagnosed patients with type 2 diabetes treated with CSII. The daily requirement of insulin at the day when euglycemia was achieved was 56.6 ± 16.1 IU (0.82 ± 0.20 IU/kg), with a steady basal to bolus ratio of 2:3 throughout the therapy. TDD in this study was higher than that in previous studies performed in patients with longer diabetes durations [16–18] and type 1 diabetes [19], probably due to higher mean BMI found in subjects from our study. Based on the physiological insulin secretion pattern, TDD was initially divided 1:1 for basal insulin and pre-meal bolus. Our data, however, indicated that around 60% of TDD should be assigned to pre-meal bolus, and around 40% to basal insulin. Carbohydrates supply up to 60% [20] of total calories in daily Chinese diet. During therapy, although foods with lower GI index were suggested and calories from carbohydrates were restricted, slightly more insulin was still required to cover post-prandial glucose excursion. The proportion of basal insulin in this study is higher than that reported in patients with type 1 diabetes [19], in which about 70% of TDD was assigned as pre-meal bolus dose, because higher insulin resistance requires a higher proportion of basal insulin to overcome basal liver gluconeogenesis [21]. Another characteristic of daily insulin administration in this study was, unlike the situation in type 1 diabetes and advanced type 2 diabetes [19], that basal insulin infusion rate is nearly constant throughout the day, which may be attributed to more residual functional beta cell mass in newly diagnosed patients.

Some practical guidelines recommend estimating initial insulin dose simply with body weight [22,23], and that a higher insulin dose should be applied in patients with higher BMI [22]. However, this view is not completely supported by the results from this study. We developed a formula for insulin requirement for achieving euglycemia. Besides body weight, factors indicating insulin resistance (waist circumference and triglyceride) and magnitude of baseline glycemic abnormality (FPG) should be taken into account. To avoid hypoglycemia, one could initiate insulin dose with 70% of eTDD-1, because in this case eTDD-1 was higher than real TDD-1 in only 1 patient (1%) of the 104 subjects. In addition, we do not recommend a higher initial insulin dose per body weight in obese patients because both BMI categories shared similar TDD per kilogram of body weight in this study as well as others [16,21].

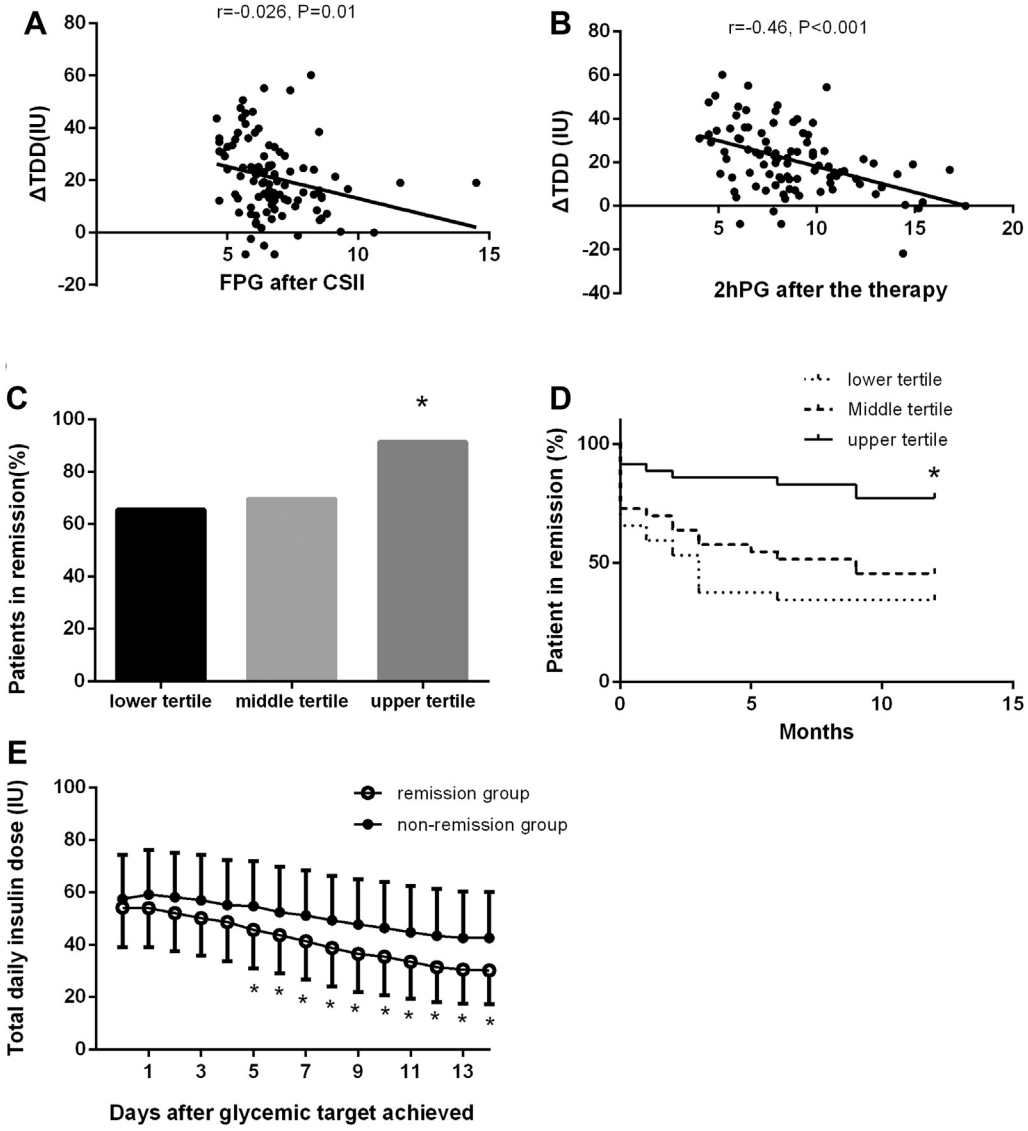

Fig. 2 – Association of decrement of total daily insulin dose after euglycemia achieved (ΔTDD) with glycemic remission. ΔTDD was correlated with Fasting plasma glucose (FPG) (A) and 2 h post-prandial plasma glucose (2hPG) (B). Patients in different ΔTDD tertile categories manifested different remission rates immediately after CSII(C) and during 1-year follow-up (D). E: comparison of total daily insulin dose during CSII therapy in remission and non-remission group. * $P < 0.05$ compared with non-remission group.

A significant and steady decline of TDD (ΔTDD) during the treatment period was observed in this study. ΔTDD was found to associate with amelioration of HOMA-IR, but not recovery of β cell function. Reduction of HOMA-IR induced by short-term CSII therapy was reported in previous studies [7,8], but the underlying mechanism is not fully understood. There are several possible explanations: first, high glucose per se could impair insulin signal pathways in peripheral organs [24,25]. Correction of hyperglycemia by intensive insulin therapy may therefore ameliorate hyperglycemia-induced insulin resistance. Second, abnormal body fat distribution and raised serum free fatty acids are both important etiologies of lipid-induced insulin resistance. Our previous studies have shown that both serum free fatty acid [7] and intramyocellular lipid were decreased after CSII therapy [14]. Son et al. also reported a decrease of visceral fat after early intensive insulin therapy in type 2 diabetes [6]. Increased proportion of visceral fat is known to increase basal insulin requirement [26]. Third, although prolonged administration of insulin increases body weight [27], lifestyle modification in this study resulted in a slight decrease of body weight, thereby potentially improving insulin sensitivity.

Another finding about ΔTDD was its association with glycemic remission. So far, proposed predictors of glycemic remission include blood glucose shortly after the therapy [11,13], 1,5 anhydroglucitol 1 month after the therapy [12], amelioration of beta cell function indices [7,8], reduction of insulin resistance [8], and compliance with lifestyle modification and positive attitude towards hyperglycemic management [28]. All of these variables could only be obtained after

the therapy or during follow-up. Reduction of TDD, however, could be observed during the therapy. In this study, patients in the lower tertile of ΔTDD had a 3.4 fold higher risk of hyperglycemic relapse within 1 year than those in the upper tertile. The remission group showed a more significant reduction of TDD than the non-remission group within a week after euglycemia achieved. Once hyperglycemic relapse is predicted in advance, appropriate subsequent treatment could be scheduled without unnecessary waiting and delay.

The continuous decline of TDD also implied that careful glycemic monitoring and insulin dose adjustment were necessary throughout the whole therapy. In this study, although we applied 8 point capillary blood glucose monitoring and frequently adjusted the insulin dose to avoid severe hypoglycemia, some mild hypoglycemia episodes still occurred. There have been some attempts [29,30] using prolonged simplified insulin regiment without hospitalization in newly diagnosed type 2 diabetes patients. We suggest applying these methods with caution because good patient compliance, comprehensive patient education, and frequent monitoring and contact with physicians are indispensable. Otherwise, the risk of hypoglycemia may increase and lead to adverse outcomes.

There are some limitations in this study. First, all subjects were from one center of China. They represented a subgroup of patients with relatively high blood glucose (mean HbA1c 10.9% [96 mmol/mol]). Whether the results could also be adapted in more representative cohorts is uncertain. Second, clamping techniques were not employed in this study. Using this gold standard to evaluate insulin resistance and β cell function may better reveal the relationship among ΔTDD, insulin resistance, and improvement of β cell function. Third, both insulin aspart and insulin lispro were used in the trials because they share similar pharmacokinetic properties. Although patients using different rapid insulin analogs did not differ in insulin requirement profiles, its relationship with glycemic remission and clinical parameters (data not shown), it might be a confounding factor.

To our knowledge, this study is the first to demonstrate detailed insulin requirement profiles during short-term intensive insulin therapy in patients with newly diagnosed type 2 diabetes as well as showing its relationship with glycemic remission. These findings provide useful information for facilitating titration of insulin dose during CSII and for subsequent follow-up. The results from this study should be validated in more representative cohorts using more comprehensive methods evaluating β cell function and insulin resistance (e.g., clamping technique or oral tolerance tests) in the future.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Acknowledgements

This study is funded by The 5010 Project of SunYat-sen University; Guangzhou Municipal Science and Technology special fund (No. 1346000270); Industrial Technology Research and Development funding projects, Guangdong provincial department of science and technology (No. 2012A030400006); Doctoral Fund of Ministry of Education,China (No. 20130171110067); The Fund of Key Laboratory of Endocrinology of Health Department of Guangdong Province. The funding sources are not involved in any part of the study design, data collection, data analysis or manuscript preparation.

Yanbing Li designed the study, analyzed the data and reviewed the manuscript. Liehua Liu analyzed the data, wrote the manuscript and contributed to data collection. Weijian Ke contributed to data collection and data analysis. Xuesi Wan and Pengyuan Zhang contributed to data collection, Xiaopei Cao reviewed the manuscript. Wanping Deng performed the tests and sample collection in the study.

We thank Dr. Yue Song, First Affiliated Hospital of Sun Yat-sen University, for her assistance in data collection. We thank all the nurses and patients who participated in the study. We thank Dr. Bilal Omar, Biomedical Center of Lund University, Lund, Sweden, for his kind help in preparing the manuscript.

This study was presented in 74th Scientific session of American Diabetes Association Annual Meeting in June 13, 2014, San Francisco.

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