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Safety and efficacy of sitagliptin in combination with transient continuous subcutaneous insulin infusion (CSII) therapy in patients with newly diagnosed type 2 diabetes

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Abstract. Sitagliptin was used as monotherapy or in combination with metformin, thiazolidinedione or sulfonylurea. It is not clear whether effects are enhanced or unique when in combination with transient continuous subcutaneous insulin infusion (CSII) therapy. The aim of this study was to assess the safety and efficacy of sitagliptin in combination with transient CSII therapy in patients with newly diagnosed type 2 diabetes. Eighty patients with newly diagnosed type 2 diabetes from July 2011 to May 2013 were recruited into the study. These patients were randomly divided into a CSII monotherapy group (group A, n = 40) or a sitagliptin in combination with CSII therapy group (group B, n = 40) and received insulin intensive therapy. Treatments were maintained for 2 weeks. 75g oral glucose tolerance test (OGTT) was performed before and after treatments, and the levels of glucose, insulin and C-peptide were examined. The results indicated that, compared with CSII therapy group, the level of plasma glucose significantly decreased, the levels of insulin and C-peptide strikingly increased and homeostasis model assessment for beta-cell function (HOMA- β) and Insulinogenic index (Ins index) were improved in the group of sitagliptin in combination with CSII therapy. Above all, the incidence of hypoglycemia was lower, insulin doses were less and the rate of recovery to normal glucose tolerance (NGT) or impaired glucose tolerance (IGT) determined by 75gOGTT was higher in the latter. So, Sitagliptin in combination with CSII therapy can be a new safe and effective therapy in patients with newly diagnosed type 2 diabetes.

Key words: Sitagliptin, Continuous subcutaneous insulin infusion (CSII), Newly diagnosed, Type 2 diabetes, Dipeptidyl peptidase-4 (DPP-4)

DIABETES MELLITUS is a global epidemic, and type 2 diabetes accounts for almost 90% of patients with the disease. In many countries, almost 10% of the health care budget is allocated for type 2 diabetes care. The prevalence of type 2 diabetes is globally increasing and the International Diabetes Federation has predicted that the number of people with diabetes will increase from 366 million to 552 million by 2030 [1, 2].

Type 2 diabetes is a chronic disease marked by progressive β -cells dysfunction leading to insulin deficiency. Insulin secretion declines because of the toxic

effects of hyperglycemia (glucotoxicity) and free fatty acids (lipotoxicity) on pancreatic β -cells [3]. The vicious cycle of elevated glucose further impairs and possibly destroys β -cells, which will eventually lead to complete failure of insulin production [4]. Therefore, early and intensive correction of these insults might preserve endogenous pancreatic function. Several short-term studies have shown that intensive insulin therapy for 2–3 weeks at the time of diagnosis leads to rapid improvement in insulin secretion, which may be maintained months after therapy was stopped [5–6]. Transient continuous subcutaneous insulin infusion (CSII) could be effectively used in achieving adequate glycemic control as well as significant improvement of β -cells secretion in newly diagnosed type 2 diabetic patients with severe hyperglycemia. Nearly one-half of the patients can maintain euglycemia on diet only

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for >12 months [4].

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) potentiate glucose induced insulin release. In addition, GLP-1 also suppresses glucagon release and slows down gastric emptying [7]. Both GLP-1 and GIP have very short half-lives because several peptidases clear them from plasma in a few minutes. Among the peptidases, dipeptidyl peptidase 4 (DPP-4) plays a quantitatively important role, whose specific inhibition delays clearance of GLP-1 and GIP, thereby augmenting active incretin levels. Fonseca *et al.* reported that vildagliptin decreased haemoglobin A1c (HbA1c) by 0.3% in patients with type 2 diabetes who received high doses of insulin in a 24-week study [8]. In another 24-week study, Kothny *et al.* found that vildagliptin 50mg bid added to insulin significantly reduced HbA1c in patients with type 2 diabetes inadequately controlled by insulin, with or without metformin [9]. Rosenstock *et al.* showed that the addition of alogliptin to the existing insulin therapy significantly improved the glycaemic control of patients with type 2 diabetes, when it was previously controlled inadequately by insulin alone [10]. A 52-week randomized, double-blind study showed linagliptin added to basal insulin therapy significantly improved glycemic control relative to placebo without increasing hypoglycemia or body weight [11]. Vilsboll *et al.* showed that the addition of sitagliptin to insulin therapy in a 24-week study improved the glycaemic control of patients with type 2 diabetes. The insulin dose remained stable throughout the 24-week period, unless the insulin dose had to be reduced because of hypoglycaemia [12]. Katsuno *et al.* showed that adding sitagliptin to insulin injections therapy (MDI) significantly improved glycemic control and decreased the daily glucose fluctuation in subjects with type 2 diabetes inadequately controlled with MDI, without weight gain or an increase in the incidence of hypoglycemia. HbA1c significantly decreased during the first 12 weeks ($-0.64 \pm 0.60\%$), and was sustained over 24 weeks ($-0.69 \pm 0.85\%$) [13]. Hong *et al.* reported that compared to a 25% increase in insulin dose, adding sitagliptin to an insulin-based regimen was more effective at lowering HbA1c and associated with less hypoglycaemia and weight gain over 24 weeks [14].

In these studies, however, the patients have suffered from type 2 diabetes for at least several years and the effect of adding a DPP-4 inhibitor was not compared with transient CSII therapy. So it is not clear whether

effects are enhanced or unique when sitagliptin is used in combination with transient CSII therapy. This study is aimed to assess the safety and efficacy of sitagliptin in combination with transient CSII therapy in patients with newly diagnosed type 2 diabetes.

Materials and Methods

Patients

Eighty patients (41 men and 39 women) with newly diagnosed type 2 diabetes at the Affiliated Hospital of Jiangsu University (Zhenjiang, Jiangsu, China) hospitalized in the Department of Endocrinology from July 2011 to May 2013 were recruited into the study. Diabetes mellitus was diagnosed according to the criteria published by the World Health Organization in 1999. The patients had no history of using any antihyperglycemic drugs and were negative for anti-glutamic acid decarboxylase antibodies. Patients were excluded from the trial if they were unlikely to adhere to the protocol and if they had acute or severe dysfunction of the heart, brain, lungs, liver or kidneys or intercurrent illness or pregnancy. This work was approved by the ethical committee of the Affiliated Hospital of Jiangsu University, registered to Head of Chinese Clinical Trial Registry (ChiCTR-TRC-13003782) and informed consent was given by all subjects.

Study design and treatment

Patients were hospitalized and assigned to a CSII monotherapy group (group A, $n = 40$) or a sitagliptin in combination with CSII therapy group (group B, $n = 40$) according to the random number method. All patients participated in diabetes education programs during hospitalization. Patients in group A received rapid-acting insulin analog (insulin Lispro, Eli Lilly and Company, USA) as basal and prandial insulin with an insulin pump (Medtronic, USA). Patients in group B received rapid-acting insulin analog with an insulin pump (the types of insulin and pump were the same as group A) and oral sitagliptin 100 mg once every morning. Total initial insulin doses were 0.4–0.6 IU/kg in the two groups (including basal and boluses insulin) and total daily doses were divided into 50% basal and 50% bolus injection. The basal and boluses of insulin doses were adjusted respectively with a range of 4 to 6 units daily according to the fasting and postprandial capillary blood glucose of three meals. The glycemic control target was defined as fasting plasma glu-

cose (FPG) <6.1 mmol/L and 2-h postprandial plasma glucose (PPG) <8.0 mmol/L, which should be achieved within five to seven days in the intensive glycemic control therapy. Treatments were maintained for 2 weeks. During the intervention, patients' capillary blood glucose was monitored by nurses using a blood glucometer (Johnson, USA) seven times per day, namely, at fasting, before lunch/dinner, 2 h postprandial (after breakfast, lunch, and supper respectively), and at bedtime. During intervention patients were instructed to continue diet and physical exercise. A balanced diet (60% carbohydrate, 15% protein, and 25% fat of the total energy value) was prescribed to all participants. Total energy value was calculated based on relative metabolic rate (RMR) and physical activity, as follows: $\text{RMR} \times \text{physical activity} - 500 - 1000 \text{ kcal/day}$. The training program consisted of 40-minute aerobic exercise, such as walking, three times a week (on alternate days), at 70% of heart rate (HR) reserve. And no other antidiabetic drugs or antihyperlipidemic drugs were used during the intervention. The intervention was stopped after 2 weeks.

Assessments

Height and body weight were measured after fasting for more than 12 h. After resting for 10 min, blood pressure was measured with a desktop mercury sphygmomanometer while patients were in a seated position. Blood pressure was measured twice on each patient and the average of the two values was recorded and used in the data analysis. Before intervention and 48 hours after treatment cessation, overnight fasting blood samples were obtained for measurement of glucose, insulin, C-peptide, HbA1c, and lipid levels. All patients received an oral glucose tolerance test (OGTT) on the basis of 75 g glucose, and blood samples were obtained 30, 60, 120, and 180 min after the oral glucose load to measure insulin and C-peptide concentrations. Routine clinical biochemical analyses [HbA1c, plasma triglycerides (TG), total cholesterol (CHOL), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)] were performed in the hospital laboratory. FPG was measured by the glucose oxidase method. Plasma insulin and C-peptide levels were measured using a chemiluminescence enzyme-linked immunosorbent assay kit (Insulin and C-peptide ELISA Kits, Mercodia, Sweden). Homeostasis model assessment was used to estimate insulin resistance (HOMA-IR) and β -cell function (HOMA- β).

Insulinogenic index (Ins index) and Matsuda index (ISI_M) were used to assess β -cell function and insulin sensitivity. $\text{HOMA-IR} = (\text{FPG} \times \text{fasting insulin}) / 22.5$. $\text{HOMA-}\beta = (20 \times \text{fasting insulin}) / (\text{FPG} - 3.5)$. $\text{Ins index} = [(\text{Ins}_{30} - \text{Ins}_0) (\text{pmol/L})] / [(\text{Glu}_{30} - \text{Glu}_0) (\text{mmol/L})]$ and $\text{ISI}_M (\mu\text{IU/mL, mg/mL}) = 10,000 / [\text{Glu}_0 (\text{mg/dL}) \times \text{Ins}_0 (\mu\text{IU/mL}) \times \text{average glucose OGTT} (\text{mg/dL}) \times \text{average insulin OGTT} (\mu\text{IU/mL})]^{1/2}$. The rate of recovery to NGT or IGT determined by 75gOGTT was calculated (the criteria: $\text{FPG} < 7.0 \text{ mmol/L}$, 2-h $\text{PPG} < 10.0 \text{ mmol/L}$). Basal and boluses insulin doses were recorded when treatment cessation. The occurrence of hypoglycemia was recorded during treatment. Hypoglycemia was defined as capillary blood glucose <3.9 mmol/L with or without clinical symptoms.

Statistical analyses

For sample size, the calculation was made in statistical tables, with the following settings: power ($1 - \beta$) was set at 80%, α was set at 0.05, and $\delta/\sigma = 0.7$, resulting in a sample size of 68 subjects, for future losses 20% were included. The sample consisted of 80 adult subjects (27 women and 53 men). Normally distributed and quantitative data were expressed as mean $\pm$ SD values. Quantitative variable differences between the two groups were compared by samples-independent Student's *t* tests; the differences before and after treatment were analyzed with samples-paired Student's *t* test. The χ^2 test was performed to compare for discrete variables. All statistical analyses were conducted by using the SPSS version 16.0 statistical package. A value of $P < 0.05$ was considered statistically significant.

Results

Patients studied

A total of 80 patients completed this research. None dropped out, and no serious adverse effects were observed during the intervention. The two groups were well balanced. There were no significant differences in age, sex, BMI, WHR, SBP, DBP, TG, CHOL, HDL-C and LDL-C before treatment ($P > 0.05$). No significant differences in body weight of both groups, BMI, WHR, SBP, DBP and HDL-C were observed before and after 2 weeks' intensive treatment ($P > 0.05$). After treatment, TG, CHOL and LDL-C of both groups were significantly lower than the levels before treatment ($P < 0.05$), while TG and CHOL between the two groups were of no significant differences ($P > 0.05$) (Table 1a, 1b).

Table 1a Baseline comparisons between the two groups before treatment

Parameter	Group A	Group B	<i>P</i>
Age (year)	53.13±12.24	49.37±11.82	0.315
Patient number (male/female)	26/14	27/13	0.813
BMI (kg/m ²)	24.43±4.78	24.56±3.01	0.712
WHR	0.93±0.05	0.94±0.05	0.534
SBP (mmHg)	130±9	128±10	0.765
DBP (mmHg)	78±7	80±8	0.863
HbA1C (%)	10.81±1.91	10.35±1.76	0.567

Table 1b Background characteristics comparisons of the two groups before and after treatment

Parameter	Group A			Group B			<i>P</i>	
	before treatment	after treatment	<i>P</i>	before treatment	after treatment	<i>P</i>	#	*
BMI(kg/m ²)	24.43±4.78	24.50±4.82	0.216	24.56±3.01	24.28±2.81	0.535	0.776	0.918
WHR	0.93±0.05	0.94±0.06	0.882	0.94±0.05	0.92±0.06	0.531	0.698	0.735
SBP (mmHg)	130±9	128±8	0.203	128±10	126±9	0.415	0.575	0.582
DBP (mmHg)	78±7	76±7	0.511	80±8	81±6	0.534	0.304	0.317
TG (mmol/L)	2.02±1.54	1.61±0.75	0.041	2.43±1.48	1.83±1.01	0.020	0.412	0.455
CHOL (mmol/L)	4.98±1.37	4.30±0.67	0.003	5.30±2.29	4.31±0.89	0.033	0.273	0.590
HDL-C (mmol/L)	1.05±0.21	1.06±0.20	0.484	1.09±0.23	1.13±0.22	0.339	0.298	0.087
LDL-C (mmol/L)	2.97±0.88	2.63±0.68	0.037	3.34±0.73	2.77±0.70	0.000	0.164	0.313

#, Group A vs. Group B before treatment; *, Group A vs. Group B after treatment

Table 2 Daily blood glucose profile of the two groups before and after treatment

Parameter (mmol/L)	Group A			Group B			<i>P</i>	
	before treatment	after treatment	<i>P</i>	before treatment	after treatment	<i>P</i>	#	*
FBG(before breakfast)	12.04±3.13	6.66±1.39	0.000	11.65±2.58	6.52±1.27	0.000	0.694	0.248
2 h PBG(after breakfast)	20.99±4.69	12.84±3.16	0.000	21.68±4.20	11.39±3.18	0.000	0.513	0.000
FBG (before lunch)	17.41±4.48	8.18±2.59	0.000	17.64±4.37	7.33±2.61	0.000	0.918	0.034
2 h PBG(after lunch)	18.44±3.94	9.65±2.17	0.000	18.69±4.41	9.01±2.20	0.000	0.462	0.041
FBG (before dinner)	15.63±4.17	8.15±2.16	0.000	16.12±5.26	7.12±1.73	0.000	0.539	0.000
2 h PBG (after dinner)	17.34±5.51	9.84±2.51	0.000	17.41±4.34	9.03±2.38	0.000	0.276	0.023
FBG (at bedtime)	11.97±4.15	7.74±1.49	0.000	12.12±3.00	6.56±1.25	0.000	0.715	0.000

FBG, fasting capillary blood glucose; 2h PBG, 2h postprandial of three meals; #, Group A vs. Group B before treatment; *, Group A vs. Group B after treatment

Glycemic control

From daily blood glucose profile (Table 2), we can conclude that before treatment, the levels of the fasting and postprandial capillary blood glucose of three meals between the two groups were of no significant differences ($P > 0.05$). After 2 weeks' intensive treatment, the levels of plasma glucose at all points of both groups were respectively significantly lower than the levels before treatment ($P < 0.05$). The levels of plasma glucose at all points decreased with the exception of that before breakfast ($P < 0.05$). As shown in Table 3, before treatment the levels of plasma glucose at fasting and 4 points (30min, 60min, 120min and 180min) after OGTT between the two groups were of no significant

differences ($P > 0.05$). After 2 weeks' intensive treatment, the levels of plasma glucose at all points of both groups were respectively significantly lower than the levels before treatment ($P < 0.05$). There were great decreases in the levels of plasma glucose at 60min, 120min and 180min (group B vs. group A) ($P < 0.05$).

Effects on β -cell function

Compared with those before treatment, the levels of insulin and C-peptide at fasting and 4 points (30min, 60min, 120min and 180min) after insulin release test (IRT) and C-peptide release test (CRT) increased significantly in group B ($P < 0.05$). The levels of insulin and C-peptide at 30min, 60min, 120min and 180min

Table 3 Plasma glucose comparisons, insulin comparisons, and C-peptide comparisons of the two groups before and after treatment

Parameter	Group A			Group B			<i>P</i>	
	before treatment	after treatment	<i>P</i>	before treatment	after treatment	<i>P</i>	#	*
Glu0 (mmol/L)	12.34±2.78	7.00±1.26	0.000	11.90±3.46	6.40±1.52	0.000	0.821	0.199
Glu30 (mmol/L)	16.78±3.90	9.70±1.79	0.000	15.74±4.12	8.89±2.36	0.000	0.653	0.547
Glu60 (mmol/L)	22.00±3.89	13.88±2.07	0.000	20.69±4.47	12.27±2.41	0.000	0.734	0.000
Glu120 (mmol/L)	22.80±4.24	14.25±3.44	0.000	22.79±4.57	11.64±3.20	0.000	0.375	0.000
Glu180 (mmol/L)	19.79±4.80	11.65±3.46	0.000	20.18±5.28	9.70±4.01	0.000	0.590	0.000
Ins0 (μIU/L)	4.93±1.05	4.97±0.86	0.512	4.81±0.91	5.59±1.10	0.015	0.597	0.637
Ins30 (μIU/L)	9.52±1.03	12.40±1.45	0.000	8.94±0.98	13.11±1.32	0.000	0.631	0.812
Ins60 (μIU/L)	13.69±1.12	21.38±1.71	0.000	14.26±1.07	26.14±1.34	0.000	0.710	0.000
Ins120 (μIU/L)	15.70±0.97	30.10±2.43	0.000	13.56±1.85	36.00±4.13	0.000	0.663	0.000
Ins180 (μIU/L)	13.50±1.86	28.13±2.74	0.016	13.42±1.33	34.84±3.79	0.000	0.549	0.000
C-P0 (ng/dL)	1.78±0.75	1.86±0.65	0.412	1.57±0.74	1.98±0.70	0.000	0.638	0.473
C-P30 (ng/dL)	2.40±1.02	2.79±1.11	0.029	2.10±0.89	2.97±1.18	0.000	0.713	0.198
C-P60 (ng/dL)	3.32±1.87	4.10±1.24	0.003	3.35±2.35	5.20±2.46	0.000	0.529	0.024
C-P120 (ng/dL)	3.91±2.02	5.85±1.76	0.000	3.87±1.62	7.55±4.27	0.000	0.326	0.000
C-P180 (ng/dL)	3.84±2.18	5.31±2.10	0.001	3.83±2.06	6.84±3.90	0.000	0.864	0.000

#, Group A vs. Group B before treatment; *, Group A vs. Group B after treatment

after IRT and CRT increased significantly in group A ($P < 0.05$) as well, however, no significant differences were found at the fasting insulin and C-peptide. After 2 weeks' intensive treatment, there were great increases in the levels of insulin and C-peptide at 60min, 120min and 180min (group B vs. group A) ($P < 0.05$) (Table 3).

No differences in HOMA-IR, HOMA- β , Ins index and ISI_M were found between the two groups before treatment ($P > 0.05$). After 2 weeks' intensive treatment, HOMA-IR declined significantly in both groups ($P < 0.05$) (Fig. 1a) and there was no significant difference between the two groups ($P > 0.05$). HOMA- β , Ins index and ISI_M increased significantly in both groups after treatment ($P < 0.05$). HOMA- β and Ins index of group B increased more significantly than those of group A ($P < 0.05$) (Fig. 1b, Fig. 2).

The rate of recovery to NGT or IGT and insulin doses

According to the criteria of FPG < 7.0 mmol/L and 2-h PPG < 10.0 mmol/L, after 2 weeks intensive treatment, the rate of recovery to NGT or IGT determined by 75gOGTT of group A and group B was respectively 15% (6/40) and 35% (14/40). There was statistically significant difference between the two groups (Table 4). After 2 weeks' intensive treatment, the basal, boluses and total insulin doses of group B were all less than those of group A ($P < 0.05$) (Table 4).

Incidence of hypoglycemia

In group A, 8/40 patients (20.0%) experienced a total of 14 hypoglycemic events, among which two patients (2/40, 5%) experienced twice severe hypoglycemia including drowsiness and epilepsy. In group B, 2/40 patients (5.0%) experienced a total of 6 hypoglycemic events without severe hypoglycemia. Incidence of hypoglycemia decreased obviously for group B vs. group A ($P < 0.05$).

Discussion

Glucotoxicity is one of the major factors involved in progressive deterioration of β -cell function and mass in type 2 diabetes mellitus [15]. β -cell function can be improved, resulting in temporary remission in newly diagnosed type 2 diabetes mellitus treated with short-term intensive insulin therapy [6, 15]. Patients with type 2 diabetes mellitus who received intensive glucose therapy had a lower risk of microvascular and macrovascular complications than those receiving conventional dietary therapy [16].

The study of Weng's showed that more patients with newly diagnosed type 2 diabetes achieved target glycaemic control in the CSII group in less time than those treated with oral hypoglycaemic agents. Remission rates after 1 year achieved 51.1% in the

Fig. 1a HOMA-IR comparison of the two groups before (open bars) and after (closed bars) treatment Group A, CSII monotherapy group; Group B, sitagliptin in combination with CSII therapy group.
 $\#P < 0.05$ (group A before treatment vs. after treatment),
 $*P < 0.05$ (group B before treatment vs. after treatment).

Fig. 1b HOMA-β comparison of the two groups before (open bars) and after (closed bars) treatment Group A, CSII monotherapy group; Group B, sitagliptin in combination with CSII therapy group.
 $\#P < 0.05$ (group A before treatment vs. after treatment),
 $*P < 0.05$ (group B before treatment vs. after treatment),
 $§P < 0.05$ (group A vs. group B after treatment).

Fig. 2a Ins index comparison of the two groups before (open bars) and after (closed bars) treatment Group A, CSII monotherapy group; Group B, sitagliptin in combination with CSII therapy group.
 $\#P < 0.05$ (group A before treatment vs. after treatment),
 $*P < 0.05$ (group B before treatment vs. after treatment),
 $§P < 0.05$ (group A vs. group B after treatment).

Fig. 2b ISI_M comparison of the two groups before (open bars) and after (closed bars) treatment Group A, CSII monotherapy group; Group B, sitagliptin in combination with CSII therapy group.
 $\#P < 0.05$ (group A before treatment vs. after treatment),
 $*P < 0.05$ (group B before treatment vs. after treatment).

Table 4 Rate of recovery to NGT or IGT and insulin doses comparisons between the two groups

Parameter	Group A	Group B	P
Rate of recovery to NGT or IGT (%)	15	35	0.039
Basal insulin doses (U)	16.52±8.61	11.89±6.37	0.022
Boluses insulin doses (U)	18.43±9.17	13.59±6.42	0.016
Total insulin doses (U)	34.89±17.04	25.48±12.07	0.009

CSII group. β -cell function and acute insulin response improved significantly after intensive interventions. The increase in acute insulin response was sustained in the CSII group but significantly declined in the oral hypoglycaemic agents group at 1 year in all patients in the remission group [6]. Short-term studies with CSII showed that CSII compared with MDI is a more efficient method of improving prompt glucose control and it does not lead to the increase in the insulin dosage [17, 18]. Insulin pumps provide precise insulin delivery throughout the day and improve the accuracy of bolus dose calculations to closely follow the physiologic patterns of secretion observed in patients without diabetes. In this way, improved glycemic control with less frequent and severe hypoglycemic episodes can be achieved. Therefore, CSII may be the best current therapeutic option for patients with diabetes [19]. In our study, the levels of plasma glucose at all points of both groups after 2 weeks' intensive treatment were respectively significantly lower than those before treatment. The levels of insulin and C-peptide after IRT and CRT increased significantly in both groups. HOMA-IR declined and HOMA- β increased significantly in both groups after treatment. These improvements were due to early intensive glucose control of type 2 diabetes, elimination of malignant effects induced by glucotoxicity and lipotoxicity, rest of islet cell and recovery of β -cell damage. Irreversible β -cell dysfunction and β -cell number decrease could be avoided in diabetic deterioration. Improvement of β -cell function is the main reason for blood glucose remission [20]. The progressive deterioration of glycaemic control in individuals with type 2 diabetes mellitus results from insulin resistance combined with the ongoing loss of β -cell function. Although it has been suggested that most β -cell dysfunction occurs after the development of type 2 diabetes mellitus, studies have documented a substantial early loss of β -cell function, particularly during the prediabetic state. In patients diagnosed with type 2 diabetes mellitus, β -cell function continues to decline despite treatment with commonly prescribed antihyperglycaemic medications, and ultimately exogenous insulin administration is required to maintain optimal glycaemic control. Thus, interventions to address the early decline in β -cell function could potentially alter the course of type 2 diabetes mellitus, preventing or delaying its onset and decreasing the incidence of complications [21].

GLP-1 can enhance glucose-stimulated insulin secre-

tion, which is abolished upon DPP-4-mediated removal of their N-terminal dipeptides *in vitro* [22]. DPP-4 inhibitor can block the inactivation of GLP-1 and GIP, thus raising plasma concentrations of the intact, active form of these peptides and thereby improving islet function by increasing α -cell and β -cell sensitivity to glucose [23, 24]. Recently, DPP-4 inhibitor became one of second-line regimens after metformin in the treatment of type 2 diabetes in the position statement suggested by the American Diabetes Association and the European Association for the Study of Diabetes [25]. Previous studies have shown that DPP-4 inhibitors can significantly decrease HbA1c concentration when added to insulin regimens, without an additional risk of hypoglycemia [8-11]. A study indicated that add-on therapy with sitagliptin to various insulin regimens could decrease daily insulin doses and improve glycemic control without severe hypoglycemia and/or weight gain [13]. In a 24-week, randomized, active-competitor trial, the addition of sitagliptin resulted in improvement in lowering of HbA1c with less hypoglycaemia and no weight gain as compared with the 25% insulin-increasing approach in subjects using insulin with uncontrolled type 2 diabetes [14]. In our study, there were great decreases in the levels of plasma glucose at 60min, 120min and 180min (sitagliptin in combination with CSII therapy group *vs.* CSII monotherapy group), and there were great increases in the levels of insulin and C-peptide at 60min, 120min and 180min (sitagliptin in combination with CSII therapy group *vs.* CSII monotherapy group). HOMA- β and Ins index of sitagliptin in combination with CSII therapy group increased more significantly than those of CSII monotherapy group. Improvements in glycaemic control in the sitagliptin group appear to have been because of improved postprandial glucose control. This finding is consistent with the known mechanism of action of sitagliptin, which enhances glucose-dependent insulin secretion by β -cells and inhibits glucagon release from α -cells [26].

GIP seems to be a physiological pancreatic islet regulator with diverging effects on the two main pancreatic glucoregulatory hormones insulin and glucagon. A strong scientific rationale suggests that DPP-4 inhibitors can prevent or counteract hypoglycemia. This is especially important for the management of insulin-treated patients since the limiting factor in this population is iatrogenic hypoglycemia [27]. The insulinotropic effects of incretins are glucose-dependent and

decline as postprandial serum glucose levels return to normal ranges. The incretin GIP increases glucagon levels during fasting and hypoglycemic conditions, while potentiating glucose-induced insulin secretion during hyperglycemia [28]. In particular, for critical patient populations, the combination of DPP-4 inhibitors with basal insulin can be recommended to minimize the risk of hypoglycemia [29]. It showed that linagliptin as add-on therapy to basal insulin in elderly patients (aged 70 years) with inadequately controlled T2DM did not increase the risk of hypoglycemia, relative to placebo [30]. This was confirmed by a *post hoc* pooled analysis through data from seven randomized, double-blind, placebo-controlled Phase 3 trials. Included were patients aged 65 years, treated with linagliptin 5 mg once daily as monotherapy or in addition to common glucose-lowering therapies. The treatment was well tolerated, linagliptin improved glycemic control, and the incidence of hypoglycemia was comparable with that of the placebo [31]. In our study, after 2 weeks' intensive treatment, the basal, boluses and total insulin doses of sitagliptin in combination with CSII therapy group were all less than those of CSII monotherapy group ($P < 0.05$), while the rate of recovery to NGT or IGT determined by 75gOGTT of the former was higher than that of the latter. The incidence of hypoglycemia decreased obviously for sitagliptin in combination with CSII therapy group vs. CSII monotherapy group.

All in all, we firstly explore safety and efficacy of

sitagliptin in combination with transient CSII therapy in patients with newly diagnosed type 2 diabetes, and we demonstrated the efficacy of this combination therapy to improve pancreatic beta cell function and the safety to reduce hypoglycemia. This can be a new safe and effective therapy in patients with newly diagnosed type 2 diabetes. Since the study period is too short, further long-term and comparative efficacy and tolerability data are required to gather substantial knowledge on the prolonged use of Sitagliptin in addition to CSII.

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Disclosure

There are no conflicts of interest that interfere with the impartiality of the research, and there are no potential conflicts of interest that are not fully declared within the text of the article.

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