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Effect of short-term intensive insulin therapy on α-cell function in patients with newly diagnosed type 2 diabetes

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Abstract

The effect of intensive insulin therapy on hyperglucagonemia in newly diagnosed type 2 diabetes (T2DM), and its associations with β-cell function, has not been elucidated. This study assessed the effect of 12 weeks of intensive insulin therapy on hyperglucagonemia in newly diagnosed T2DM and its associations with β-cell function, with reference to the effects of 12 weeks of oral hypoglycemic agents (OHAs).

One hundred eight patients with newly diagnosed T2DM were enrolled from January 2015 to December 2015. The patients were randomly divided to receive, for 12 weeks, either intensive insulin therapy or OHAs. Meal tolerance tests were conducted at baseline before treatment (0 week), at 12 weeks (end of treatment), and 12 months after the initiation of treatment. The levels of glucagon, proinsulin, C-peptide (CP), and blood glucose were measured at timepoints 0, 30, and 120 minutes during the meal tolerance test.

Intensive insulin treatment was associated with a decrease in glucagon levels (at 0, 30, and 120 minutes) and proinsulin/CP, and an increase in the insulin-secretion index $\Delta CP_{30}/\Delta G_{30}$ and $\Delta CP_{120}/\Delta G_{120}$, at 12 weeks and 12 months during the follow-up, compared with the corresponding effects of OHAs. Intensive insulin therapy could reduce but failed to normalize glucagon levels at 12 weeks. There were no correlations between the change of percentages in total area under the curve of glucagon and other glycemic parameters (proinsulin/CP; $\Delta CP_{30}/\Delta G_{30}$; or $\Delta CP_{120}/\Delta G_{120}$). Patients who received intensive insulin therapy were more likely to achieve their target glycemic goal and remission, compared with those who received OHAs.

Short-term intensive insulin therapy facilitates the improvement of both β-cell and α-cell function in newly diagnosed T2DM mellitus. Decline of β-cell secretion and concomitant α-cell dysfunction may both be involved in the pathogenesis of T2DM.

Abbreviations: CP = C-peptide, IIT = intensive insulin therapy, OHA = oral hypoglycemic agent, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglyceride.

Keywords: glucagon, intensive insulin therapy, type 2 diabetes mellitus

1. Introduction

Type 2 diabetes mellitus (T2DM) is a global problem, and its prevalence is rapidly increasing. T2DM is characterized fundamentally by a disorder in the metabolism of carbohydrates, resulting from the relative or absolute lack of insulin secretion.[1] Excess secretion of glucagon may underlie the important manifestations of diabetes, since chronic sustained hyperglucagonemia appears in T2DM patients.[2,3]

Islets are clusters of cells in the pancreas that regulate blood glucose by producing insulin and glucagon, which together are part of a feedback system ensuring a stable blood glucose level. The glucagon-secreting α-cells are scattered among the β-cells, functioning reciprocally. About 40 years ago, Unger et al[4] proposed a bi-hormonal theory to explain the pathophysiology of diabetes, that is, insulin deficiency or resistance accompanied by an absolute or relative excess of glucagon. Thus, T2DM is a complex disorder resulting from impaired function of α- and β-cells, as well as abnormal secretion patterns of insulin and glucagon. However, a controversy remains regarding the role of α-cell dysfunction in the pathogenesis of diabetes, and especially whether α-cell hyperactivity is secondary to, or concomitant with, the decline of β-cell secretion.

During the early course of diabetes, insulin secretion defects are considered reversible. Recent studies have shown that in patients with newly diagnosed T2DM, short-term intensive insulin therapy can improve β-cell function, decrease glycemic variability, induce glycemic remission, and even maintain glucose homeostasis after the therapy is stopped.[5–9] However, few studies have focused on the function of α-cells. Questions, such as whether α-cell hyperfunction is a primary defect or secondary to the decline of β-cell function, remain unanswered.

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In addition, treatment durations have varied in most studies, from 2 to 4 weeks[5–7,10,11]; in others, patients with diabetes were given 4 to 8 weeks of intensive insulin therapy.[12] These latter focused on the effects of short-term intensive therapy on β-cell function as well as the heterogeneity of response to insulin intensive therapy in different patients.

The China guidelines recommend courses of intensive insulin therapy of 2 weeks to 3 months for the prevention and treatment of T2DM.[13] Yet, it is unknown whether patients may not benefit more by prolonging the duration of intensive insulin therapy, and there is no consensus regarding the proper indicator (eg, hemoglobin A1c, or glycated hemoglobin [HbA1c]) for initiating treatment.[14,15]

This study compared the effect of 12 weeks of intensive insulin therapy, relative to 12 weeks of oral hypoglycemic agents (OHAs), on hyperglucagonemia in newly diagnosed T2DM. The function of β and α cells after intensive insulin therapy and their correlations were evaluated, and the glycemic and lipid outcomes were compared in a 1-year follow-up.

2. Materials and methods

2.1. Subjects and grouping

Patients with newly diagnosed T2DM (n = 108, defined as diagnosis within the previous 6 months) were consecutively enrolled for this prospective study from January 2015 to December 2015. The inclusion criteria were the following: age >18 years; newly diagnosed T2DM; and HbA1c between 9% and 11%. Patients with acute diabetic complications such as diabetic ketoacidosis or severe heart, liver, or kidney dysfunction were excluded. All patients provided written informed consent before participation.

The 108 patients were assigned to 2 groups to receive either intensive insulin therapy or OHAs (IIT and OHA, respectively) by using computer-generated random numbers. All patients were initially hospitalized for 2 weeks, and then discharged and followed up in outpatient clinics. The blood glucose was checked 7 to 8 times during hospitalization and 4 to 5 times after discharge by self-monitoring blood glucose.

Patients in the IIT group were administered intensive BIT (rapid-acting insulin analogs at 3 meals + insulin glargine at bedtime) + metformin 0.5 g tid, for 12 weeks. Patients in the OHA group received metformin 0.5 g tid + gliclazide sustained-release tablets (60–120 mg daily), with acarbose (50–100 mg tid), if the postprandial glucose reached >10 mmol/L, or pioglitazone 15 to 30 mg qd for body mass index >25 kg/m^2, for 12 weeks. The dose of OHAs or insulin was adjusted every 3 days to achieve or maintain within the following glycemic ranges: fasting glucose 4.4 to 6.1 mmol/L and postprandial glucose level 4.4 to 7.8 mmol/L. Remission was defined as achievement of target glycemic goal (HbA1c <7%) without use of hypoglycemic agents, lasting >6 months.

After 12 weeks, patients in the IIT group discontinued the insulin and were maintained on metformin; the patients were treated with other hypoglycemic agents (gliclazide sustained-release tablets 60–120 mg daily, with or without acarbose 50–100 mg tid, pioglitazone 15 mg qd). Patients in the OHA group remained with the original regimen. No lipid-lowering agents were used in either group. In the course of follow-up, OHAs were adjusted to maintain the glycemic goal. The patients discontinued the hypoglycemic agents and were encouraged with dietary and physical activity intervention for glycemic control, if they achieved the glycemic goal for more than 1 month on 2 or fewer hypoglycemic agents.

Thirty normal healthy volunteers were enrolled as the control group.

2.2. Laboratory tests

The level of proinsulin was determined via enzyme-linked immunosorbent assay with a microplate reader (Biocell Ht-1, R&D system). The glucagon and C-peptide (CP) were measured by radioimmunoassay (Roche Diagnostics). Blood glucose was measured using the glucose oxidation method with a Roche Diagnostics Biochemistry Analyzer (Roche Diagnostics). HbA1c was detected with high-performance liquid chromatography (Bio-Rad Laboratories). Immunoturbidimetry and Benedict–Behre creatinine colorimetry were used to determine the concentrations of albumin and creatinine in the urine samples, respectively. The urinary albumin-to-creatinine ratio was calculated as urinary albumin (mg/L) divided by urinary creatinine (g/L).

All patients were routinely examined with urine/blood tests, liver and renal function, blood lipids, electrolytes, and electrocardiogram. The blood samples were collected at the start of therapy (baseline) and at 12 weeks and 12 months after treatment.

2.3. Meal tolerance test

The subjects in all 3 groups underwent a meal tolerance test, with 100 g of standardized steamed bread. During the testing period, levels of glucagon, proinsulin, CP, and blood glucose were measured at timepoints 0 (fasting), 30, and 120 minutes.

The area under the receiver operating characteristic curve (AUC) of glucagon (AUCg) was calculated using the following formula: (fasting glucagon value, ng/L × 15) + (postprandial glucagon value at 30 minutes × 60) + (postprandial glucagon value at 120 minutes × 45).

The early insulin secretion index consisted of the CP/glucose (Glu) ratio response over the first 30 minutes of the test ($\Delta CP_{30}/\Delta G_{30}$) as follows: $\Delta CP_{30}/\Delta G_{30} = CP_{30} - CP_0$, pmol/L/$Glu_{30} - Glu_0$, mmol/L.

The overall insulin secretion index was defined as the CP/Glu ratio response over the 120 minutes of the test ($\Delta CP_{120}/\Delta G_{120}$) as follows: $\Delta CP_{120}/\Delta G_{120} = CP_{120} - CP_0$, pmol/L/$Glu_{120} - Glu_0$, mmol/L.

2.4. Statistical analysis

All statistical analyses were performed using SPSS 13.0. The continuous and discrete variables are expressed as mean ± standard deviation or the number of patients (percentage). Continuous variables were compared using the paired *t* test to evaluate intragroup differences before and after treatment, and the independent-samples *t* test to evaluate intergroup differences. Measurements at multiple timepoints were analyzed by the repeated measures analysis of variance method. Categorical variables were compared using the Chi-squared test. Correlations between data were analyzed using Spearman correlation analysis. $P < .05$ was considered statistically significant.

Table 1

Baseline characteristics of subjects in the ITT, OHA, and control groups.

	IIT	OHA	Control	F/χ	P	P*	P†
Subjects, n	56	52	30				
Male, n (%)	26 (46.4)	26 (50.0)	15 (50)	0.17	.92	.49	.23
Age, yr	47.2±13.8	46.9±16.1	48.4±16.6	0.09	.91	.68	.18
Duration, mo	4.5±1.3	4.1±1.8	–	–	–	.09	–
BMI, kg/m^2	25.8±4.3	25.2±3.4	25.3±5.2	0.304	.739	.11	.25
FBG, mmol/L	8.9±2.4	8.8±2.2	5.2±0.8	34.95	<.01	.73	.00
HbA1c, %	10.6±1.2	10.2±1.1	5.4±0.5	270.16	<.01	.55	.00
SBP, mmHg	139.5±14.5	140.6±19.6	139.2±20.2	0.08	.93	.16	.13
DBP, mm Hg	79.6±9.6	79.7±9.7	77.9±12.9	0.33	.72	.87	.34
TC, mmol/L	5.5±1.3	5.6±1.4	5.1±0.9	1.56	.22	.65	.25
TG, mmol/L	2.6±0.9	2.5±0.7	2.2±0.6	2.68	.07	.56	.33
ACR, mg/g	22.1 (7.8, 42.2)	23.8 (8.4, 45.8)	–	–	–	.45	–

ACR = urinary albumin-to-creatinine ratio, BMI = body mass index, DBP = diastolic blood pressure, FBG = fasting blood glucose, IIT = intensive insulin therapy, OHA = oral hypoglycemic agent, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride.

* Between the IIT group and OHA group.

† Among the 3 groups.

3. Results

3.1. Baseline characteristics of the subjects

The study included 108 patients with newly diagnosed T2DM, each given 12 weeks of therapy: 56 in the IIT group (intensive BIT + metformin), and 52 in the OHA group (OHAs + metformin). Another 30 healthy volunteers were enrolled as the control group. The diabetic patients exhibited significantly higher levels of fasting blood glucose, HbA1c, total cholesterol (TC), and triglyceride (TG) compared with the control group (Table 1). However, the IIT and OHA groups were similar with regard to age, gender ratio, duration of disease, body mass index, fasting blood glucose, HbA1c, urinary albumin-to-creatinine ratio, systolic and diastolic blood pressure, TC, and TG (all, $P > .05$).

3.2. Changes in glycemic parameters at 12 weeks and 12 months after treatment

Before treatment, the diabetic patients in both the IIT and OHA groups exhibited higher glucagon levels at 0, 30, and 120 minutes of the meal tolerance test, as well as AUCg, compared with the control group (Fig. 1 and Table 2, and Supplementary Table 1, http://links.lww.com/MD/E21). In addition, the ratio of fasting proinsulin-to-CP (proinsulin/CP) was significantly higher, and $\Delta CP_{30}/\Delta G_{30}$ and $\Delta CP_{120}/\Delta G_{120}$ were significantly lower, compared with the control group.

Between the OHA and IIT groups, there were no significant differences in any of the analyzed glycemic parameters at baseline. In the IIT group, after intensive BIT for 12 weeks, compared with baseline the glucagon levels (0, 30 minutes and 120 minutes) and proinsulin/CP were significantly lower, whereas $\Delta CP_{30}/\Delta G_{30}$ and $\Delta CP_{120}/\Delta G_{120}$ were significantly higher (all, $P < .01$). In contrast, in the OHA group at 12 weeks, $\Delta CP_{30}/\Delta G_{30}$ and $\Delta CP_{120}/\Delta G_{120}$ were significantly higher compared with the baseline; while glucagon levels (0, 30 minutes, and 120 minutes) and proinsulin/CP were slightly lower, which failed to achieve statistical significance.

At 12 weeks, patients in the IIT group exhibited significantly lower glucagon levels and proinsulin/CP, and higher $\Delta CP_{30}/\Delta G_{30}$ and $\Delta CP_{120}/\Delta G_{120}$, compared with the OHA group, indicating that intensive BIT was superior to OHAs in glycemic control. On the other hand, although the proinsulin/CP, $\Delta CP_{30}/\Delta G_{30}$, and $\Delta CP_{120}/\Delta G_{120}$ of the IIT group were comparable to that of the control group at 12 weeks, the glucagon levels were still significantly higher than the normal levels.

In the OHA group, all the analyzed glycemic parameters differed significantly from the normal levels of the control group.

A 12 months, in the IIT group there were no significant changes in any of the glycemic parameters compared with their respective levels at 12 weeks. However, in the OHA group the levels of glucagon and proinsulin/CP were significantly higher at 12 months compared with the corresponding parameters at 12 weeks.

3.3. Spearman correlations of glycemic variables with the percentage change in total AUCg in the ITT group

There were no correlations between the percentage change in total AUCg (change between baseline *cf.* 12 weeks) and other glycemic parameters (proinsulin/CP, $\Delta CP_{30}/\Delta G_{30}$, and $\Delta CP_{120}/\Delta G_{120}$; Table 3).

3.4. Glycemic and lipid outcomes at 12 weeks and 12 months

In the IIT group, 97.9% and 80.9% of patients achieved the target glycemic goal (defined as HbA1c <7%) at 12 weeks and 12 months, respectively; whereas in the OHA group, only 62.5% and 44.4% achieved the target glycemic goal (both $P < .05$ compared with the IIT group at the same timepoint; Table 4). Compared with the OHA group, patients in the IIT group had lower TC and TG levels at 12 weeks and 12 months. Interestingly, patients in the IIT group used significantly fewer types of OHAs (1.5±0.8 at 12 months), but achieved a significantly higher remission rate (31.0%, defined as achievement of target glycemic goal without use of hypoglycemic agents lasting >6 months) compared with the OHA group (2.4±0.9, 5.6%, respectively).

4. Discussion

Proinsulin is the precursor of insulin and CP. In the secretory granules of β-cells, proinsulin can be cleaved by a combination of

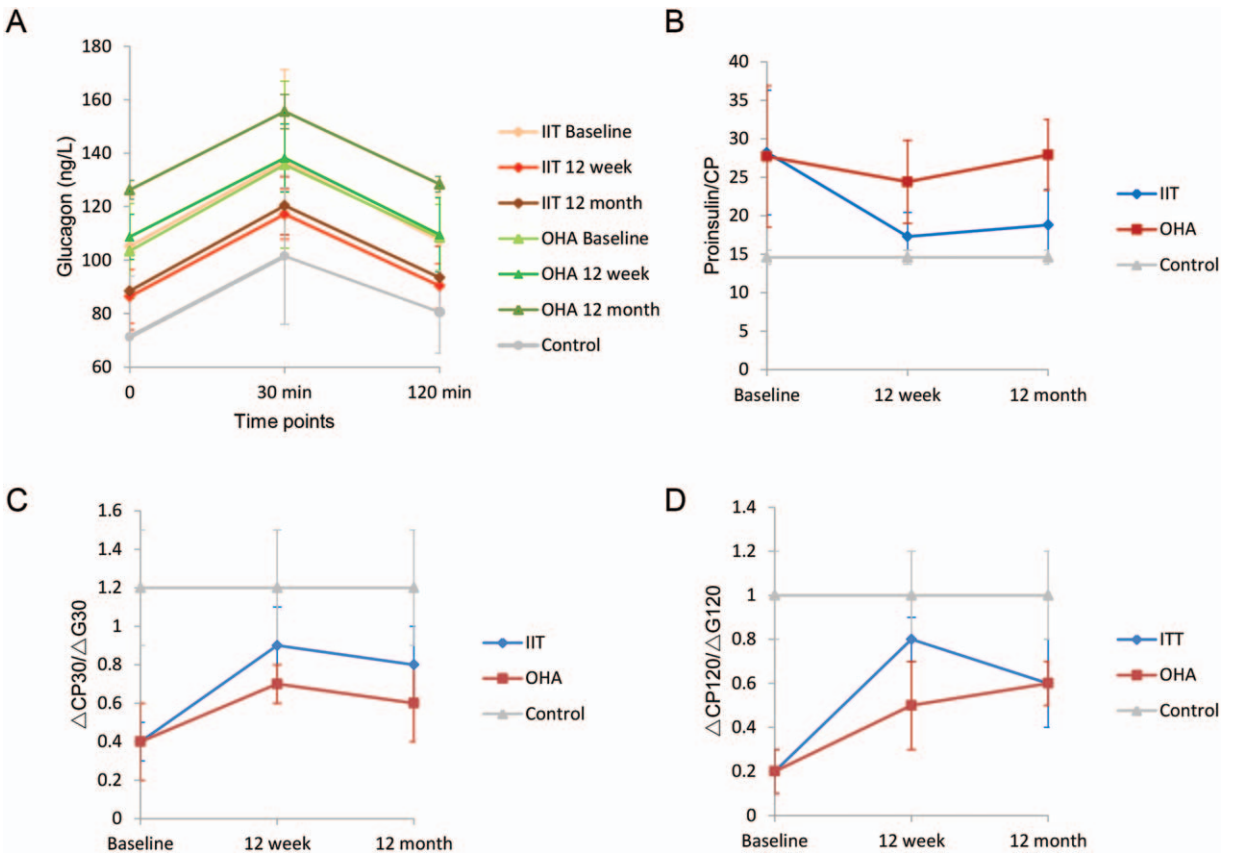

Figure 1. Changes in glycemic parameters at 12 wk and 12 mo after treatment in the ITT, OHA, and control groups. (A) Glucagon levels at 0, 30, and 120 min of the meal tolerance test. (B) Ratio of fasting proinsulin-to-C-peptide (proinsulin/CP); (C) ΔCP30/ΔG30; (D) ΔCP120/ΔG120. The data are expressed as mean ± SD. Glucagon, ng/L; proinsulin, pmol/L; CP, pmol/L. CP = C-peptide, IIT = intensive insulin therapy, OHA = oral hypoglycemic agent, SD = standard deviation.

pancreatic trypsin and carboxypeptidase, which leads to a conversion of proinsulin into equimolar concentrations of insulin and CP. Proinsulin-like material represents only 15% of serum immunoreactive insulin in fasting healthy individuals.[16] However, circulating proinsulin levels and proinsulin/CP ratios are significantly higher than normal in T2DM patients, and may serve as highly specific markers of insulin synthesis dysfunction as well as insulin resistance.[17]

In our present study, the basal proinsulin/CP ratio of the newly diagnosed patients was ~28%, which was significantly higher than that of the normal glucose tolerance group (14%). In addition, $\Delta CP_{30}/\Delta G_{30}$, and $\Delta CP_{120}/\Delta G_{120}$, the indices reflecting early and overall insulin secretion, were remarkably lower than normal. This suggests impairment of β-cell function in the newly diagnosed T2DM patients.

The above data revealed abnormalities in both synthesis and secretion of insulin. On the other hand, the newly diagnosed T2DM patients exhibited hyperglucagonemia compared with the subjects with normal glucose metabolism, suggesting functional hyperactivity of α-cells. The ratio of proinsulin/CP in the T2DM patients of the IIT group was significantly lower after a short term of intensive BIT compared with the baseline, accompanied by higher $\Delta CP_{30}/\Delta G_{30}$ and $\Delta CP_{120}/\Delta G_{120}$. This indicates that intensive BIT could improve insulin synthesis and secretion of β-cells. Intensive BIT was also associated with a reduction in the amount of glucagon at all timepoints of the meal tolerance test,

Table 2

Comparison of glycemic parameters.

				Comparisons with BL				Comparisons between groups at 12 wk						12 mo *cf.* 12 wk			
		BL, all groups		IIT		OHA		IIT and OHA		ITT and control		OHA and control		IIT		OHA	
		F	*P*	*t*	*P*	*t*	*P*	*t*	*P*	*t*	*P*	*t*	*P*	*T*	*P*	*t*	*P*
Glucagon, h	0.0	34.19	.00	43.01	.00	2.97	.08	46.95	.00	18.02	.00	65.44	.00	0.78	.38	478.34	.00
	0.5	14.40	.00	17.09	.00	2.58	.11	27.14	.00	17.05	.00	42.19	.00	2.77	.09	93.88	.00
	2.0	39.00	.00	45.12	.00	2.13	.06	17.35	.00	14.77	.00	33.49	.00	2.62	.11	92.13	.00
Proinsulin/CP		35.64	.00	88.45	.00	2.24	.05	36.88	.00	3.23	.08	61.35	.00	4.09	.05	31.26	.00
$\Delta CP_{30}/\Delta G_{30}$		195.05	.00	280.00	.00	93.6	.00	42.19	.00	3.78	.07	129.82	.00	3.31	.08	3.14	.07
$\Delta CP_{120}/\Delta G_{120}$		456.87	.00	140.00	.00	93.6	.00	16.36	.00	4.07	.06	122.09	.00	4.01	.06	4.24	.06

BL = baseline, CP = C-peptide, IIT = intensive insulin therapy, OHA = oral hypoglycemic agent.

Table 3

Spearman correlations of glycemic variables with the percentage change in total AUC (glucagon)* in the ITT group.

	r	*P*
FBG	0.02	.87
HbA1c	–0.01	.92
Proinsulin/CP	0.06	.65
$\Delta CP_{30}/\Delta G_{30}$	–0.22	.36
$\Delta CP_{120}/\Delta G_{120}$	–0.10	.10

AUC = area under the receiver operating characteristic curve, CP = C-peptide, FBG = fasting blood glucose, HbA1c = hemoglobin A1c.
* Change between baseline *cf.* 12 wk.

Table 4

Glycemic and lipid outcomes at 12 wk and 12 mo in the IIT and OHA groups.

	IIT		OHA	
	12 wk	12 mo	12 wk	12 mo
Subjects, n	49	42	48	36
HbA1c <7%, n (%)	48 (98.0)	34 (81.0)	30 (62.5)	16 (34.4)
TG, mmol/L	1.7±0.4	1.9±0.3	2.2±0.5	2.3±0.8
TC, mmol/L	4.8±0.3	5.0±0.4	5.2±0.7	5.4±0.8
Types of OHAs	1.0	1.5±0.8	2.8±1.0	2.4±0.9
Remission, n (%)*	–	13 (31.0)	–	2 (5.6)

HbA1c = hemoglobin A1c, IIT = intensive insulin therapy, OHA = oral hypoglycemic agent, TC = total cholesterol, TG = triglyceride.
* Defined as achievement of target glycemic goal (HbA1c <7%) without use of hypoglycemic agents lasting >6 mo.

although it still failed to normalize glucagon levels. This result is consistent with other studies.[5,7]

There is no consensus regarding whether α-cell hyperactivity is secondary to, or concomitant with, a decline of β-cell secretion. It has been reported that the elevations in glucagon levels observed in diabetic patients develop due to diminished islet β-cell function.[2,18] However, there is also a view that α-cell hyperfunction develops concomitantly with the onset of β-cell dysfunction in T2DM patients, and the inhibitory effect of hyperglycemia and insulin on glucagon secretion are both weakened.[5,19] In the present study, the proinsulin/CP ratio was significantly lower at 12 weeks after intensive BIT, which were close to the normal levels, suggesting great improvement in β-cell function. However, the AUCg in diabetic patients after intensive treatment was still significantly higher than that of the normal subjects. Especially, there were no correlations between the percentage change in total AUCg and various glycemic parameters, such as proinsulin/CP, $\Delta CP_{30}/\Delta G_{30}$, and $\Delta CP_{120}/\Delta G_{120}$. These data indicated a possibility of primary α-cell defect which did not improve in parallel with the recovery of β-cell function.

Similarly, Kramer et al[5] found a significant reduction in AUCg after intensive insulin therapy. However, the decrease in AUCg was not associated with the change in either β-cell function or in glycemic variability. Thus, it is presumed that the partial reversibility of α-cell function may be independent of the recovery of insulin secretion. The exact mechanism by which intensive insulin therapy ameliorates reversible α-cell dysfunction at the early stage of the course of T2DM remains unclear. One possible reason is that, in addition to the known adverse effects of chronic hyperglycemia on β-cells, there may be one (or more) unknown or unmeasured factors that affect α-cell function or the secretion of glucagon. Such unfavorable factor(s) could be at least partially eliminated by intensive insulin therapy, and as a result hyperglucagonemia was alleviated.[20,21]

There is a view that for newly diagnosed T2DM patients with HbA1c >9.0%, intensive insulin therapy can facilitate remission of diabetes in some patients, not only achieving acute correction of hyperglycemia and avoiding glucotoxicity, but also successfully laying a foundation for prolonged good glycemic control after discontinuation of insulin.[15,22] Short-term intensive insulin therapy has been reported to improve the underlying pathophysiological defects in early T2DM, and maintain normoglycemia without use of anti-diabetic medication after discontinuation of insulin.[6,23] In the present study, the newly diagnosed T2DM patients were treated with intensive BIT for 12 weeks and then followed for 1 year. A higher percentage of patients with intensive BIT achieved the target glycemic goal (HbA1c <7%), and had lower levels of TC and TG at 12 weeks and 12 months, compared with those given OHAs. In addition, patients treated with short-term intensive BIT used fewer types of OHAs after discontinuation of insulin, but achieved a high remission rate without the use of hypoglycemic agents. These data indicate that better, longer metabolic improvements may be achieved in patients with newly diagnosed T2DM after short-term intensive insulin therapy, as compared with the use of OHAs.[1,9,14]

This study had several limitations. First, it is based on a single-center with a relatively small sample size. Second, the role of some unmeasured confounding factors that could have possibly influenced the observed association cannot be entirely ruled out. For example, the extent to which lifestyle and dietary habits affected our study population was not known.

In conclusion, in this study short-term intensive BIT was associated with improvements in both β-cell and α-cell function in patients with newly diagnosed T2DM, allowing better, long-term metabolic control with minimal OHAs. A decline of β-cell secretion and concomitant α-cell dysfunction may together be involved in the pathogenesis of T2DM.

Author contributions

Conceptualization: Hai-Lan Zheng, Yan Xing, Fan Li, Shan-Dong Ye.
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Visualization: Hai-Lan Zheng, Yan Xing, Fan Li, Wei Ding, Shan-Dong Ye.
Writing – original draft: Hai-Lan Zheng, Yan Xing, Fan Li.
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