Efficacy of switching from premixed insulin to insulin glargine regimen in Type 2 diabetes mellitus patients with different islet functions

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Received August 13, 2013; Accepted April 2, 2014

DOI: 10.3892/mmr.2014.2263

Abstract. The present study evaluated the efficacy of switching from premixed insulin or an insulin analogue to insulin glargine plus oral antidiabetic drugs (OADs) in patients with type 2 diabetes mellitus (T2DM). The feasibility and suitability of the regimen to the patients was examined based on islet function. Patients with T2DM (n=30) treated with stable doses of premixed insulin or an insulin analogue for eight weeks were divided into two groups according to islet function. Group A had a 2 h of C peptide (2hCP)/fasting C peptide (FCP) ratio ≤3, whereas group B had a 2hCP/FCP ratio >3. Eight weeks following the switch to insulin glargine plus OADs, a significant decrease in fasting blood glucose (FBG), 2 h postprandial blood glucose (2hPBG) and glycosylated-haemoglobin (HbA1c) were observed in the two groups, with effective rates of 75, 42.9 and 39.3%, respectively. A distinct reduction in the insulin dose was particularly evident in group B. There was a marked decrease in FBG in group A, more so than that observed in group B. By contrast, the decrease in HbA1c was more evident in group B following the switch. A larger number of patients in group B had HbA1c≤7.0%, compared with group A. No difference in the incidence of hypoglycaemia and change of body weight were observed. Following the switch to insulin glargine plus OADs, patients with T2DM demonstrated improved blood glucose control and reduced insulin dosage. The results revealed that this switch in regimen is more suitable for patients with T2DM with 2hCP/FCP>3 and that administration of insulin glargine plus OADs is more efficacious for patients with T2DM with increased FBG levels.

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Key words: type 2 diabetes mellitus, islet function, C peptide, insulin glargine, premixed insulin

Introduction

Diabetes mellitus (DM) is an endocrine metabolic disease characterised by hyperglycaemia. Of all diabetic patients, 95% are classified as having type 2 DM (T2DM). In developed countries, T2MD has become a major chronic disease that seriously threatens human health, affecting an increasing number of people every year. Chronic complications, particularly macroangiopathy, are considered an important cause of death and disability in patients with T2DM (1). Efficient control of blood glucose is the basic strategy utilized to delay the initiation and development of DM complications (2). Insulin effectively reduces the risk of macroangiopathy in patients with T2DM (3). Thus, optimizing the efficacy of insulin therapy for patients with T2DM is crucial.

Currently, ~80% of patients with T2DM receive premixed insulin and insulin analogues in the form of two subcutaneous injections, one in the morning and the other in the evening, and a number of clinical studies have proven the effectiveness of such regimen on glycaemic control (4-9). This is a simplified approach in DM treatment, which minimizes the number of injections patients must receive daily. However, it is limited by its fixed ratio, which does not fulfil normal physiological needs or provide enough flexibility, and it is associated with increasing the risk of hypoglycaemia (4,8). The key application of premixed insulin enabling regular monitoring of blood glucose, which allegedly establishes good glycaemic control. However, the majority of patients with diabetes in China still have poor control of blood glucose or suffer from frequent hypoglycaemia. Therefore, simplified treatment strategies that decrease the risk of hypoglycaemia and improve blood glucose control are essential to improve the efficacy of diabetes therapeutics.

Several studies have investigated such novel treatment strategies (10-14) by adopting a two-back-one strategy, where premixed insulin/insulin analogues that were ineffective in patients with T2DM were replaced with insulin glargine plus OADs. Improved glycaemic control was observed in the patients following the switch in regimen. Insulin glargine is a long-term human insulin analogue with slow and stable absorption and is thus capable of functioning for 24 h with stable bioavailability. When injected once daily, it lowers

the incidence of hypoglycaemia and possibly stimulates physiological insulin secretion. When combined with OAHs, it has the capacity to control blood glucose to a safe range by promoting endogenous insulin secretion and glucose advantage, as well as by inhibiting glucose absorption. However, the two-back-one strategy currently focuses on the standard-reaching rate of glycosylated-haemoglobin (HbA1c), incidence of hypoglycaemia and satisfaction of patients. The suitability of this strategy for different patients has not been reported. Furthermore, previous studies reported that patients who received two-back-one treatment continued to have poor glycaemic control, which is presumably correlated with inter-patient differences in islet function. However, to the best of our knowledge, no studies have yet confirmed this hypothesis. In the present study, two-back-one treatment was administered to patients with T2DM by an injection of premixed insulin or an insulin analogue. Patients were grouped according to islet function and the efficacy of the new treatment in these groups was observed. The aim was to examine the feasibility of the two-back-one strategy and its suitability to different patients, with the purpose of providing data that will optimise insulin therapy for T2DM patients.

Materials and methods

Subjects. Between 2010 and 2011, T2DM patients who were injected with stable doses of premixed insulin or analogue twice a day for at least eight weeks were selected from the First Subsidiary Hospital of the Medical College of Dalian (Liaoning, China). The subjects were aged 18-75 years and had been diabetic for <15 years. These patients received an insulin dose of 50 IU/day, and had laboratory values of fasting blood glucose (FBG)<11 mmol/l, 5.5% <HbA1c≤10% and fasting C peptide (FCP)≥0.8 ng/ml. This study also included patients with frequent glycopenia (frequent mild, severe nighttime glycopenia), those with irregular life styles and those willing to reduce the number of injections. Patients with the following conditions were excluded: Liver dysfunction with alanine transaminase exceeding twice the normal upper limit, obvious renal disease or serum creatinine ≥133 mmol/l, various diseases affecting blood glucose (such as hyperthyroidism and hypercortisolism), prior systemic corticosteroid therapy or hormone replacement therapy, diabetes with acute complications, concomitant disease or stressful situation, severe heart failure at level III or IV and/or left ventricular ejection fraction <40%, pregnancy, gestation or lactation. Patients who were allergic or intolerant to the test drugs, had poor compliance, did not cooperate, changed food or drugs or were lost in the follow-up period, as well as those whose blood glucose levels were not controlled (FBG>7.0 mmol/l, 2 h postprandial blood glucose (2hPBG)>10 mmol/l) three weeks following the switch, were also not included. The present study was conducted in accordance with the declaration of Helsinki and with approval from the Ethics Committee of Henan province people's hospital. Written informed consent was obtained from all participants.

Methods. After the selected patients signed the informed consent form, their treatment was switched from premixed insulin or analogue to insulin glargine (300 U/vial; Sanofi-Aventis China Co., Ltd., Beijing, China) or insulin glargine with a glimepiride tablet (2 mg/tablet; Sanofi-Aventis China Co., Ltd.). The original oral medicine therapy was retained. The specific treatment was as follows: Initial dose of insulin glargine was 0.15 U/kg/day, which was subcutaneously injected prior to sleeping every night and a 2 mg glimepiride tablet was taken prior to breakfast every day. The target value of parameters was set as 4.4 mmol/l ≤FBG≤7.0 mmol/l and 2hPBG≤10 mmol/l. Glucose levels were monitored through fingerstick testing to adjust drug dose. Glargine insulin (≤1 U) was added every time FBG exceeded the target value of 1 mmol/l; in patients with hypoglycaemia (<3.3 mmol/l), glargine insulin was reduced by 2 U to 6 U. The doses were adjusted every 2-3 days. Patients with 2hPBG exceeding 10 mmol/l received 50-100 mg acarbose (50 mg/tablet; Bayer China Co., Ltd., Beijing, China) during mealtimes, depending on their actual condition. Antihypertensive and lipid-lowering therapy remained constant. The subjects were monitored for eight weeks.

Evaluation indices. Efficacy indices included HbA1c, FBG, 2hPBG (with a target range of FBG≤7.0 mmol/l, 2hPBG≤10 mmol/l and HbA1c≤7.0%) and insulin dose.

Islet function and insulin sensitivity indices were as follows: Homeostasis model assessment-function of β cells (HOMA-β)=0.27xFCP/(FPG-3.5); homeostasis model assessment-insulin resistance (HOMA-IR)=1.5+FPGxFCP/2800. Insulin therapy was administered to all patients in the study. As the connecting peptide or C-peptide was secreted at the same rate as insulin (which was not affected by external insulin), FCP was used as an alternative to fasting insulin to evaluate insulin resistance and pancreatic β-cell function (15).

Safety indices included the following: i) Hypoglycaemic events (hypoglycaemia and severe hypoglycaemia were defined as blood glucose ≤4.0 mmol/l and blood glucose ≤2.8 mmol/l, whereas symptomatic hypoglycaemia was characterised by palpitation, sweating and hunger without a corresponding record of glycaemia or the monitored blood glucose not reaching the above standard); ii) body weight and body mass index (BMI) and iii) any adverse events.

Statistical analysis. All data were analysed using SPSS 13.0 software (SPSS, Inc., Chicago, IL, USA). Variable values of measurement data are presented as the mean ± standard deviation and were subjected to normality and F-tests. The t-test was employed to compare between the groups prior to and following the switch. The χ^2 test was used for comparing the rates. Classified indices were described as a case number and % of each type. $P<0.05$ was considered to indicate a statistically significant difference between values.

Results

General data comparison. Among the 30 patients selected for this study, only 28 remained at the end of the investigations, due to two patients leaving the study early. Of these two patients, one had high blood glucose levels due to an insufficiently controlled diet and the other switched back to premixed insulin from insulin glargine due to high blood glucose. The subjects were divided into two groups according

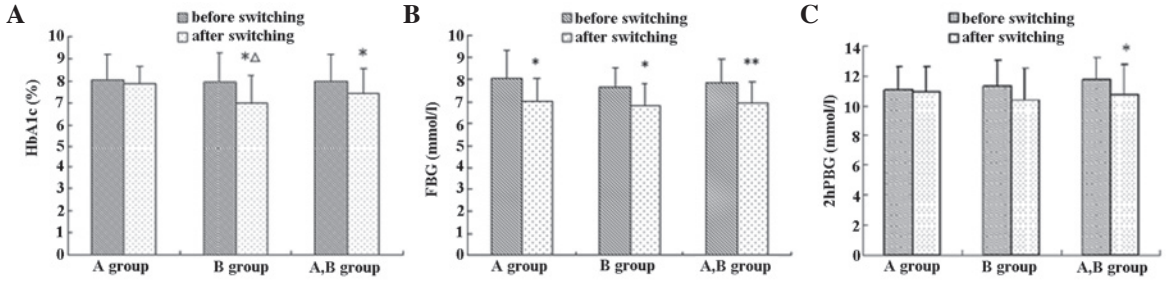

Figure 1. Comparison of HbA1c, FBG and 2hPBG levels before and after the switch. (A) HbA1c levels. *P<0.05 as compared with the value before the switch; ΔP<0.05 for comparison between group A and B after the switch. (B) FBG levels. *P<0.05, **P<0.01 as compared with the value before the switch. (C) 2hPBG levels.*P<0.05 as compared with value before the switch. Group A, 2hCP/FCP≤3; group B, 2hCP/FCP>3. HbA1c, glycosylated-haemoglobin; FBG, fasting blood glucose; 2hPBG, 2 h postprandial blood glucose; FCP, fasting C-peptide.

Table I. Comparison of general data between two groups.

	Group A	Group B
Gender (M/F)	7/7	6/8
Age (years)	52.93±10.74	53.57±13.15
Disease course (year)	8.00±3.96	6.25±5.26
BMI (kg/m^2)	27.76±5.53	26.28±2.17
Bodyweight (kg)	77.00±14.00	70.43±5.84
FBG (mmol/l)	8.05±1.22	7.64±0.87
2hPBG (mmol/l)	11.08±1.51	11.32±1.66
HbA1c (%)	8.04±1.16	7.94±1.32
FCP (ng/ml)	2.29±1.32	1.64±0.65
2hCP (ng/ml)	4.86±2.59	7.78±2.99*
HOMA-IR	0.81±0.45	0.54±0.18
HOMA-β	10.87±6.95	8.70±4.96
Insulin dose (U)	30.79±8.15	26.07±6.13

*P<0.05, compared with before the switch. Group A, 2hCP/FCP≤3; group B, 2hCP/FCP>3. BMI, body mass index; FBG, fasting blood glucose; 2hPBG, 2 h postprandial blood glucose; HbA1c, glycosylated-haemoglobin; FCP, fasting C-peptide; HOMA-IR, homeostasis model assessment-insulin resistance; HOMA-β, homeostasis model assessment-function of β cells.

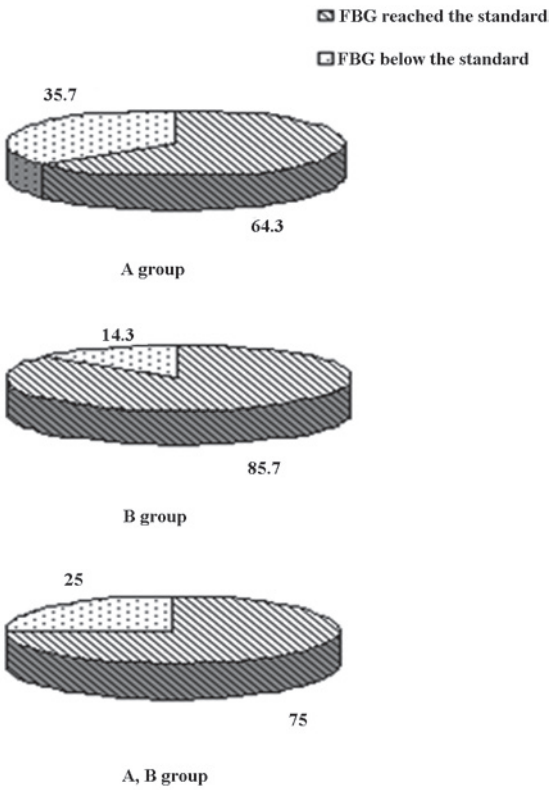

Figure 2 Comparison of standard-reaching rate of FBG. Group A, 2hCP/FCP≤3; group B, 2hCP/FCP>3. FCP, fasting C-peptide; FBG, fasting blood glucose.

to islet function: Group A, 2hCP/FCP≤3; seven males, seven females (mean, 52.93±10.74 years old). Group B, 2hCP/FCP>3; six males, eight females (mean, 53.57±13.15 years old).

No significant differences were observed between the two groups in terms of age, gender ratio, disease course, body weight, BMI, HbA1c, FBG, 2hPBG, FCP, HOMA-IR, HOMA-β and insulin dose. The difference in 2hCP between the two groups was statistically significant (P<0.05), as demonstrated in Table I.

Efficacy after switch. Eight weeks following the treatment switch, the average HbA1c, FBG and 2hPBG of the 28 patients decreased by 9.18, 11.61 and 8.04%, respectively, compared with the values prior to switching, which was a statistically significant difference (P<0.05), particularly for FBG reduction (P<0.01). HbA1c, FBG and 2hPBG decreased by 4.65, 12.55 and 1.17%, respectively, in group A and by 13.81, 10.73 and 8.04%, respectively, in group B, compared with values prior to switching. A significant decrease in FBG was observed in group A and in the HbA1c and FBG in group B (P<0.05). Statistical significance in HbA1c reduction was higher in group B than in group A (P<0.05), as demonstrated in Table II and Fig. 1.

Prior to the switch, standard values of HbA1c, FBG and 2hPBG were noted in six, five and three cases, respectively (two, two and one of the cases were in group A and four, three and two of the cases were in group B, respectively). No significant difference was observed between the two groups. Eight weeks after the switch in treatment, the standard-reaching rates of HbA1c, FBG and 2hPBG in the 28 patients were 39.3, 75.0 and 42.9%, respectively. This result demonstrates that the standard-reaching rate of FBG was markedly higher compared with that of HbA1c and 2hPBG (P<0.05). The standard-reaching rates of HbA1c,

Table II. Comparison of main efficacy indices prior to and after switch in the selected patients (± standard deviation).

	Before switch			After switch		
Group	A	B	A+B	A	B	A+B
HbA1c	8.04±1.16	7.94±1.32	7.99±1.22	7.84±0.79	6.99±1.26$^{*\Delta}$	7.42±1.12*
FBG (mmol/l)	8.05±1.22	7.64±0.87	7.84±1.05	7.04±0.99*	6.82±0.97*	6.93±0.96**
2hPBG (mmol/l)	11.08±1.51	11.32±1.66	11.69±1.51	10.95±1.63	10.41±2.04	10.75±2.00*
Insulin dose (U)	30.79±8.15	26.07±6.13	28.43±7.48	15.29±3.00**	12.57±3.72$^{**\Delta}$	13.93±3.59**
Body weight (kg)	77.0±14.0	70.43±5.84	73.71±11.04	76.36±13.67	70.29±6.17	73.32±10.86
BMI (kg/m^2)	27.76±5.53	26.28±2.17	27.02±4.19	27.16±5.29	26.05±2.03	26.76±0.76

*P<0.05, **P<0.01 for comparison before and after the switch; $^{\#}$P<0.05 for comparison between group A and B after switch. A, 14 cases; B, 14 cases; A+B, 28 cases. Group A, 2hCP/FCP≤3; group B, 2hCP/FCP>3. FCP, fasting C-peptide; HbA1c, glycosylated-haemoglobin; FBG, fasting blood glucose; 2hPBG, 2 h postprandial blood glucose; BMI, body mass index.

Table III. Comparison of glycemic standard-reaching rate.

Group	A		B		A+B	
Standard-reaching	Cases (n)	Rate (%)	Cases (n)	Rate (%)	Cases (n)	Rate (%)
FBG (mmol/l)	9	64.3	12	85.7	21	75.0
2hPBG (mmol/l)	4	28.6	8	57.1	12	42.9*
HbA1c (%)	3	21.4*	8	57.1$^{\Delta}$	11	39.3*

*P<0.05 for comparison of standard-reaching rate of HbA1c and 2hPBG with that of FBG; $^{\Delta}$P<0.05 for comparison of various indices between group A and B. A, 14 cases; B, 14 cases; A+B, 28 cases. Group A, 2hCP/FCP≤3; group B, 2hCP/FCP>3. FCP, fasting C-peptide; HbA1c, glycosylated-haemoglobin; FBG, fasting blood glucose; 2hPBG, 2 h postprandial blood glucose.

Table IV. Comparison of incidence of hypoglycemia between group A and B.

	Cases (n)	Patients with hypoglycemia (n)	Incidence of hypoglycemia (%)	χ^2	P-value
Group A	14	0	0		
Group B	14	1	7.1	1.04	0.05

A, 14 cases; B, 14 cases; A+B, 28 cases. Group A, 2hCP/FCP≤3; group B, 2hCP/FCP>3. FCP, fasting C-peptide; 2hCP, 2h C-peptide.

FBG and 2hPBG were 21.4, 64.3 and 28.6% in group A and 57.1, 85.7 and 57.1% in group B (Fig. 2). The standard-reaching rates of HbA1c in group B were markedly higher compared with those in group A (P<0.05), as demonstrated in Table III.

Comparison of insulin dose. The average insulin dose decreased by 51.0% in the 28 patients following the switch in treatment, and statistical significance was measured at P<0.01. The average insulin dose markedly decreased by 50.34 and 53.7% in groups A and B, respectively (P<0.01). However, the insulin doses in group B were distinctly lower than those in group A (P<0.05), as shown in Table II and Fig. 3.

Safety evaluation. During the study, one case of mild hypoglycaemia (1/28, 3.6%) was identified, but no cases of severe hypoglycaemia were observed. No significant difference was identified between groups A and B in terms of the incidence of hypoglycaemia (P>0.05). Table IV demonstrated that there were hypoglycaemic cases observed in group A (0%), but one case of mild hypoglycaemia was seen among the 14 cases in group B (7.1%).

Eight weeks following the treatment switch, there was no significant change in body weight and BMI (P>0.05). The difference in body weight and BMI between groups A and B was also non-significant (P>0.05), as demonstrated in Table II.

Discussion

Previous studies (10-14) have demonstrated improved glycaemic control after premixed insulin/insulin analogue

Table V. Conditions of patients who are suitable for switching of diabetes treatment as indicated by associated studies.

	Conditions of patients			
	FBG (mmol/l)	HbA1c (%)	Course of disease (years)	Dose of premixed insulin (U/day)
Chinese study (14) Group A	10.2±1.8	8.8	10 (6-13)	35±19
Group B	10.9±3.0	8.9	11 (8-20)	32±10
Hammer's study (10)		9.9	8.3	8.6±6.1 35.5±15.0
Optimization study (14)		8.94±2	8.36	7.42±2.49 34.4
Treatment switch recommended	~10	<9%	<10	<40

Group A, 2hCP/FCP≤3; group B, 2hCP/FCP>3. FCP, fasting C-peptide; HbA1c, glycosylated-haemoglobin; FBG, fasting blood glucose.

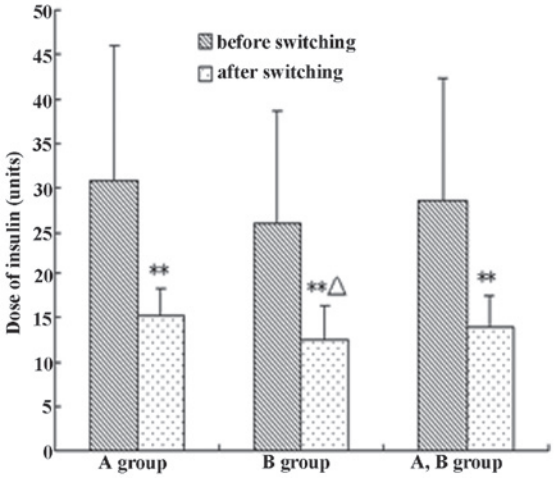

Figure 3. Comparison of insulin doses before and after the switch. *P<0.05, **P<0.01, comparison before and after the switch. ΔP<0.05, comparison between group A and B after the switch. Group A, 2hCP/FCP≤3; group B, 2hCP/FCP>3. FCP, fasting C-peptide.

regimens, that were ineffective in treating T2DM patients, were replaced with insulin glargine plus OADs. In the present study, the treatment of 28 T2DM patients was switched from premixed insulin or analogue to insulin glargine with OADs. HbA1c, FBG and 2hPBG decreased by 9.18, 11.61 and 8.04%, respectively, eight weeks after the switch (P<0.05). FBG reduction was statistically significant (P<0.01), which is consistent with that observed in previous studies (10-14). In a study by the AT.LANTUS group (12), the treatment of 384 T2DM patients with poor glycaemic control was switched from premixed insulin plus OADs to insulin glargine plus OADs and the level of HbA1c and FBG highly improved. In the study by Hammer *et al* (10), treatment was switched from premixed insulin to insulin glargine plus OADs, in 6308 T2DM patients who had an average disease course of 8.6 years; 8.3% of HbA1c, 9.9 mmol/l of FBG and 10.8 mmol/l of 2hPBG. A distinct decrease in the patients' HbA1c, FBG and 2hPBG was observed 12 weeks following the switch. Yang *et al* (14) performed a multicentre, prospective study where treatment was switched to insulin glargine in 313 T2DM patients, who were not responsive to premixed insulin. The average FBG and 2hPBG improved, compared with the baseline values. Average HbA1c also markedly decreased 16 weeks after the switch.

In the present study, HbA1c≤7.0%, FBG≤7.0 mmol/l and 2hPBG≤10 mmol/l were defined as the standard. Their corresponding standard-reaching rates eight weeks after the switch were 39.3, 75 and 42.9%, respectively, which further confirmed the effectiveness of the two-back-one strategy. Of note, the differences in standard-reaching rates that have been reported in various studies were mainly due to differences in the standards adopted. Hammer *et al* (10) set the standard as HbA1c<7.5%, FBG<6.7 mmol/l and 2hPBG<7.2 mmol/l. The corresponding standard-reaching rates were 73.9, 48.9 and 38.4%, respectively. In the study by Yang *et al* (14), the standard was HbA1c<7.0% and the standard-reaching rate was only 19.5%, which is lower than the value in the present study, which is mainly due to the effects of the course of treatment. The average treatment course of the patients in the present study was shorter (group A, 8±3.96 years; group B, 6.25±5.26 years), whereas that of patients in the study by Yang *et al* was increased by ~10 years. Patients with a shorter treatment course may have maintained relatively good islet function and therefore, the converted compliance rate would have been higher as a result. In the study by Yang *et al*, the standard-reaching rate of FBG is evidently higher than that of HbA1c and PBG (P<0.05), because basic insulin effectively reduces FBG and glycogen output, enhances insulin sensitivity and increases insulin secretion in DM patients (7). By contrast, in the present study, the standard-reaching rate of FBG was higher and the standard-reaching rate of HbA1c was lower, compared with the results of other studies, because the target values were different.

Following the switch, our results demonstrated a significant reduction in average insulin dose (51%) of the patients (P<0.01). In another study, Ligthelm *et al* demonstrated that long-acting insulin analogues combined with oral drugs reduce the amount of insulin approximately by half, but deliver similar blood glucose control compared with premixed insulin/analogues (16). Although the insulin dose decreased by 20% following the switch in regimen in the study by Yang *et al* (14), the present study yielded a higher reduction in insulin dose, which is correlated with the FBG standard setting (FBG≤6.0 mmol/l). Furthermore, in the present study, certain patients had short disease courses, whereas others had better insulin function and achieved HbA1c≤7.0% prior to the switch, and thus, the insulin dose was lower.

Hypoglycaemia was observed in only one case (3.6%), in which the insulin dose was not reduced, according to the decrease in blood glucose. However, hypoglycaemia was no longer evident when the insulin dose was decreased. Thus, the incidence of hypoglycemia was low in this study, as it was observed in only nine of all the patients who received premixed insulin or insulin analogues eight weeks prior to the treatment switch. No significant change was identified in the body weight and BMI of the patients following the switch. Domestic and foreign studies have demonstrated a dramatic decrease in the incidence of hypoglycaemia after the switch in regimen. Furthermore, patients were more satisfied with the fewer injections and easy administration of insulin glargine, proving that the glargine treatment promotes increased safety and compliance (17,18), which is inseparable from the biological characteristics of the long-acting insulin analogues (19).

The treatment of diabetes should be individualised, and each treatment program, including long-acting insulin analogues, has its adaptation (20). Therefore, treatment conversions are often only successful in a number of patients, while the glucose levels of certain patients are not controlled effectively after converting. Summarizing the findings of several recent studies (10-14), patients with the following characteristics are suitable to undergo a treatment switch: i) Poor glycaemic control from premixed insulin (FPG ~10 mmol/l, HbA1c<9%); ii) frequent hypoglycaemia, severe hypoglycaemia or nocturnal hypoglycaemia; iii) evident increase in body weight; iv) poor life quality, including receiving too many/inconvenient injections, as well as extra meals or limited mealtimes; and v) certain pancreatic β-cell function. Relevant studies were summarised to determine the conditions of patients who were ready for the treatment switch (Table V).

However, the majority of studies investigating the two-back-one strategy have focused only on the standard-reaching rate of HbA1c, incidence of hypoglycaemia and satisfaction of patients. The suitability of different patients for this strategy has not been reported. Therefore, the T2DM patients in this study were divided into two groups according to the 2hCP/FCP ratio and administered two-back-one treatment by injection with premixed insulin or an insulin analogue to examine the feasibility of the strategy and identify suitable patients based on islet function. The higher standard-reaching rate of HbA1c in group B (2hCP/FCP>3) compared with group A (2hCP/FCP≤3) was significant ($P<0.05$), whereas the difference in the standard-reaching rates of FBG and 2hPBG was not significant. The evident reduction in HbA1c in group B was higher compared with group A after the switch ($P<0.05$). The decrease in the amount of insulin injection in the patients (group A, 50.34% and group B, 53.70%) was significant ($P<0.01$). The patients in group B received less insulin compared with those in group A, indicating a higher standard-reaching rate, more significant decrease in blood glucose and less insulin dosage in patients with better islet function. In addition, insulin glargine combined with OADs was suitable as a treatment for diabetes patients who received premixed insulin or insulin analogues in the case of FCP≥0.8 ng/ml, particularly when 2hCP/FCP>3.

Two patients left the study because in one case, the blood glucose of the patient was too high during the follow-up, which was caused by an insufficiently controlled diet. In the other case, the patient switched back to premixed insulin from insulin glargine due to high blood glucose. These two cases indicated that diet control remains an important basis of T2DM treatment. The blood glucose of patients did not reach the standard owing to the following reasons: i) Uncontrolled diet (unscheduled timing or quantity) or insufficient exercise; ii) inadequate dosage of hypoglycaemic drugs or non-adherence to the drug combination and iii) unsystematic monitoring of blood glucose. Therefore, it is concluded that drug therapy is only one component of diabetes therapeutics, and efficacious treatment relies also on diet control and exercise adjustment, good compliance and regular blood glucose monitoring, to ensure qualified blood glucose levels (21,22). The present study adopted only a small number of patients and no specific subgroup was subjected to different oral hypoglycaemic drugs. In future investigations, the sample size should be increased to study the efficacy of the two-back-one strategy more reliably.

In conclusion, switching diabetic treatment regimens from premixed insulin or insulin analogues to insulin glargine plus OADs, i.e., the two-back-one strategy, allows better glycaemic control, shorter injection times, more convenient application and lower incidence of hypoglycaemia without body weight increase in T2DM patients who have certain islet functions. Insulin glargine plus OADs is particularly suitable for T2DM patients with high FBG, minimal amounts of insulin injections and relatively good islet function. The 2hCP and FCP ratios, as demonstrated in this study, indicated the success rate of the two-back-one strategy in the treatment of T2DM.

References

1. Yang Y, Yao JJ, Du JL, *et al*: Primary prevention of macroangiopathy in patients with short-duration type 2 diabetes by intensified multifactorial intervention: seven-year follow-up of diabetes complications in Chinese. Diabetes Care 36: 978-984, 2013.
2. Gaede P, Lund-Andersen H, Parving HH and Pedersen O: Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 358: 580-591, 2008.
3. Holman RR, Paul SK, Bethel MA, Matthews DR and Neil HA: 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 359: 1577-1589, 2008.
4. Rizvi AA and Ligthelm RJ: The use of premixed insulin analogues in the treatment of patients with type 2 diabetes mellitus: advantages and limitations. Insulin 2: 68-79, 2007.
5. Miser WF, Arakaki R, Jiang H, Scism-Bacon J, Anderson PW and Fahrbach JL: Randomized, open-label, parallel-group evaluations of basal-bolus therapy versus insulin lispro premixed therapy in patients with type 2 diabetes mellitus failing to achieve control with starter insulin treatment and continuing oral antihyperglycemic drugs: a noninferiority intensification substudy of the DURABLE trial. Clin The 32: 896-908, 2010.
6. Levit S, Toledano Y and Wainstein J: Improved glycaemic control with reduced hypoglycaemic episodes and without weight gain using long-term modern premixed insulins in type 2 diabetes. Int J Clin Pract 65: 165-171, 2011.
7. Vaag A and Lund SS: Insulin initiation in patients with type 2 diabetes mellitus: treatment guidelines, clinical evidence and patterns of use of basal vs premixed insulin analogues. Eur J Endocrinol 66: 159-170, 2012.
8. Fritsche A, Larbig M, Owens D, Häring HU and the GINGER study group: Comparison between a basal-bolus and a premixed insulin regimen in individuals with type 2 diabetes-results of the GINGER study. Diabetes Obes Metab 12: 115-123, 2010.
9. Giugliano D, Maiorino MI, Bellastella G, Chiodini P, Ceriello A and Esposito K: Efficacy of Insulin Analogs in Achieving the Hemoglobin A1c Target of <7% in Type 2 Diabetes: Meta-analysis of randomized controlled trials. Diabetes Care 34: 510-517, 2011.

10. Hammer H and Klinge A: Patients with type 2 diabetes inadequately controlled on premixed insulin: effect of initiating insulin glargine plus oral antidiabetic agents on glycaemic control in daily practice. Int J Clin Pract 61: 2009-2018, 2007.
11. Bu S, Guo XH, Yang WY, *et al*: Post-hoc analyses of type 2 diabetes patients switch from premixed insulin regimen to basal insulin plus oral hypoglycemic agents regimen. Zhong Hua Yi Xue Za Zhi 87: 3115-3118, 2007 (In Chinese).
12. Davies M, Lavalle-González F, Storms F, Gomis R and AT.LANTUS Study Group: Initiation of insulin glargine therapy in type 2 diabetes subjects suboptimally controlled on oral antidiabetic agents: results from the AT.LANTUS trial. Diabetes Obes Metab 10: 387-399, 2008.
13. Gómez-Peralta F, Carramiñana-Barrera F, Félix-Redondo FJ, Fraile-Gómez J and Extreme Rescue Study Group: Glycaemic control in patients with type 2 diabetes switching from premixed insulin to long-acting basal insulin analogue plus oral antidiabetic drugs: an observational study. Int J Clin Pract 66: 959-968, 2012.
14. Yang W, Lv X, Li Q, Jia W and Tian H: A prospective study to optimize insulin treatment by switching to insulin glargine in type 2 diabetic patients previously uncontrolled on premixed insulin: the optimization study. Curr Med Res Opin 28: 533-541, 2012.
15. Li X, Zhou ZG, Qi HY, Chen XY and Huang G: Replacement of insulin by fasting C-peptide in modified homeostasis model assessment to evaluate insulin resistance and islet beta cell function. Zhong Nan Da Xue Xue Bao Yi Xue Ban 29: 419-423, 2004 (In Chinese).
16. Ligthelm RJ, Gylvin T, DeLuzio T and Raskin P: A comparison of twice-daily biphasic insulin aspart 70/30 and once-daily insulin glargine in persons with type 2 diabetes mellitus inadequately controlled on basal insulin and oral therapy: a randomized, open-label study. Endocr Pract 17: 41-50, 2011.
17. Standl E, Maxeiner S, Raptis S, Karimi-Anderesi Z, Schweitzer MA and HOE901/4009 Study Group: Good glycemic control with flexibility in timing of basal insulin supply: a 24-week com-parison of insulin glargine given once daily in the morning or at bedtime in combination with morning glimepiride. Diabetes Care 28: 419-420, 2005.
18. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA and Yki-Järvinen H: Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care 28: 254-259, 2005.
19. Porcellati F, Lucidi P, Rossetti P, *et al*: Differential effects of adiposity on pharmacodynamics of basal insulins NPH, glargine, and detemir in type 2 diabetes mellitus.. Diabetes Care 34: 2521-2523, 2011.
20. Nathan DM, Buse JB, Davidson MB, *et al*: Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 32: 193-203, 2009.
21. Romero-Márquez RS, Díaz-Veja G and Romero-Zepeda H: Style and quality of life in patients with type 2 diabetes. Rev Med Inst Mex Seguro Soc 49: 125-136, 2011 (In Spanish).
22. Shrestha P and Ghimire L: A review about the effect of life style modification on diabetes and quality of life. Glob J Health Sci 4: 185-190, 2012.