Original Article
Comparative research on insulin detemir combined with repaglinide and insulin aspart 30 in treating aged type 2 diabetes mellitus

Xiaomei Wang[1*], Liang Zhao[2*], Yihui Liu[3]

[1]Department of Endocrinology, Zaozhuang Municipal Hospital, Zaozhuang 277102, China; [2]Department of Endocrinology, Hedong District People's Hospital, Linyi 276034, China; [3]Department of Radiotherapy, Affiliated Hospital of Weifang Medical University, Weifang 256603, China. *Equal contributors.

Abstract: Background: Oral anti-diabetic drugs (OAD) cannot effectively control blood glucose for patients with type 2 diabetes mellitus (T2DM). The selection of insulin in elderly patients should be smooth in lowering blood glucose, and as far as possible to reduce blood glucose fluctuation, hypoglycemia and weight gain to ensure the safety of medicine. Purpose: To compare the efficacy and safety between insulin detemir combined with repaglinide and insulin aspart 30 (BIAsp30) in treating aged type 2 diabetes mellitus (T2DM) patients who were inefficacious to OAD drugs therapy. Methods: 98 elderly T2DM patients inefficacious to oral anti-diabetic drugs therapy were randomized into detemir combined with repaglinide (Det+Rep) group (50 cases) and BIAsp30 group (48 cases), which were treated with corresponding drugs, respectively. The treatment duration was 12 weeks. Before and after treatment, the indexes in blood glucose, blood lipids, islet cell function, weight increase, hypoglycemia and insulin dosage between two groups were compared. Results: After treatment, the levels of FPG, 2hPG, HbA1c, HOMA-IR, TG, TC, LDL-C in two groups were decreased significantly (P < 0.05), and the levels of FC-P, 2hC-P and HOMA-β were increased (P < 0.05). The levels of MAGE, CV and HOMA-IR in Det+Rep group were significantly lower than those in BIAsp30 group (P < 0.05), and the levels of FC-P and HOMA-β in Det+Rep group were significantly higher than BIAsp30 group (P < 0.05). The weight increase rate, incidence of hypoglycemia and insulin dosage in Det+Rep group was significantly lower than BIAsp30 group (P < 0.01). Conclusion: Insulin detemir combined with repaglinide have better efficacy and safety in treating T2DM patients inefficacious to OAD therapy, compared with insulin aspart 30.

Keywords: Detemir, repaglinide, diabetes mellitus, BIAsp30, efficacy

Introduction

The development of chronic complications of diabetes is not only related to the persistent hyperglycemia, and is closely related to blood glucose fluctuation [1]. Oral anti-diabetic drugs (OAD) can not effectively control blood glucose. The selection of insulin in elderly patients should be smooth in lowering blood glucose and as far as possible to reduce blood glucose fluctuation, hypoglycemia and weight gain to ensure the safety of medicine [2]. In this study, the efficacy and safety of insulin detemir combined with repaglinide and insulin aspart 30 (BIAsp30) in treating elderly type 2 diabetes mellitus (T2DM) patients who were inefficacious to OAD therapy were compared. The objective was to provide a reference for further application of detemir combined with repaglinide to treatment of T2DM.

Subjects and methods

Subjects

One hundred and fifty elderly patients with T2DM in our hospital from March 2012 to February 2013 were collected. According to 1999 WHO diabetes diagnostic criteria, the acute complications of the diabetes, myocardial infarction, cerebrovascular accident, infection, severe liver and kidney dysfunction and mental illness patients are ruled out. Finally 98 patients (51 male and 47 female cases; aged 60-85 years, average 72.6 years; diabetes duration 2-17 years, average 5.8 years) were included. The CONSORT diagram was shown in **Figure 1**. All patients who had not previously used insulin therapy took two or more than OAD for 3 months at least. The fasting blood glucose was > 10.0 mmol/l, with glycated haemoglobin
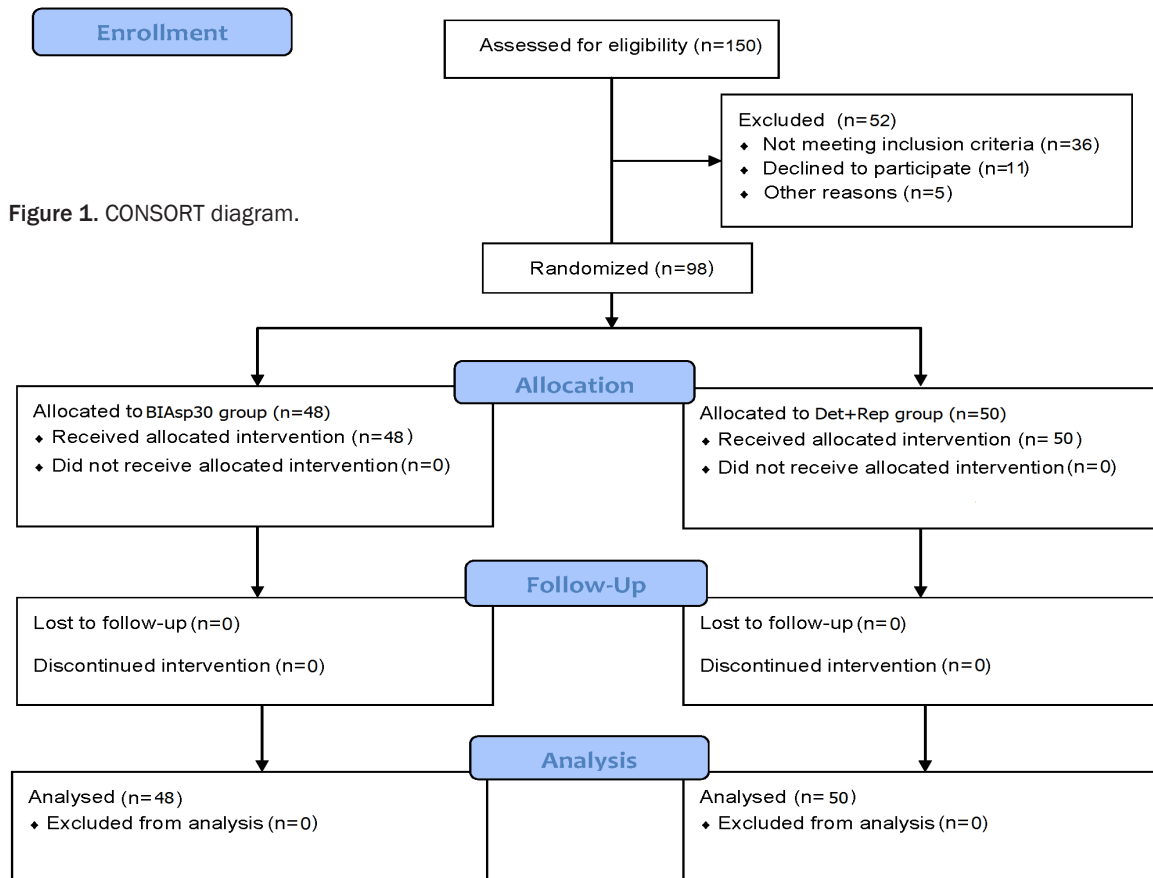
Figure 1. CONSORT diagram.

Table 1. General data of patients in two groups

Group	Gender (male/female)	Age (year)	Course of DM (year)	SBP (mmHg)	DBP (mmHg)	BMI (Kg/m²)
BIAsp30	48 (23/25)	72.9±8.2	5.9±3.4	156.3±12.6	97.4±10.5	27.4±6.1
Det+Rep	50 (24/26)	73.4±7.6	6.1±2.9	157.9±13.1	101.3±12.4	28.2±5.3
P	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

DM, diabetes mellitus; SBP, systolic blood pressure; diastolic blood pressure; BMI, body mass index.

(HbA1c) > 9.0%. This study was approved by the ethics committee of Hedong District People's Hospital. Written informed consent was obtained from all participants.

Treatment

All patients stopped using the original OAD. According to the random number table, patients were divided into detemir combined with repaglinide (Det+Rep) group (50 cases) and BIAsp30 group (48 cases). In Det+Rep group, the patients were injected with detemir at 22:00 every night (the initial dose was 0.1-0.2 u·kg^{-1}·d^{-1}), and took repaglinide 15 min before meals (the initial dose was 1 mg for each time, 3 times/day). In BIAsp30 group, the patients were injected with premixed insulin aspart 30 (15 min before breakfast and dinner; the initial

dose was 0.2-0.4 u·kg^{-1}·d^{-1}). The dosage of drug was adjusted according to the blood glucose level. The treatment duration was 12 weeks. Fasting plasma glucose (FPG) of 5-8 mmol/L, 2-h plasma glucose (2hPG) of 6-10 mmol/L and HbA1c < 7.5% were used as control target. Before and after treatment, the 24 h mean blood glucose (MBG), mean amplitude of glycemic excursion (MAGE) in one day, blood glucose coefficient of variation (CV), FPG, 2hPG, HbA1c, fasting C peptide (FC-P), 2-h C peptide (2hC-P), fasting insulin (Fins), triglycerides (TG), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C) and free fatty acids (FFA) were measured, and the body mass index, incidence of hypoglycemia (< 3.9 mmol/L) and insulin dosage were recorded. The insulin resistance index

Table 2. Comparison of blood glucose before and after treatment

Group		FPG (mmol/l)	2hPG (mmol/l)	HbA1C (%)	MBG (mmol/l)	MAGE (mmol/l)	CV (%)
BIAsp30	Before	15.9±4.1	21.6±6.4	10.9±1.6	18.12±4.25	5.68±1.46	4.09±1.21
BIAsp30	After	7.1±0.8*	9.3±2.1*	7.3±0.6*	8.06±1.13*	5.25±0.94	3.98±1.17
Det+Rep	Before	16.1±3.8	21.3±6.6	11.2±1.7	18.29±3.97	5.76±1.50	4.13±1.27
Det+Rep	After	6.8±0.7*	8.9±1.9*	7.1±0.5*	7.98±1.06*	2.12±0.83*,#	2.86±0.35*,#

*P < 0.01 compared with before treatment; #P < 0.01 compared with BIAsp30 group. FPG, fasting plasma glucose; 2hPG, 2-h plasma glucose; HbA1c, glycated haemoglobin; MBG, mean blood glucose; MAGE, mean amplitude of glycemic excursion; CV, coefficient of variation.

Table 3. Comparison of TG, TC, LDL-C, HDL-C, FFA before and after treatment

Group		TG (mmol/l)	TC (mmol/l)	LDL-C (mmol/l)	HDL-C (mmol/l)	FFA (mmol/l)
BIAsp30	Before	3.17±0.95	6.82±1.43	4.52±1.21	0.87±0.22	0.83±0.19
BIAsp30	After	1.60±0.86$^\Delta$	4.71±0.94$^\Delta$	2.79±0.87$^\Delta$	0.96±0.25*	0.62±0.11$^\Delta$
Det+Rep	Before	3.24±0.98	6.76±1.50	4.61±1.33	0.84±0.18	0.86±0.23
Det+Rep	After	1.58±0.84$^\Delta$	4.52±0.87$^\Delta$	2.62±0.84$^\Delta$	0.98±0.27*	0.57±0.10$^\Delta$

*P < 0.05 and $^\Delta$P < 0.01 compared with before treatment. TG, triglycerides; TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; FFA, free fatty acids.

Table 4. Comparison of FC-P, 2hC-P, HOMA-IR, HOMA-β before and after treatment

Group		FC-P (ng/ml)	2hC-P (ng/ml)	HOMA-IR	HOMA-β
BIAsp30	Before	1.81±0.16	2.92±0.21	12.91±6.21	144.68±59.71
BIAsp30	After	2.45±0.13*	3.17±0.35*	8.27±3.26$^\Delta$	278.13±98.26$^\Delta$
Det+Rep	Before	1.93±0.18	2.86±0.20	12.78±6.04	146.23±61.52
Det+Rep	After	2.84±0.17$^{\Delta,\#}$	3.43±0.42$^\Delta$	7.12±3.15$^{\Delta,\#}$	297.25±103.84$^{\Delta,\#}$

*P < 0.05 and $^\Delta$P < 0.01 compared with before treatment; #P < 0.01 compared with BIAsp30 group. FC-P, fasting C peptide; 2hC-P, 2-h C peptide; HOMA-IR, insulin resistance index; HOMA-β, insulin β cell function index.

Table 5. Comparison of weight, hypoglycemia, dosage insulin between two groups

Group		Weight (kg)	Weight increment rate	Incidence of hypoglycemia [n (%)]	Insulin dosage (u/d)
BIAsp30	Before	77.6±9.8			
BIAsp30	After	80.3±10.2	0.039	4 (8.3%)	38.4±9.2
Det+Rep	Before	78.3±10.7			
Det+Rep	After	79.1±10.4	0.028*	2 (4.0%)*	17.3±6.8*

*P < 0.01 compared with BIAsp30 group.

(HOMA-IR = FPG×Fins/22.5) and insulin β cell function index (HOMA-β = 20×Fins/(FPG-3.5)) with the steady state model were calculated.

Statistical analysis

All statistical analysis was carried out using SPSS17.0 software (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± SD. Comparisons between two groups were performed using t test, and χ^2 test was adopted for quantitative data and rate comparisons. P < 0.05 was considered as statistically significant.

Results

General data of patients

All 98 patients completed the trial. There was no statistical difference before treatment between two groups in gender, age, course of disease, blood glucose, blood lipid, blood pressure, weight, etc (P > 0.05) (Table 1).

Changes of blood glucose index

Compared with before treatment, FPG, 2hPG, HbA1c, MBG in each group were significantly lower after treatment (P < 0.01). There was no statistical difference in the reduction of above indexes between the two groups (P > 0.05). However, after treatment, the levels of MAGE

and CV in Det+Rep group were significantly lower than those in BIAsp30 group (P < 0.01) (**Table 2**).

Changes of blood lipid index

After treatment, the levels of TG, TC, LDL-C and FFA in BIAsp30 group and Det+Rep group significantly decreased, compared with before treatment (P < 0.01 or < 0.05), and the level of HDL-C significantly increased (P < 0.05). There was no significant difference of each blood lipid index between two groups after treatment (P > 0.05) (**Table 3**).

Changes of islet cell function

After treatment, the levels of FC-P, 2hC-P and HOMA-β in two groups significantly increased, compared with before treatment (P < 0.01 or < 0.05), and the HOMA-IR level significantly decreased (P < 0.01). After treatment, the levels of FC-P and HOMA-β in Det+Rep group were significantly higher than BIAsp30 group (P < 0.05), and the HOMA-IR level in Det+Rep group were significantly lower than BIAsp30 group (P < 0.05) (**Table 4**).

Changes in weight, incidence of hypoglycemia and insulin dosage

After treatment, the weight in two groups increased slightly, compared with before treatment (P > 0.05), but the weight increase rate in Det+Rep group was significantly lower than BIAsp30 group (P < 0.01). There were 2 cases of hypoglycemia in Det+Rep group, without severe hypoglycemia. There were 4 cases of hypoglycemia in BIAsp30 group, including 1 case of severe hypoglycemia. The incidence of hypoglycemia in Det+Rep group was significantly lower than BIAsp30 group (P < 0.01), and the insulin dosage of Det+Rep group was significantly lower than BIAsp30 group (P < 0.01) (**Table 5**).

Discussion

The elderly patients are a high-risk group of sugar metabolic abnormalities. Previous research [3] shows that the prevalence of diabetes in the age over 60 is more than 20%. Results of this study showed that, FPG, 2hPG, HbA1c, MBG and blood lipid were decreased obviously in Det+Rep group, but the MAGE, CV

after treatment in Det+Rep group were significantly lower than BIAsp30 group. Insulin detemir combined with repaglinide had more advantages in the aspects of smoothy hypoglycemic and reduce blood glucose fluctuations. It confirmed that insulin detemir combined with repaglinide in elderly patients with diabetes had more reliable security [4].

Insulin detemir is a new type of long-acting insulin analogue, with 14 carbon fatty acid side chains existing in the structure which increasing the self together between the molecules and combined with plasma albumin reversely, extending the time of in and out of the blood circulation and the effect, making the hypoglycemic activity steady and durable, and having no obvious peak [5]. Some scholars [6] deem that insulin detemir has more advantages in terms of efficacy, cost-benefit than insulin glargine. The research [7] of scholars in the asia-pacific region prompt Asian patients with diabetes is mainly a significant reduction in the early insulin secretion. Repaglinide as a glucose regulator during the meal has the advantages of fast absorption and short time effect, playing the unique role in improving the early phase insulin secretion [8]. Two fungicides simulate physiological insulin secretion mode, control blood glucose throughout the day.

Hypoglycemia and weight gain are not only the main obstacles of starting treatment, but also important risk factors for cardiovascular disease [9]. Insulin analog has the advantages of controlling blood glucose, reducing hypoglycemia compared with human insulin [10, 11]. This study found that insulin detemir had obvious advantages in reducing the incidence of hypoglycemia and the effects of weight. The reason is that Insulin detemir combined with albumin is reversible, with a more predictable hypoglycemic curve [12], thus effectively reducing the risk of hypoglycaemia [13]. Alternatively, Insulin detemir can decrease defensive eating, act in the liver and suppress appetite central mechanisms to reduce the effects of weight gain [14, 15]. In our study, we found that the dosage of insulin detemir was less than insulin aspart 30 that may also a factor of reducing weight gain. In our study, we also found that the FC-P, HOMA-β were obviously higher while HOMA-IR was significantly lower in detemir group, which Prompting islet beta cell function improved sig-

nificantly. We consider that the toxicity of high glucose fat in body tissues and organs including the beta cell release after comprehensive control of high blood glucose [16, 17], tissue sensitivity to insulin enhanced, thus improving the function of islet beta cells.

We believe that the insulin detemir combined with repaglinide in treating elderly T2DM patients that OAD therapy is failure has more advantages, such as good hypoglycemic lipid regulating effect, low blood glucose fluctuation, low incidence of hypoglycemia, less insulin dosage, less the effect of weight. It also can improve the islet beta cell function. It is simple, safe and effective to use insulin detemir injected subcutaneous once day before the meal associated with repaglinide, also is worthy of popularization and application.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yihui Liu, Department of Radiotherapy, Affiliated Hospital of Weifang Medical University, Weifang 256603, China. E-mail: liuyihui11@yeah.net

References

[1] Cavalot F, Pagliarino A, Valle M, Di Martino L, Bonomo K, Massucco P, Anfossi G, Trovati M. Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: lessons from the SAN Luigi Gonzaga Diabetes Study. Diabetes Care 2011; 34: 2237-2243.

[2] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 35: 1364-1379.

[3] Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, Shan Z, Liu J, Tian H, Ji Q, Zhu D, Ge J, Lin L, Chen L, Guo X, Zhao Z, Li Q, Zhou Z, Shan G, He J; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. N Engl J Med 2010; 362: 1090-1101.

[4] Kamieli E, Baeres FM, Dzida G, Ji Q, Ligthelm R, Ross S, Svendsen AL and Yale JF. Observation study of once-daily insulin detemir in people with type 2 diabetes aged 75 years or older: a sub-analysis of date from the study of once-daily levemir (SOLVE). Drugs Aging 2013; 30: 167-175.

[5] Nelson SE. Detemir as a once-daily basal insulin in type 2 diabetes. Clin Pharmacol 2011; 3: 27-37.

[6] Yang L, Christensen T, Sun F, Chang J. Cost-effectiveness of switching patients with type 2 diabetes from insulin glargine to insulin detemir in Chinese srtting: a health economic model based on the PREDICTIVE study. Value Health 2012; 15: S56-S59.

[7] Oka R, Yagi K, Sakurai M, Nakamura K, Moriuchi T, Miyamoto S, Nohara A, Kawashiri MA, Takeda Y, Yamagishi M. Insulin secretion and insulin sensitivity on the oral glucose tolerance test (OGTT) in middle-aged Japanese. Endocrine J 2012; 59: 55-64.

[8] Wang W, Bu R, Su Q, Liu J, Ning G. Randomized study of repaglinide alone and in combination with metformin in Chinese subjects with type 2 diabetes naïve to oral antidiabetes therapy. Expert Opin Pharmacother 2011; 12: 2791-2799.

[9] Raskin P, Gylvin T, Weng W, Chaykin L. Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. Diabetes Metab Res Rev 2009; 25: 542-548.

[10] Ma Z, Parkner T, Frystyk J, Laursen T, Lauritzen T, Christiansen JS. A comparison of pharmacokinetics and pharmacodynamics of insulin aspart, biphasic insulin aspart 70, biphasic insulin aspart 50, and human insulin: a randomized, quadruple crossover study. Diabetes Technol Ther 2012; 14: 589-595.

[11] Oyer DS, Shepherd MD, Coulter FC, Bhargava A, Deluzio AJ, Chu PL, Trippe BS; Initiateplus Study Group. Efficacy and tolerability of self-titrated biphasic insulin aspart 70/30 in patients aged > 65 years with type 2 diabetes: an exploratory post hoc subanalysis of the INITIATE plus trial. Clin Ther 2011; 33: 874-883.

[12] Le Floch JP. Critical appraisal of the safety and efficacy of insulin detemir in glycemic control and cardiovascular risk management in diabetes. Diabetes Metab Syndr Obes 2010; 3: 197-213.

[13] DeVries JH, Bain SC, Rodbard HW, Seufert J, D'Alessio D, Thomsen AB, Zychma M, Rosenstock J; Liraglutide-Detemir Study Group. Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets. Diabetes Care 2012; 35: 1446-1454.

[14] Khunti K, Caputo S, Damci T, Dzida GJ, Ji Q, Kaiser M, Karnieli E, Liebl A, Ligthelm RJ, Nazeri A, Orozco-Beltran D, Pan C, Ross SA, Svendsen AL, Vora J, Yale JF, Meneghini LF; SOLVE Study Group. The safety and efficacy of adding once-daily insulin detemir to oral hypo-glycaemic agents in patients with type 2 diabetes in a clinical practice setting in 10 countries. Diabetes Obes Metab 2012; 6: 25-27.

[15] Hollander PA. Insulin detemir for the treatment of obese patients with type 2 diabetes. Diabetes Metab Syndr Obes 2012; 5: 11-19.

[16] Wang M, Crager M, Pugazhenthi S. Modulation of apoptosis pathways by oxidative stress and autophagy in β cells. Exp Diabetes Res 2012; 2012: 647-914.

[17] Prentki M, Madiraju SR. Glycerolipid/free fatty acid cycle and islet beta-cell function in health,obesity and diabetes. Mol Cell Endocrinol 2012; 353: 88-100.