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A meta-analysis of clinical therapeutic effect of insulin glargine and insulin detemir for patients with type 2 diabetes mellitus

Y.G. ZHUANG, H. PENG, F. HUANG

Department of Emergency, Shanghai Tenth People's Hospital, Tongji University, Shanghai, China

Abstract. – BACKGROUND: Insulin have been recommended to decrease glycosylated hemoglobin (HbA1c) level in type 2 diabetes mellitus (T2DM) patients whose blood glucose control are unsatisfactory by using oral hypoglycemic drugs.

AIM: To systematically estimate the therapeutic effect and security of insulin glargine and insulin detemir for treatment of type 2 diabetes mellitus.

MATERIALS AND METHODS: We searched the Cochrane library, PubMed, EMBASE, etc databases. Quality evaluation of all randomized control tests (RCT) enrolled was conducted according to Cochrane manual, and meta-analysis was performed by using RevMan5.0 software.

RESULTS: Both insulin glargine and insulin detemir can effectively control T2DM patient's blood glucose.

CONCLUSIONS: Insulin detemir has evident superiority on reducing body weight than insulin glargine. As the doses are concerned, daily insulin dose of insulin detemir is higher than insulin glargine.

Key Words:
Insulin glargine, Insulin detemir, Type 2 diabetes mellitus

Introduction

Insulin have been recommended to decrease glycosylated hemoglobin (HbA1c) level in Type 2 diabetes mellitus (T2DM) patients whose blood glucose control are unsatisfactory by using oral hypoglycemic drugs. If insulin supplementary therapy is timely initiated for T2DM patient, blood glucose can be well controlled and the decline of pancreatic islet B cells can be suspended[1], resulting in low risk of complication. Therefore, accessorial rudimentary insulin based on oral hypoglycemic drugs is a common method for initiation of insulin therapy for T2DM[2]. Traditional neutral protamine Hagedorn (NPH) has some limitations on action duration and variability[3,4], while the occurrence of long-acting insulin analogues surmounts these limitations to a certain extent. Insulin glargine and insulin detemir are two new basal insulin analogs with long action duration, low variability and occurrence of adverse reaction (such as glucopenia and body weight increase)[5]. Are there any differences of effect on controlling T2DM between insulin glargine and insulin detemir? Meta-analysis is a statistical analysis method, which supplys an approach to solve controversial and uncertain problems by integrating multiple separate clinical studies that can be synthesized for quantitative analysis. This study estimated the effect and security of the two basal long-acting insulin analogs for T2DM by using meta-analysis.

Materials and Methods

Criterion for Inclusion and Exclusion

Research type: A randomized control test (RCT) was performed about the effect of insulin glargine and insulin detemir on T2DM treatment. The therapy time last at least 24 weeks.

Object of study: T2DM adult patients were enrolled according to the diagnostic criteria of WHO or ADA criteria.

Intervention measure: Insulin glargine and insulin detemir were separately administrated to T2DM patients based on oral hypoglycemic drugs.

Outcome index: The major outcome indexes included glycosylated hemoglobin (HbA1c) and fasting blood-glucose. The secondary outcome indexes were body weight change, incidence of glucopenia, and daily dose of insulin.

Literature Search

We retrieved the Cochrane library, PubMed, and EMBASE dataset by computer. The keywords included insulin glargine, insulin detemir, randomized controlled trial, type 2 diabetes, etc.

Data extraction and Quality Evaluation

Data extraction and quality evaluation of literatures were cross checked by two researchers,

Corresponding Author: Yugang Zhuang, MD; e-mail: mmherofg@sina.com

contacting the author to confirm the test process when necessary. If divarication occurred, the results were determined by the third person or by discussion to achieve consensus.

Literature quality evaluation was referred to the bias risk assessment method about RCT in The Cochrane Collaboration System Evaluation Handbook 5.0.2., including 6 items: random distribution generation, allocation concealment implementation, application of blind method, data integrity, selective report with or without results, and other sources of bias. For each item, matching means low bias, and mismatching means high risk; if information reported in the literature are not enough for me to make definite judgement according to the items. The item was defined as indeterminate, indicating moderate risk.

Statistical Analysis

Meta-analysis was performed using RevMan 5.0 software supplied by The Cochrane collaboration. The heterogeneity test of enrolled studies was performed with χ^2 test. $p < 0.05$ means heterogenicity in studies and thus random effect model should be used; otherwise, combined analysis was performed with fixed effect model. Mean difference (MD) was used to represent effect-quantity for continuous variable results, and Odd's ratio (OR) was used to represent effect-quantity for discontinuous variable results, interval estimation using a 95% confidence interval (95% CI).

Results

Literature Retrieval

Thirty-four related literatures were gained by original search, all of which were English paper. After reading, we excluded the duplicate literatures or literatures either about non-randomized controlled trials, or not according with the inclusion criteria. Ultimately, 3 literatures about RCT[6-8] according with inclusion criteria were left. Essential characteristics of studies enrolled were shown as Table I.

Meta-Analysis

Variety of HbA1c

Effects of insulin glargine and insulin detemir on lowing diabetic glycated hemoglobin were compared in each of 3 studies. The results combined for meta-analysis demonstrated OR and 95%CI of insulin glargine and insulin detemir concentration for lowing diabetic glycated hemoglobin were 0.03 and [-0.08, 0.15], separately. Difference was not statistically significant (p = 0.57). Forest graph is shown as Figure 1.

Variety of Fasting Plasma Glucose (FPG)

Effects of insulin glargine and insulin detemir on lowing diabetic fasting plasma glucose were all compared in 3 studies. The results combined for meta-analysis demonstrated OR and 95% CI of insulin glargine and insulin detemir concentration for lowing diabetic fasting plasma glucose were 0.18 and [–-0.10,0.47], separately. There was no significantly statistical difference (p = 0.21). Forest graph is shown as Figure 2.

Variety of Body Weight

Effects of insulin glargine and insulin detemir on diabetic body weight were all compared in 3 studies. Meta-analysis result demonstrated: the value of effect statistic MD for index comparison was –0.08, and its 95% CI was [–1.19, –0.41]. On controlling the patient's body weight, insulin detemir is better than insulin glargine, and the difference is statistically significant ($p < 0.00001$). As you can see from Figure 3, the rhombus is entirely in the left side of vertical line, that means body weight increase of patient in insulin detemir treatment group is less than which in insulin glargine group.

Incidence of Hypoglycemia

Data in the 3 studies were compared with meta-analysis about frequency of hypoglycemia induced by insulin glargine and insulin detemir for treating type 2 diabetes mellitus. Meta-analysis result demonstrated difference of hypoglycemia prevalence induced by insulin glargine

Table I. Essential characteristics of studies enrolled (detemir/glargine).

Research	N	Age (year)	Disease course	HbA1c (%)	FGP (mmol/l)	Body mass index (kg/m^2)	Follow-up time (week)
Hollander 2008	214/105	59/58	13.6/13.4	8.6/8.8	9.5/9.8	31.5/31.7	52
Raskin 2009	254/131	55.8/55.9	12.5/11.9	8.4/8.8	9.7/9.6	32.6/33.0	26
Swinnen 2010	486/478	58.0/58.7	10.1/9.7	8.7/8.7	10.4/10.5	29.7/30.6	24

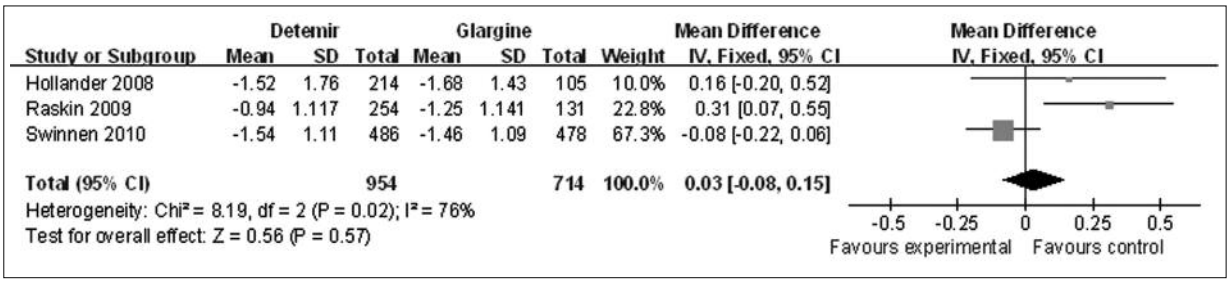

Figure 1. Meta-analysis forest graph about the improvement of diabetic glycated hemoglobin by insulin glargine and insulin detemir.

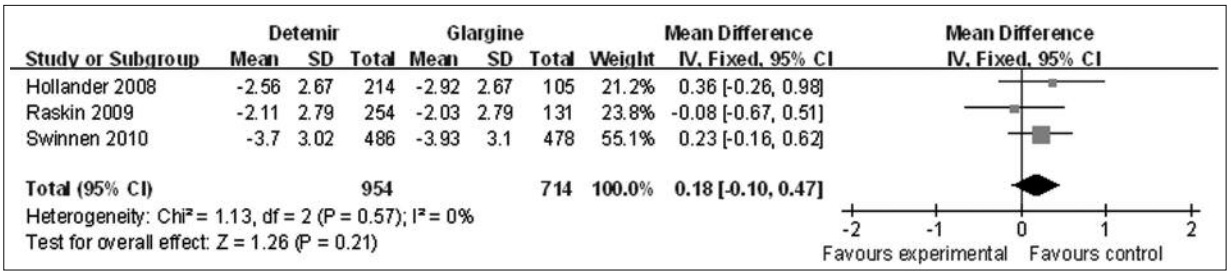

Figure 2. Meta-analysis forest graph about the improvement of diabetic fasting plasma glucose by insulin glargine and insulin detemir.

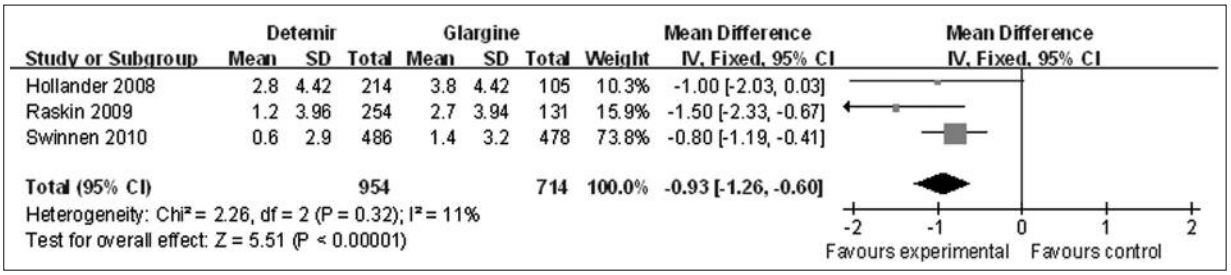

Figure 3. Meta-analysis forest graph about the controll of diabetic body weight by insulin glargine and insulin detemir.

and insulin detemir was not statistically significant [OR = 1.05, 95% CI (0.85, 1.29), $p = 0.68$]. Forest graph is shown as Figure 4.

Daily Dose of Insulin

Data in the 3 enrolled studies were compared with meta-analysis about daily insulin dose of insulin glargine and insulin detemir for treating type 2 diabetes mellitus. Results of meta-analysis demonstrated: MD value for index comparison was 0.29, and its 95% CI was [0.25, 0.32]. Daily insulin dose of insulin detemir for treating type 2 diabetes mellitus is higher than insulin glargine, and difference is statistically significant ($p < 0.00001$). Forest graph is shown as Figure 5.

Discussion

The estimation about this system have demonstrated that: insulin glargine and insulin detemir, as supplementary treatment for T2DM patients administrated with oral hypoglycemic drugs, have the similar effect on controlling blood glucose, accompanied with the similar risk of hypoglycemia. Furthermore, insulin detemir possesses evident superiority on decreasing body weight compared with insulin glargine. Insulin detemir daily dose injected is higher than insulin glargine in hormone dosage. This research had objectively evaluated the effect and security of insulin detemir and insulin glargine on T2DM treatment, providing certain evidence for their clinical application.

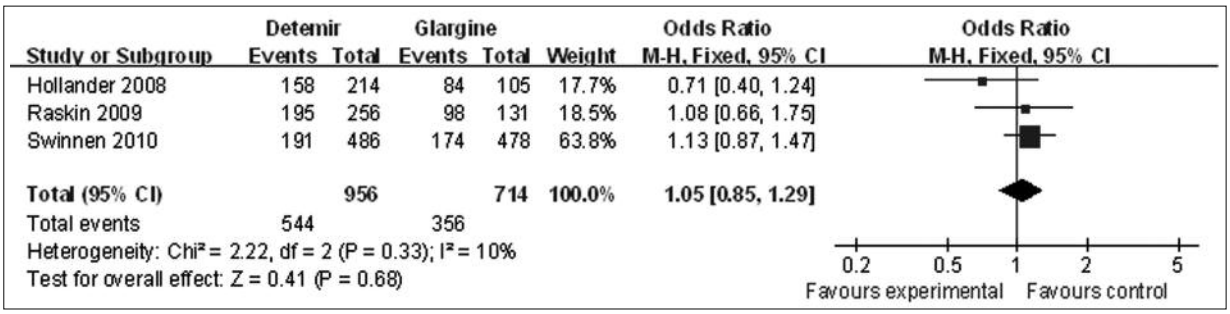

Figure 4. Meta-analysis forest graph about the incidence of diabetic hypoglycemia induced by insulin glargine and insulin detemir.

Results of the evaluation demonstrated: as supplementary treatment for T2DM patients, differences of glycosylated hemoglobin (HbA1c) variety, fasting plasma glucose (FPG) variety and hypoglycemic prevalence between insulin detemir and insulin glargine were not statistically significant; While differences of body weight increase control and hormone dosage were statistically significant, insulin detemir decreased the increase of body weight more than insulin glargine did, and insulin detemir daily insulin dose injected was higher than insulin glargine for T2DM patient's treatment.

Although only 3 randomized control trials were enrolled in this study for meta-analysis, these research objects came from 20 different countries, sex proportion was appropriate, and average age was 56 years old; they were good research objects for effect study of insulin analog to T2DM[9]. Therefore, source reliability of external results for this study was high.

The quality of this study was high and risk of bias was relatively low because the following reasons: studies enrolled in this system evaluation were all multiple central trials; objects for study were randomized; sample volume was large; patients missed follow-up rate was low; indexes reflecting therapy effect were quite a lot and most of them were objective indexes. However, blind method was not executed in trials enrolled in this study, leading to the maximal bias in this meta-analysis[10]. Thereby, this point should be considered when explaining the result of this meta-analysis.

Long acting time and low glucopenia risk are the advantages of insulin detemir and insulin glargine, which are related with their molecular structures. Insulin glargine is synthesized from human insulin, at twenty-first point on chain A of which, glycin is instead of aspartic acid, and 2 arginines are added to the end of chain B, that makes the isoelectric point turn acidic and solubility decrease in physiological pH body fluid. It forms tiny insulin microsphere precipitations after subcutaneous injection, and these microsphere precipitations continually and stably releases insulin monomer for quite a long time, thus delaying the absorption[11]. Insulin detemir is the first long-acting insulin analogs obtained by chemical modification method which threonine naturally arrays on the thirtieth point of human insulin B chain is removed; then, a C-(14) fatty acids is combined to the lysine on the twenty-ninth point. On the one hand, this C-(14) fatty acids lateral chain makes insulin detemir form double hexamers after hypodermic injection, thus, delaying its absorption, which can reversibly combine with the albumin in subcutaneous tissue at the same time, and speed of which going into blood further slow dawn. On

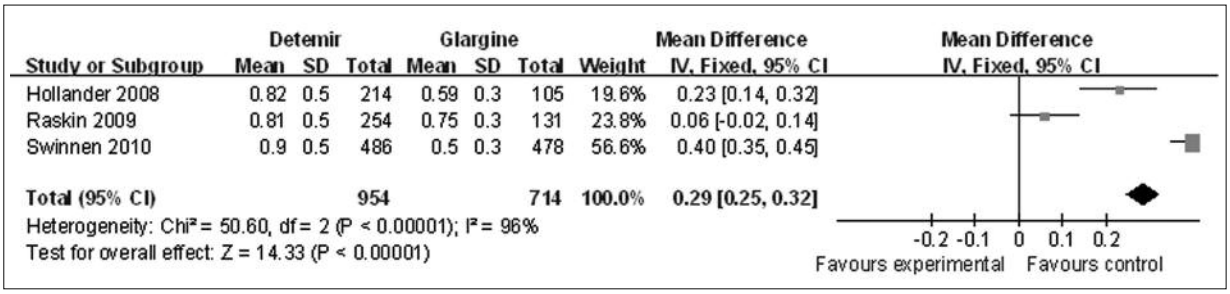

Figure 5. Meta-analysis forest graph about the daily insulin dose of insulin glargine and insulin detemir for diabetic therapy.

the other hand, 98% of insulin detemir reversibly combines with albumin after entering into peripheral blood circulation, which delays target organ distribution as well[12]. Acting time of insulin glargine and insulin detemir can last up to 24 hours, which owe to their molecular structure characteristics. They can mimic physiological insulin secretion, thus daily injection is just needed for effective glucose-lowering. Furthermore, their action curves have no evident peak value, and they can lower glucose safely and effectively[13].

Three enrolled studies for this meta-analysis have the same conclusion: both insulin glargine and insulin detemir can reduce diabetic patients weight gain, and the latter has more advantages. That further confirmed the effect, security and tolerance of insulin detemir. The mechanism that insulin detemir can reduce weight gain is still undefined. The possible mechanisms is not only related with the patients diet and exercise control, but also associated with the unique molecular structure and delay action of insulin detemir. The latter mechanism can change distribution of insulin detemir in liver and peripheral tissues, enhance insulin signal transduction in brain, lower hypoglycemia risk, as well as reduce defensive heat intake, thereby reducing weight gain[14].

Conclusions

Both insulin glargine and insulin detemir can effectively control T2DM patient's blood glucose. Their effectiveness and security are similar. For a better understanding of action difference between insulin glargine and insulin detemir, treatment effect comparison of the two basic insulin analogs should be conducted under same insulin treatment plan, which is in progress[15].

Conflict of Interest

The Authors declare that they have no conflict of interests.

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