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Original Article

Efficacy and safety of acarbose combined with insulin in treatment of type 2 diabetes mellitus: a meta-analysis of randomized controlled trials

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Abstract: *Purpose:* The efficacy and safety of acarbose combined with insulin in the treatment of type 2 diabetes mellitus was in debated. The purpose of current meta-analysis is to compare whether acarbose combined with insulin is superior than insulin alone in the treatment of type 2 diabetes mellitus. *Methods:* All randomized controlled trials (RCTs) were searched from PubMed, EMBASE, the Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biology Medicine (CBM) from inception to March 2017. Any RCTs comparing acarbose combined with insulin versus insulin alone in type 2 diabetes mellitus patients were included. Weighted mean difference (WMD) and risk ratio (RR) were used to summarized the continuous data and discontinuous data respectively. Stata 12.0 was used to perform the meta-analysis. *Results:* A total of 5 studies were included on the basis of the inclusion criteria and the exclusion criteria. The results of meta-analysis showed that acarbose plus insulin therapy significantly lowered the level of HbA1c (WMD=-0.62, 95% CI: -0.94, -0.29), fasting blood glucose (FBG) (WMD=-0.73, 95% CI: -1.30, -0.17) and weight (WMD=-10.00, 95% CI: -14.59, -5.40), compared with insulin monotherapy. There was no significant difference between the insulin dose and the occurrence of hypoglycemic (P>0.05) between the two groups. *Conclusion:* Combination therapy can gain better outcomes in glycemic control without increasing the risk of hypoglycaemic episodes. We need to well-designed multicenter RCTs to confirm this conclusion.

Keywords: Acarbose, insulin, combination therapy, systematic review, meta-analysis

Introduction

The International Diabetes Federation has estimated that diabetics (both type 1 and type 2) were 35 million in 2011, in Europe. It is likely that the figure increases by 23% to 43 million in 2030 [1]. The main measures of treatment for diabetes are lifestyle changes, drug intervention, proper diet and exercise, but it is given priority to oral medications. Diabetics need insulin in monotherapy or combination therapy when conventional drugs cannot effectively control blood sugar [2]. Acarbose was an effective drug in first-line treatment and in combination therapy in type 2 diabetic patients [3].

An increasing number of clinical trials (acarbose combined with insulin in the treatment of type 2 diabetes mellitus) are implemented. However, up to now, no adequate studies and well randomized controlled trials (RCTs) can address efficacy and safety of acarbose combined with insulin in the treatment of type 2 diabetes mellitus. Therefore, we did a systematic review and meta-analysis of RCTs about acarbose combined with insulin in the treatment of type 2 diabetes mellitus.

Materials and methods

Literature search

We searched the electronic database of PubMed, EMBASE, the Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biology

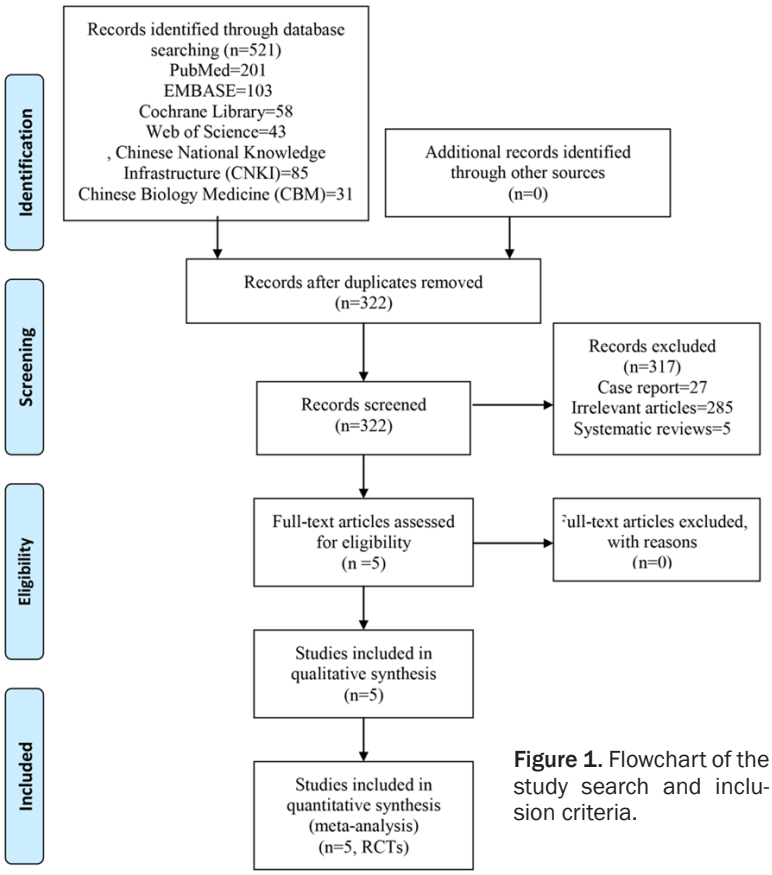

Figure 1. Flowchart of the study search and inclusion criteria.

Medicine (CBM) without date or language restrictions up to August 2016. The keywords "type 2 diabetes mellitus", "non-insulin dependent diabetes mellitus", "acarbose", "insulin", "random*", and "randomized controlled trials" were used in various combination. The reference lists of related reviews and original articles were searched for any relevant studies, including RCTs involving adult humans. Only articles originally written in English or translated into English were considered. When multiple reports describing the same sample were published, the most recent or complete report was used. This meta-analysis collected data from published articles and thus no ethic approval was necessary for this article.

Inclusion criteria and exclusion criteria

Studies were included on the basis of the inclusion criteria: (1) participants were patients with type 2 diabetes mellitus, (2) randomized controlled trials, (3) patients were randomized grouped into acarbose plus insulin combination therapy group and insulin monotherapy group (with or without placebo), (4) not less than one outcome of interest (HbA1c, FBG (fasting blood glucose)) was reported, (5) trial duration was not less than 8 weeks.

The exclusion criteria was as listed below: (1) retrospective studies, observational studies, case series, reviews, comments, (2) duplicate publication, (3) studies without original data.

Data extraction

Two investigators (Haiying Huand Jia Zheng) abstracted study design information, baseline population characteristics, intervention details, disease incidence, mortality, and harms data from all included studies into a standardized evidence table. A second investigator checked these data for accuracy. We resolved any disagreements through discussion. We collected information from eligible studies as follows: the first author; race; publication year; mean age; sex; simple size; study duration; HbA1c level; FBG; adverse events.

Quality assessment

Two investigators (Xian Chen and Jiang Diying) independently assessed the risk of bias of articles according to RCTs tool for assessing quality and risk of bias which was recommended by Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, including six items of random methods, allocation concealment, blind method, incomplete outcome data, selectivity reports, other bias. We resolved disagreements by discussion.

Statistical analysis

We performed all analyses by using Stata 12.0 (Stata Corp., College Station, TX). The weighted mean difference (WMD) and risk ratio (RR) were used to compare continuous and dichotomous variables, respectively. All results were report-

Table 1. The general characteristic of the included studies

Author (year)	N (A+I/P+I)	Average age (A+I/P+I)	Sex (male/female)	Intervention				Trial duration
				A+I		P+I		
				A (mg/day)	I	P (mg/day)	I	
Coniff 1995	207 (103/104)	NR	NR	150-900	NR	150-900	NR	
Kelley 1998	195 (98/97)	61.8/60.8	A+I: 61/37 P+I: 47/50	75-300	NR	75-300	NR	24-weeks
Schnell 2007	163 (82/81)	61.5/62.3	A+I: 41/41 P+I: 39/42	50-300	BB: 8 IU BU: 4 IU	50-300	BB: 8 IU BU: 4 IU	20-weeks
Zheng 2010	60 (30/30)	54.0/53.8	NR	150	NR	150	NR	12-weeks
Fan 2014	172 (57, 58/56)	NR	A+I: 25/32, 28/31 P+I: 30/26	150, 300	NR	0	NR	12-weeks

Notes: A+I: acarbose+insulin; P+I: placebo+insulin; NR:not report; BB: before breakfast; BU: before supper.

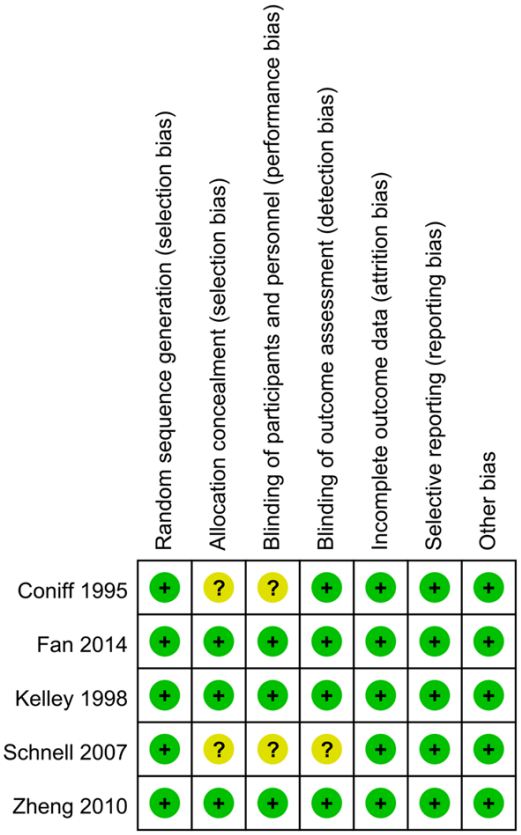

Figure 2. The risk of bias graph.

ed with 95% confidence interval (CI). I-square (I^2) test was performed to assess the impact of study heterogeneity on the results of the meta-analysis. According to the Cochrane review guidelines [4]. If severe heterogeneity was present at I^2>50%, the random effect models were chosen; otherwise, the fixed effect models were used. Moreover, sensitivity analysis was conducted by deleting each study individually to evaluate the quality and consistency of the results. Publication bias was evaluated by funnel plots.

Results

Search results and characteristics of included trials

Initial database search identified 521 relevant articles; 199 records were excluded as they were duplicates. Then after review the title and abstract, 317 records were excluded on the basis of included criteria. Finally, 5 RCTs were included in meta-analysis (797 patients) (**Figure 1**) [5-9]. A summary of the characteristics of included studies is shown in **Table 1**. The general characteristic of the included patients have comparability and has no statistically difference. The mean age ranged from to 54 to 62.3 and the dose of acarbose ranged from 150 mg to 300 mg. The follow-up duration last ranged from 12 weeks to 24 weeks. The insulin unit ranged from 4 U to 8 U.

Quality assessment

The risk of bias summary and risk of bias graph are shown in **Figures 2**, **3**, respectively. All of the included studies describe the random sequence generation; most studies were incomplete data; most studies used double blinding. There were no high quality articles in all included articles. Most included articles had moderate methodological quality.

Results for meta-analysis

HbA1c

Five studies reported the HbA1c (%) level between the two groups. The overall analysis

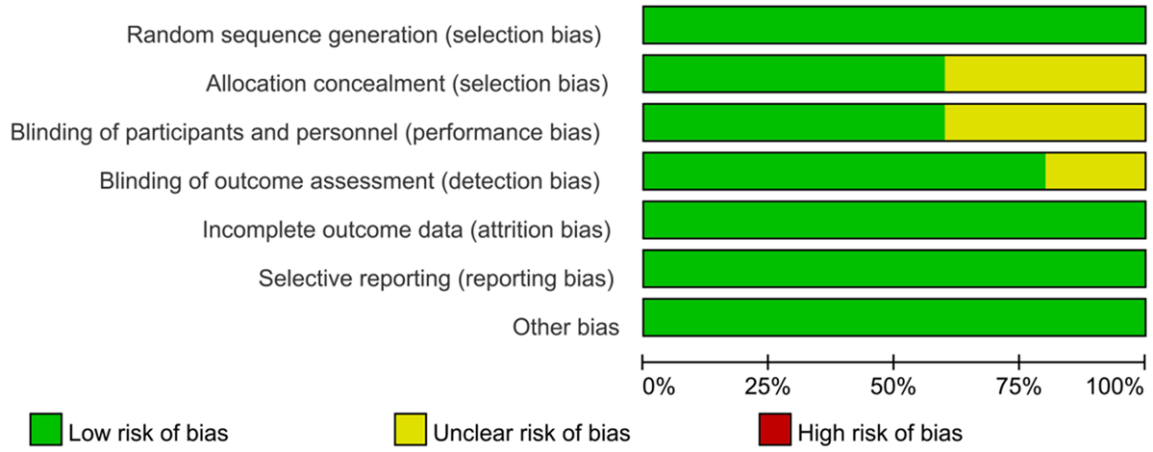

Figure 3. Risk of bias of included in randomized controlled trials. +, no bias; -, bias; ?, bias unknown.

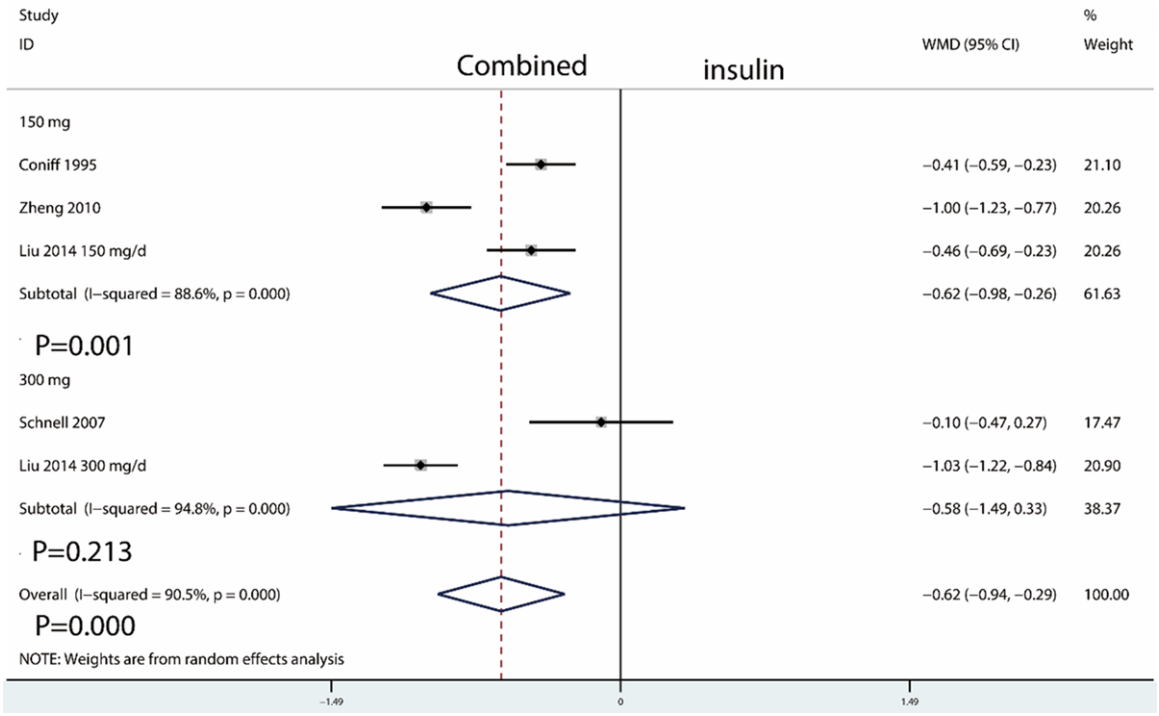

Figure 4. Forest plots of the included studies comparing HbA1c between the two groups.

illustrated that A+I (acarbose+insulin) therapy included a greater deduction of HbA1c (%) [WMD=-0.62, 95% CI (-0.94, -0.29), **Figure 4**] than insulin alone therapy. There was a high heterogeneity between the included studies (I^2=90.5%, P=0.000) and thus a random-effect model was performed.

FPG

Besides, the results showed that A+I (acarbose +insulin) therapy significantly reduced FBG (mmol/l) [WMD=-0.73), 95% CI (-1.30, -0.17), I^2=92.8%, P=0.011, **Figure 5**] compared with insulin alone therapy.

2-hour plasma glucose

A total of three studies reported the 2-hour plasma glucose, final results indicated that there was no significant difference between the 2-hour plasma glucose between the combined group and insulin group (WMD=-0.69), 95% CI (-2.67, 1.30), P=0.499, **Figure 6**). There was a

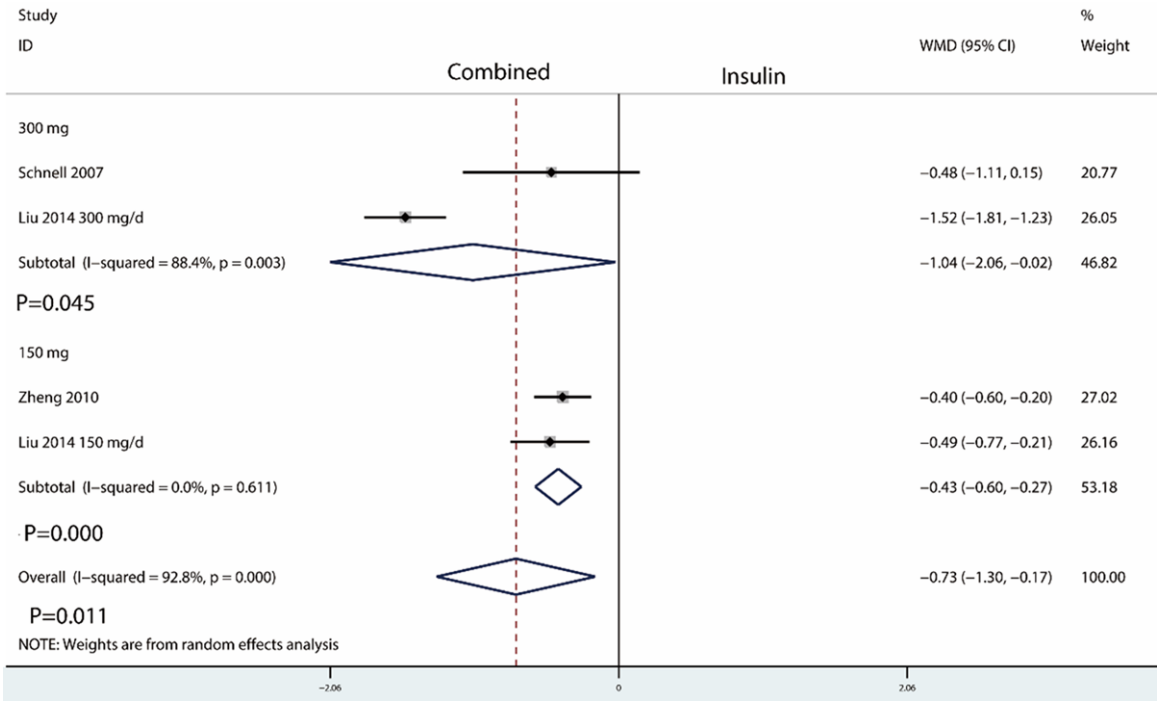

Figure 5. Forest plots of the included studies comparing FBG between the two groups.

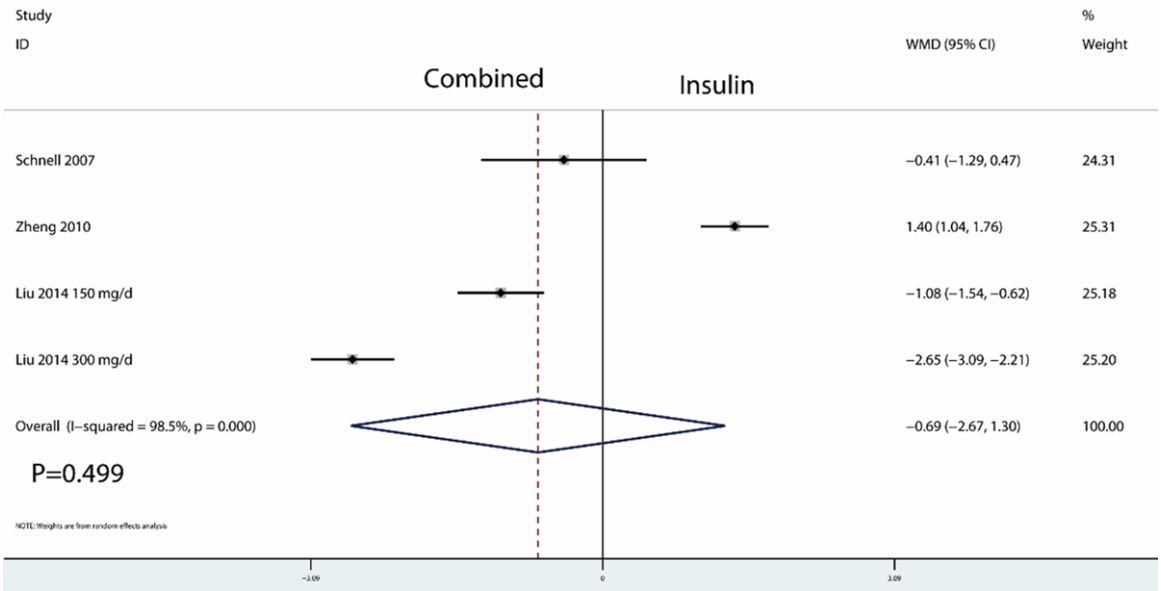

Figure 6. Forest plots of the included studies comparing 2 h blood glucose between the two groups.

large heterogeneity between the included studies (I^2=98.5%, P=0.000).

Insulin dosage

A total of two studies reported the insulin dosage between the two groups. Pooled results indicated that the insulin dosage in the combined group was less than insulin alone group with statistically significant (WMD=-7.16, 95% CI (-16.92, 1.70), P=0.109, **Figure 7**).

Weight

A total of three studies reported the weight between the two groups. Pooled results indi-

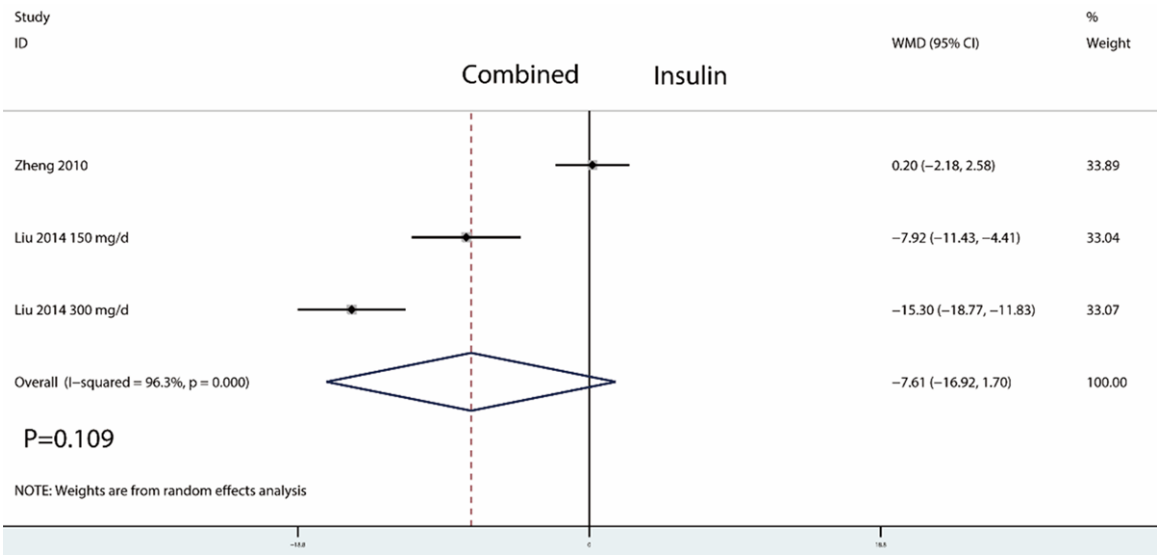

Figure 7. Forest plots of the included studies comparing the insulin dose between the two groups.

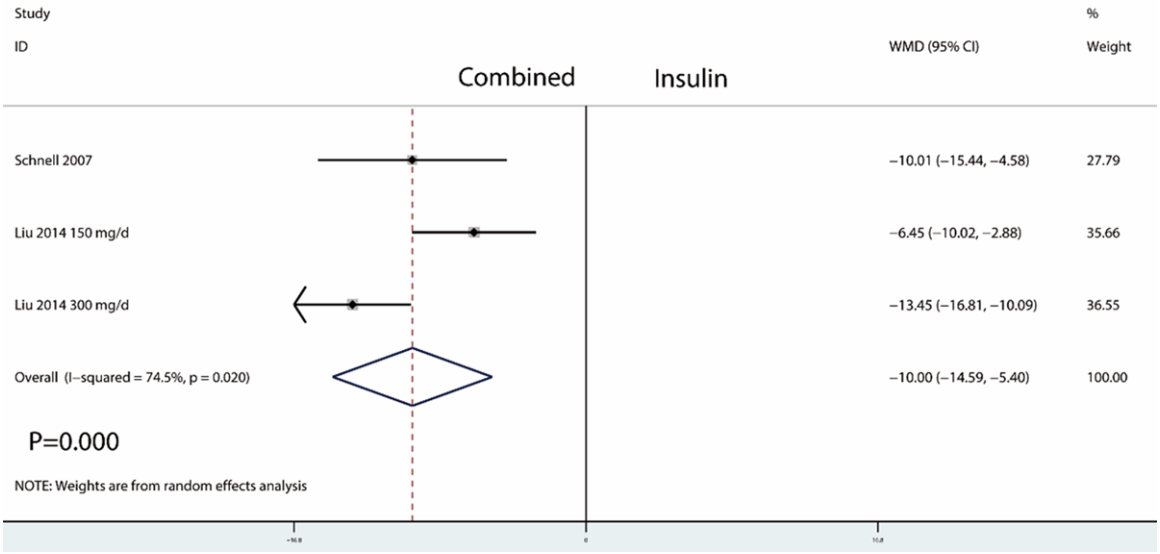

Figure 8. Forest plots of the included studies comparing the weight between the two groups.

cated that the weight in the combined group was less than insulin alone group with statistically significant [WMD=-10.00, 95% CI (-14.59, -5.40), I^2=74.5%, P=0.020, **Figure 8**].

The occurrence of hypoglycemic

The occurrence of hypoglycemic was 20.3% and 27.7% in combined group and insulin group respectively. Compared with insulin group, combined group was associated with a small reduction of the occurrence of hypoglycemic (RR= 0.84, 95% CI (0.41, 1.86), P=0.719, **Figure 9**).

Subgroup analysis and sensitivity analysis

Subgroup analysis results can be seen in **Table 2** and sensitivity analysis results can be seen in **Figure 10**. Subgroup results indicated high dose of acarbose was superior than low dose of acarbose in terms of the insulin dose. We performed a sensitivity analysis to assess the stability of the pooled results. Among the most studies, the heterogeneity results were not obviously altered after sequentially omitting each study.

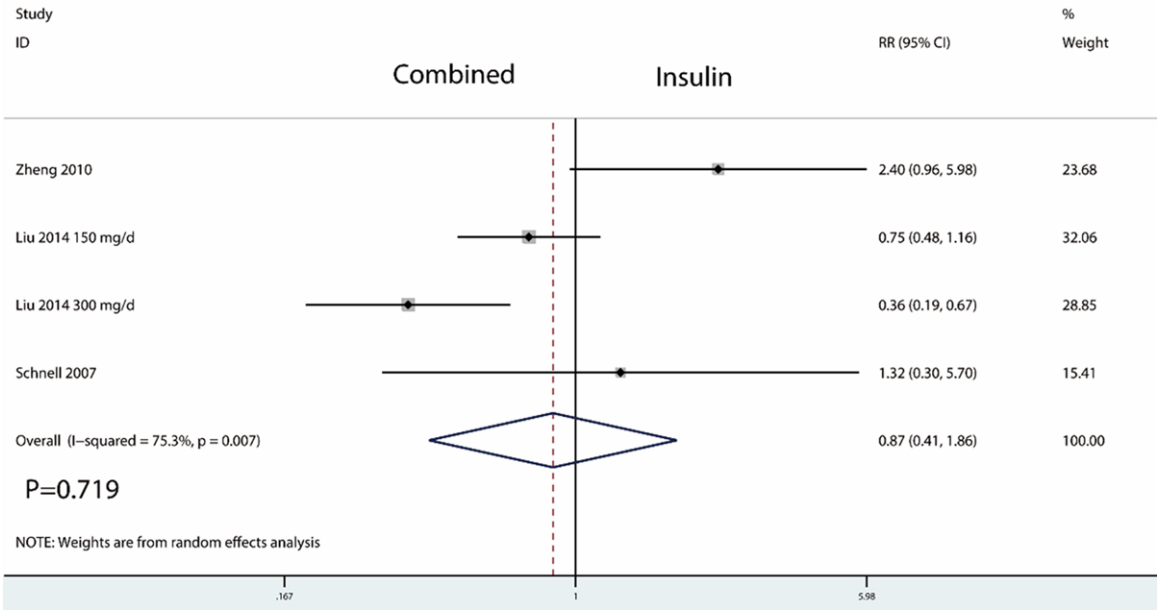

Figure 9. Forest plots of the included studies comparing the occurrence of hypoglycemic between the two groups.

Table 2. Subgroup analysis of the HbAc1, FPG, 2-hour plasma glucose, insulin dose, weight and the occurrence of hypoglycemic

Variables	Studies (n)	Patients (n)	*p*-Value	Incidence		
				Mean difference (95% CI)	Heterogeneity *p*-value (I^2)	Model
HbA1c						
High dose	2	132	0.001	-0.62 (-0.95, -0.26)	0.000, 88.6	Random
Low dose	3	178	0.213	-0.61 (-3.69, 2.46)	0.000, 94.8	Random
FPG						
High dose	2	170	0.045	-1.04 (-2.06, -0.02)	0.003, 88.4	Random
Low dose	2	340	0.000	-1.94 (-5.05, 1.15)	0.285, 19.7	Fixed
2-hour Plasma Glucose						
High dose	2	132	0.000	-1.56 (-3.76, -0.63)	0.074, 95.0	Random
Low dose	2	230	0.179	-1.64 (-2.27, 2.60)	0.552, 98.6	Random
Insulin dosage						
High dose	1	82	0.000	-6.26 (-7.49, -5.03)	0.301, 6.5	Fixed
Low dose	2	228	0.355	-3.75 (-11.71, 4.20)	0.446, 92.9	Random
Weight						
High dose	2	50	0.000	-6.45 (-10.02, -2.88)	0.291, 10.2	Fixed
Low dose	1	118	0.000	-12.42 (-15.51, -9.33)	-	-
The occurrence of hypoglycemic						
High dose	2	225	0.005	0.45 (0.26, 0.79)	0.108, 61.3	Random
Low dose	2	184	1.000	1.00 (0.68, 1.47)	0.023, 80.7	Random

Discussion

This is the first systematic review which compared the efficacy and safety of acarbose plus insulin therapy with insulin alone therapy on type 2 diabetes. Acarbose plus insulin therapy resulted in better improvement in glucose control compared with insulin alone therapy. The level of HbA1c and FBG was significant lower in the combination therapy group than insulin monotherapy group according to the results of meta-analysis. Moreover, combination therapy

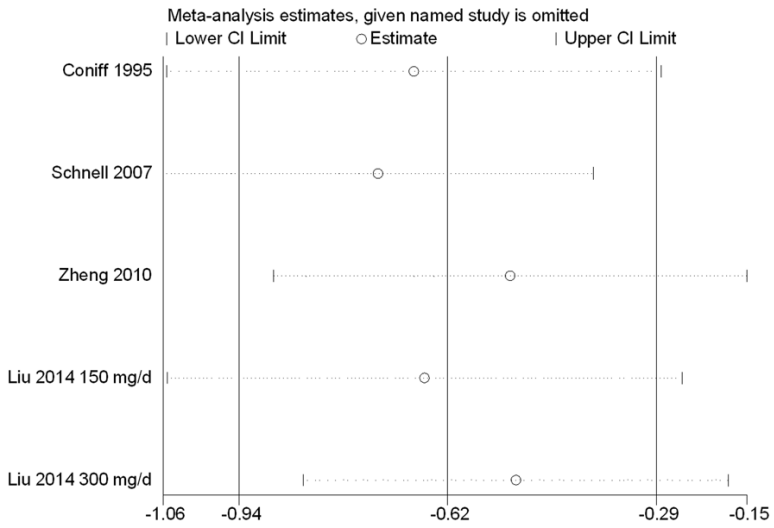

Figure 10. Sensitivity analysis of the HbA1c between the two groups.

would decrease the weight than insulin alone. And combination therapy would not result in the occurrence of hypoglycemic. Both combination therapy and insulin monotherapy reported adverse events, such as flatulence, diarrhea, flu syndrome, abdominal pain, digestive disorders, gastro-intestinal tract response and so on.

A major strength of current meta-analysis was that we comprehensively searched the electronic databases. We searched PubMed, EMBASE, the Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biology Medicine (CBM) from inception to March 2017. And we performed subgroup analysis according to the dose of acarbose.

T2DM is a prevalent condition with a high economic burden. It is reported that over 29 million people in the United States with diabetes mellitus, leading to an estimated economic burden of USD240 billion annually [10, 11]. Acarbose is an α-glucosidase inhibitor. It slows the breakdown of carbohydrates in the gut, and delays absorption of carbohydrates by inhibition of a-amylase and α-glucosidase activities, which reduces post-prandial hyperglycemia [12, 13]. Li et al. [14] reported that acarbose add-on insulin therapy was identified to be associated with greater improvements in oxidative stress and inflammation in patients with T2DM when compared with those that received insulin only therapy. Vos RC et al. [15] conducted a meta-analysis of insulin mono-therapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control. Additional weight gain can only be avoided by adding metformin to insulin. Current meta-analysis indicated that combined group can decrease the weight compared with insulin alone group.

There are some limitations in our systematic review and meta-analysis. Firstly, there was moderate methodological quality in most of included studies. Secondly, many unfinished studies which we can not get lead to a potential limitation for any meta-analysis. Thirdly, another limitation of this systematic review was caused by the lack of gray studies, such as presentations, unpublished data, government reports, and other traditional or nontraditional sources of evidence.

In conclusion, this systematic review shows that acarbose combined with insulin in the treatment of type 2 diabetes mellitus can gain better outcomes in glycemic control. But it increases the risk of hypoglycaemic episodes. There are also some adverse events in combination therapy. Well-designed multicenter RCTs are required to confirm these findings because of the poor methodological quality of the studies included in this systematic review and the short study duration.

Acknowledgements

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Disclosure of conflict of interest

None.

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