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Original Article

The effect and safety of diacerein in patients with type 2 diabetes mellitus : a systematic review and meta-analysis

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Abstract: The Background: Diacerein has been proposed as a treatment option for management of type 2 diabetes due to its anti-inflammatory properties. Purpose: The aim of this systematic review and meta-analysis of randomized controlled trials (RCTs) is to examine the effect and safety of diacerein in patients with type 2 diabetes. Data sources and Study Selection: We searched Pubmed, Embase, and Cochrane Library for RCTs published from database inception to September 2017. Data Extraction and Data Synthesis: Among 44 studies that were initially identified, four were eligible and were included in the following analysis. Diacerein significantly reduced fasting glycemia [weighted mean differences (WMD) -0.66, 95% confidence interval (95% CI) -1.16 to -0.16] and glycated hemoglobin A1c (HbA1c) (WMD -0.85, 95% CI -1.44 to -0.26). And the patients with a diacerein supplementation duration of ≤12 weeks had a greater decrease of fasting glycemia and HbA1c than the supplementation duration of >12 weeks. Furthermore, compared with placebo, diacerein revealed a significant increase in the relative risk (RR) of gastrointestinal symptoms (RR=2.50, 95% CI: 1.10 to 5.65), especially in the study subgroup with supplementation duration of >12 weeks (RR=4.01, 95% CI: 2.32 to 6.95). Limitations: The sample size was relatively small and the duration of included studies was short so that the treatment efficacy and safety for longer duration was unknown. Conclusions: Although further studies are needed, our findings clearly provide support to the use of diacerein in the clinical management of subjects with type 2 diabetes.

Keywords: Type 2 diabetes mellitus, diacerein, fasting glycemia, glycated hemoglobin A1c, safety, meta-analysis.

Introduction

Diabetes is a growing public health issue worldwide, with the recent data from the International Diabetes Federation suggesting that approximately 415 million people are currently affected by this condition. This number is estimated rise to 642 million by 2040, mainly due to the dramatic increase in diabetes [1]. Diabetes is associated with increased macrovascular and microvascular disease, disability and premature mortality [2-5].

Effectively glycaemic control can decrease some of diabetic complications. There are numerous antidiabetic drugs in clinical use such as metformin, thiazolidinediones and sulfonylureas, but they all possess some side effects [6-8]. And many patients eventually need exogenous insulin to control hyperglycemia more effectively. Hence, there remains an urgent need for new therapeutic approaches for the treatment of type 2 diabetes mellitus (T2D).

Inflammation has been recognised as a mechanism in the pathophysiology of T2D by decreasing β cell insulin secretion and increasing insulin resistance [9, 10]. Lots of studies have shown that markers of inflammation are associated with incident diabetes [11-13]. And Insulin resistance has been already defined as an inflammatory condition involving both innate and adaptive immunity [14]. Thus, targeting inflammation has become a new therapy in the wide variety of options for the treatment of T2D.

Diacerein (1,8-diacetoxy-9,10-dioxo-dihydroanthracene-3-carboxylic acid) is an anthraquinone

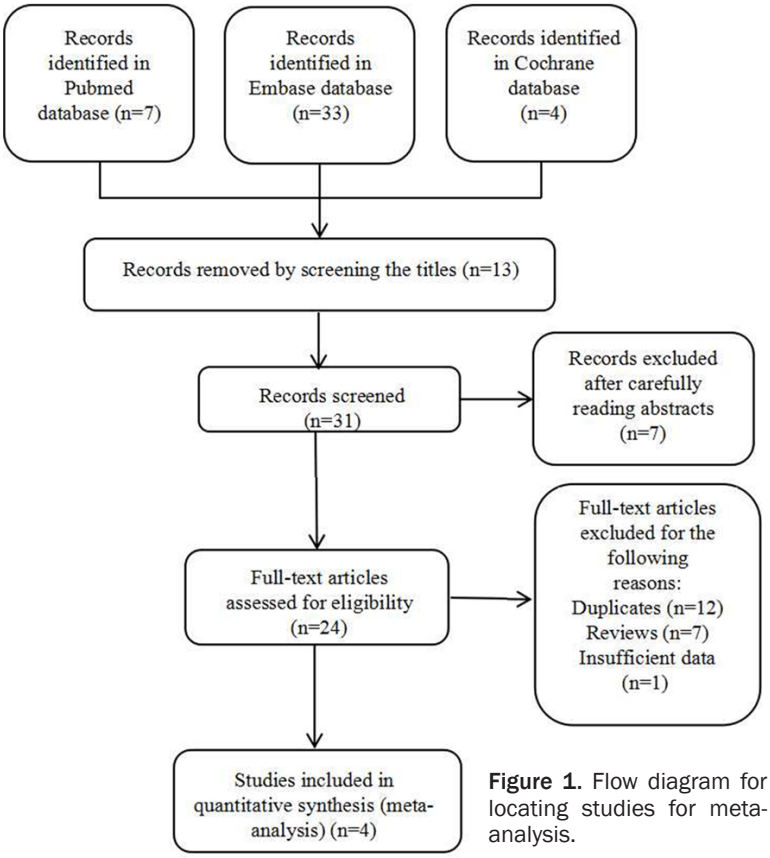

Figure 1. Flow diagram for locating studies for meta-analysis.

found in the Cassia gender plants that has anti-inflammatory properties besides mild analgesic and antipyretic characteristics [15]. The anti-inflammatory effects of diacerein due to reducing some cytokine concentrations, such as TNF-α and IL-1β, may improve insulin secretion [16]. However, the efficacy and safety of a new drug must be proved by many RCTs over a long period of observation in a large number of subjects.

Therefore, we carried out the meta-analysis of RCTs to offer an evidence-based assessment of the potential efficacy and safety of diacerhein due to the lack of an adequate number of large, multicenter RCTs. The aim of this meta-analysis is to compare the efficacy and safety of diacerein vs placebo in subjects with T2D by summarizing and pool analyzing existing RCTs.

Materials and methods

Data sources and searches

A literature search was performed in Pubmed, Embase, and Cochrane Library database inception to September 2017. The search terms were used in titles and abstracts and also in combination with MESH terms: diacerein AND (diabetes OR diabetes mellitus OR type 2 diabetes mellitus OR fasting glucose OR fasting glycemia OR hyperglycemia OR glycated hemoglobin A1c). Reference lists of selected articles were searched manually to identify further relevant studies.

Study selection

The inclusion criteria of original studies were as follows: 1) the study was a RCT in humans; 2) the baseline and endpoint values of fasting glycemia and HbA1c in both diacerein and control groups, and 3) the same basic therapy was given to the diacerein group and control group and the only difference between the two groups was diacerein.

Data extraction and quality assessment

Two investigators independently evaluated each article separately. Discrepancies were settled by a third or more investigators until consensus was reached. We contacted with the authors of relevant articles if data were incomplete. Two reviewers independently extracted the following information: 1) study characteristics that include first author's name, year of publication, sample size in the diacerein and control groups, intervention type, dose, duration of treatment, 2) population data that include age, gender, body mass index (BMI) and systolic and diastolic blood pressures of study participants; 3) mean and standard deviation of fasting glycemia and HbA1c in both the intervention and control groups at baseline, at the end of study and their changes from baseline; 4) the number of participants with each adverse events. The quality of included trials was evaluated using the Cochrane Handbook for systematic reviews of interventions [17]. Risk of bias assessment of each study included the following domains: adequacy of sequence generation, allocation sequence concealment, blind-

Table 1. Summery of the included studies

Study	Design	Population	Dose/day Diacerein	Sample Size (No.)	Duration
Villar MM 2017	Double-blind RCT	Subjects with T2DM	50 mg for 15 days and 100 mg for 75 additional days	12	12 weeks
Cardoso CRL 2017	Double-blind RCT	Subjects with T2DM	100 mg	84	48 weeks
Ramos-Zavala MG 2011	Double-blind RCT	Subjects with T2DM	50 mg for 15 days and 100 mg for 45 additional days	40	8 weeks
Pei D 2011	Double-blind RCT	Subjects with T2DM	100 mg	71	24 weeks

ing, incomplete outcome data, selective outcome reporting and other sources of bias. According to the recommendations of the same book, the judgment is categorized as 'High risk', 'Low risk' or 'Unclear risk' of bias.

Data synthesis and analysis

Data were pooled using REVMAN 5.3 software. The heterogeneity tests were performed and heterogeneity of the included studies was measured using Higgins I^2 [18]. A Random-effect model was used in case that an apparent heterogeneity was shown among studies (when $I^2 \geq 50\%$). Sensitivity analysis was conducted using the one study excluding (leave-one-out) approach for settlement of detected statistical heterogeneity. Otherwise, the Fixed-effect model was applied ($I^2<50\%$). For continuous data, we calculated the combined weighted mean differences (WMD) with their 95% Confidence Intervals (95% CI), and calculated the combined relative risk (RR) with their 95% CI for dichotomous data. P<0.05 showed that the difference was statistically significant. Begg's and Egger's tests were performed to assess potential publication bias using Stata 11.0 statistical software [19, 20].

Results

The initial literature search identified 44 citations, of which 13 were excluded on the title level. We excluded 7 articles after carefully reading the abstracts and another 19 because they were duplicates or reviews. A further 1 study that failed to meet our inclusion criteria was excluded, and 4 articles were included in the final meta-analysis [21-24] (see **Figure 1**).

Totally, four eligible studies with 207 subjects were included in this research, and the population size ranged from 12 to 84 subjects. In two trials diacerein was administrated at a dose of 50 mg for 15 days and 100 mg for the remaining days [21, 23], in another two study at a dose of 100 mg daily throughout the experiment [22, 24]. And the duration of supplementation with diacerein varied from 8 weeks to 48 weeks. All of the trials were double-blind RCTs. Summary of included trials are shown in **Table 1** and the demographic characteristics of their populations are shown in **Table 2**.

All 4 studies were evaluated using the Cochrane risk of bias assessment tool. The details about risk of bias summary, risk of bias graph and reviewer's judgements about each risk of bias item for included trials were presented in **Figure 7**. No significant publication bias was revealed in the meta-analysis of fasting glycemia and HbA1c using Begg's test and Egger's test (Begg's test: p=1.0 and 0.73, respectively; Egger's test: p=0.956 and 0.567, respectively).

The effect of diacerein on fasting glycemia and HbA1c were assessed in all the studies. Pooled results showed that diacerein significantly reduced fasting glycemia (WMD -0.66, 95% CI -1.16 to -0.16, p=0.009, see **Figure 2**) and HbA1c (WMD -0.85, 95% CI -1.44 to -0.26, p=0.005, see **Figure 3**). We used a random-effects model because we observed a high heterogeneity in the effects of diacerein on HbA1c (I^2=79%). Sensitivity analysis was performed and the heterogeneity originated from study Ramos-Zavala MG 2011 [23]. The rest of studies were re-analyzed after excluding Ramos-Zavala MG 2011; resulted in no change (WMD -0.53, 95% CI -0.86 to -0.21, p=0.001, I^2=23%).

Fasting glycemia were significantly altered by diacerein in the study subgroup with supplementation duration of ≤12 weeks (WMD -1.13, 95% CI -1.81 to -0.45, p=0.001). We found that patients with a diacerein supplementation duration of >12 weeks had a trend toward greater decrease of fasting glycemia than those with placebo supplementation, but it failed to achieve statistical significance (WMD -0.11, 95% CI -0.84 to 0.62, p=0.76). The results

Table 2. Characteristics of the included studies

First author of study and year	Group	Age (years)	Sex	BMI (kg/m^2)	SBP (mmhg)	DBP (mmhg)	WC (cm)	HBA1C (%)	FPG (mmol/L)
		Mean (SD)	No. of male (%)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Villar MM 2017	Diacerein	41.3 (9.7)	4 (66.7)	32.5 (4.2)	126.7 (15.7)	82.7 (10.2)	107.1 (12.5)	8.4 (2)	10.9 (4.4)
	Placebo	54 (3.5)	1 (16.7)	32 (2.4)	129 (9.5)	78.3 (5.4)	101.2 (10)	8.4 (1.5)	10.5 (3.1)
Cardoso CRL 2017	Diacerein	65.8 (6.3)	10 (23.3)	32.3 (5.2)	139 (24)	77 (11)	102 (8)	8.2 (0.5)	8.2 (2.7)
	Placebo	63.7 (7.9)	8 (0.2)	31.3 (5.1)	138 (18)	73 (12)	100 (11)	8.2 (0.5)	8.5 (3.4)
Ramos-Zavala MG 2011	Diacerein	47.5 (5.3)	11 (55)	30.6 (2.6)	117 (10)	77 (7)	107 (7)	8.3 (1)	7.9 (1.4)
	Placebo	47.8 (5.2)	8 (40)	30.8 (2.4)	120 (7)	78 (6)	97 (9)	7.9 (0.6)	7.8 (1)
Pei D 2011	Diacerein	NS	12 (33.3)	NS	NS	NS	NS	8.7 (1.1)	10 (1.3)
	Placebo	NS	11 (31.4)	NS	NS	NS	NS	8.6 (0.9)	9.8 (1.8)

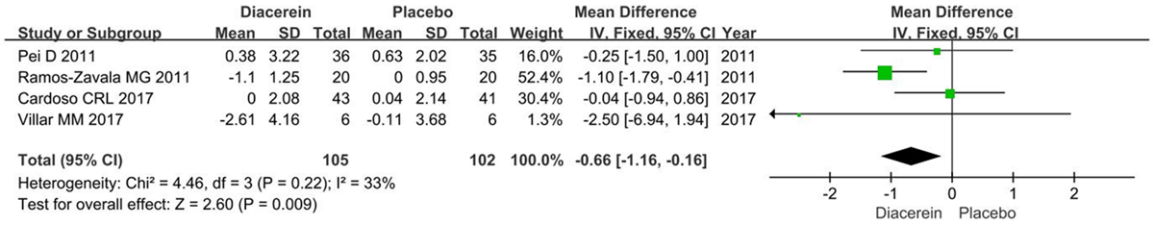

Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of diacerein supplementation on fasting glycemia.

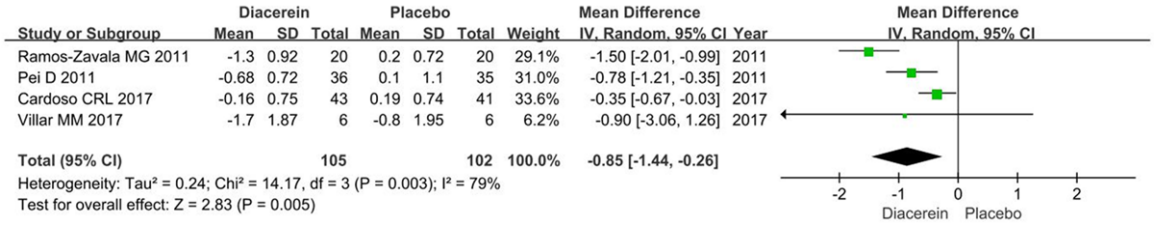

Figure 3. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of diacerein supplementation on HbA1c.

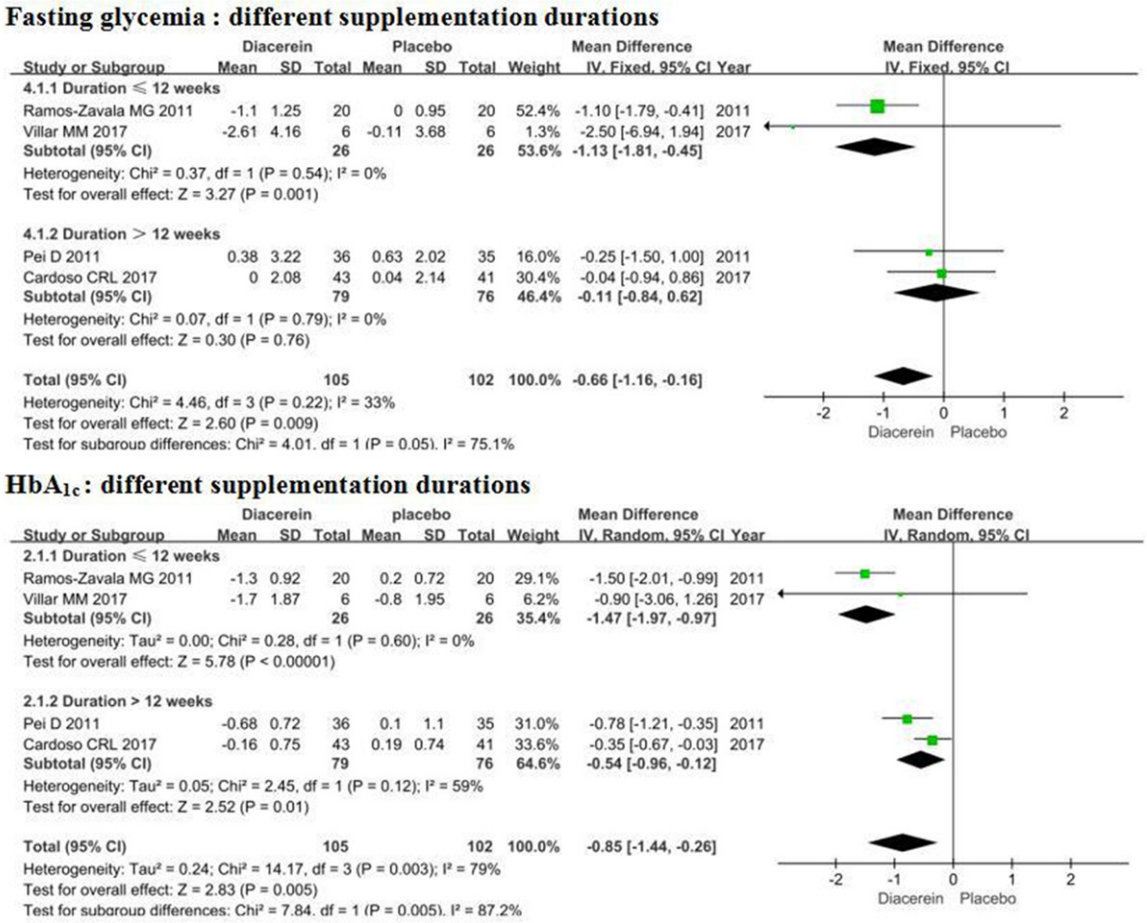

Figure 4. Forest plot detailing subgroup weighted mean differences and 95% confidence intervals for the impact of different supplementation durations of diacerein on fasting glycemia and HbA1c. Studies were categorized on the basis of supplementation duration of ≤12 weeks or >12 weeks.

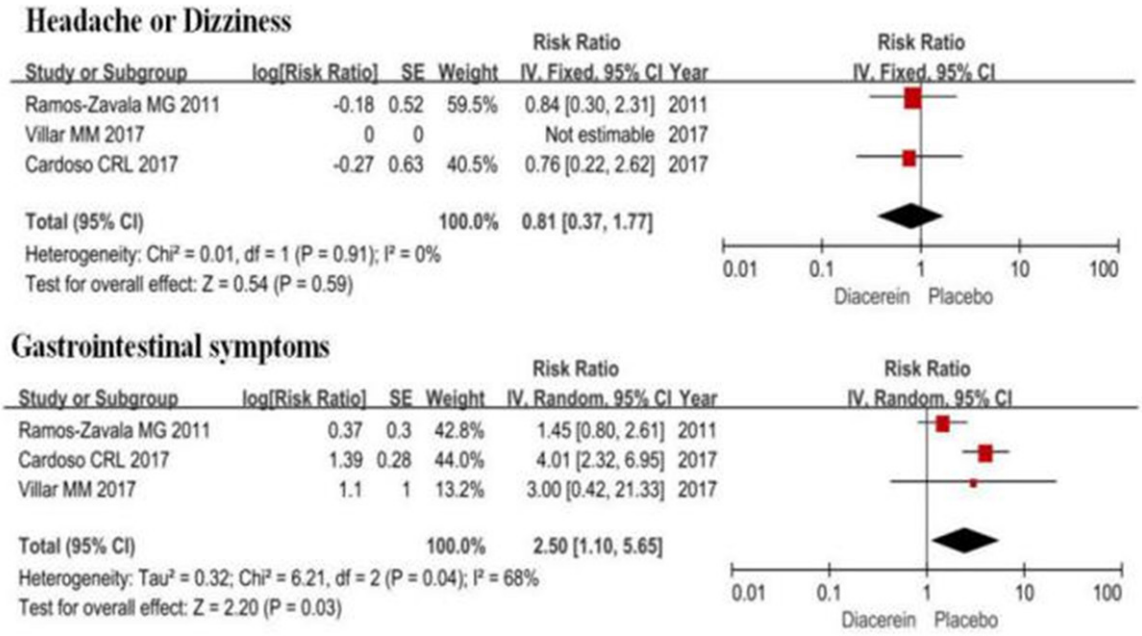

Figure 5. Forest plot detailing relative risk (RR) and 95% confidence intervals for the impact of diacerein supplementation on the headache or dizziness events and gastrointestinal symptoms.

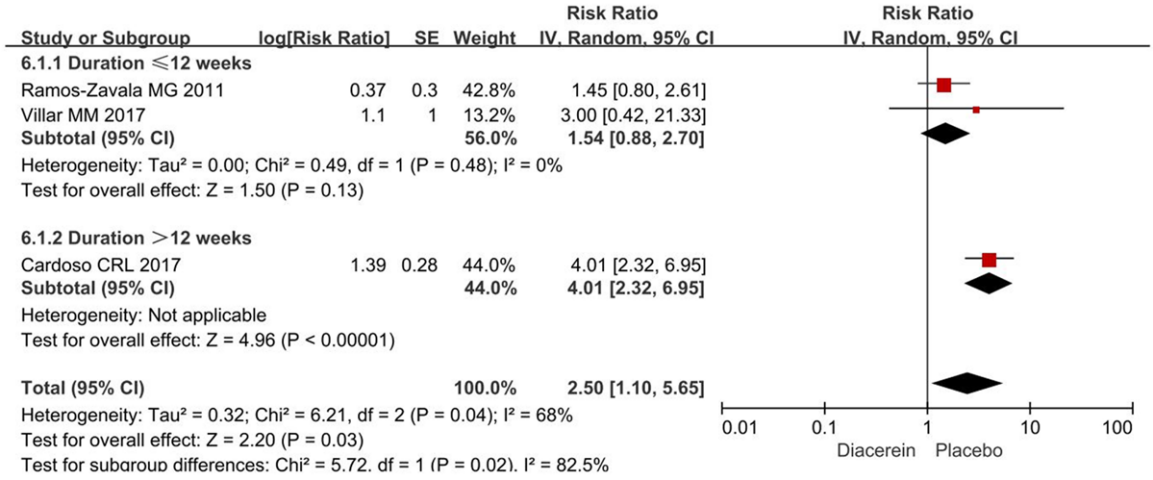

Figure 6. Forest plot detailing relative risk (RR) and 95% confidence intervals for the impact of different supplementation durations of diacerein on gastrointestinal symptoms. Studies were categorized on the basis of supplementation duration of ≤12 weeks or >12 weeks.

about the effect of diacerein on HbA1c observed in subgroup analysis were similar to the findings of combined analysis. HbA1c were significantly altered by diacerein in both the study subgroups with supplementation duration of ≤12 weeks or >12 weeks. But we found that patients with a diacerein supplementation duration of ≤12 weeks had a mean greater decrease of HbA1c than the supplementation duration of >12 weeks (WMD -1.47, 95% CI -1.97 to -0.97, p<0.01; WMD -0.54, 95% CI -0.96 to -0.12, p=0.01, see **Figure 4**).

Three studies assessed the relative risk of gastrointestinal symptoms and headache or dizziness events during treatment. Pooling the data of these trials showed no significant difference in the RR of headache or dizziness with diacerein treatment compared with placebo treatment (RR=0.81, 95% CI: 0.37 to 1.77, p=0.59).

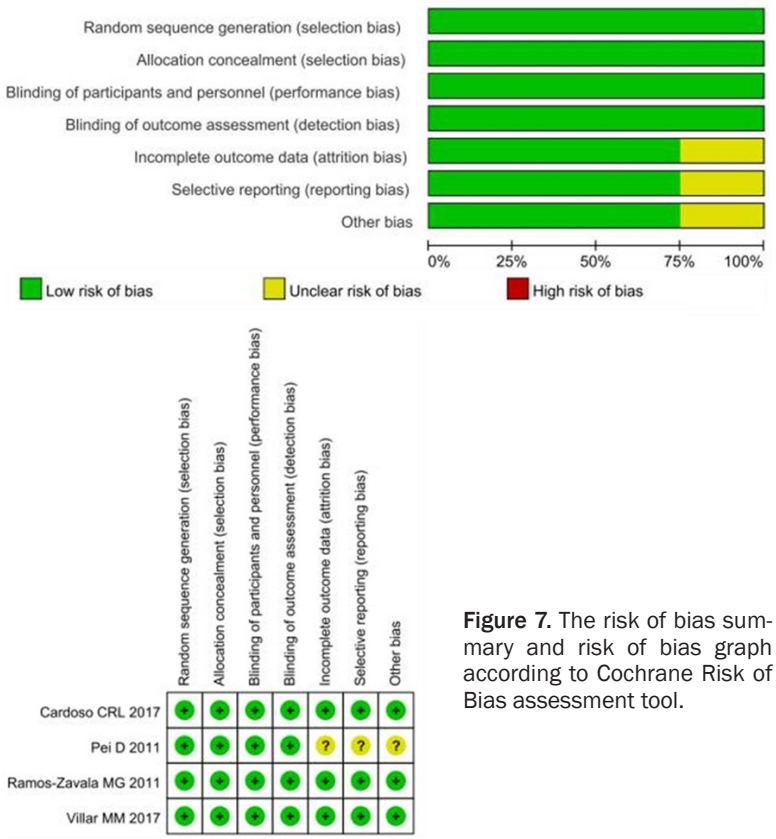

Figure 7. The risk of bias summary and risk of bias graph according to Cochrane Risk of Bias assessment tool.

The results revealed a significant increase in the RR of gastrointestinal symptoms (RR=2.50, 95% CI: 1.10 to 5.65, p=0.03, see **Figure 5**), especially in the study subgroup with supplementation duration of >12 weeks (RR=4.01, 95% CI: 2.32 to 6.95, p<0.01, see **Figure 6**).

Discussion

Our meta-analysis suggested that compared with placebo, diacerein intervention could effectively reduce fasting glycemia and HbA1c. However, adverse event of gastrointestinal symptoms increased after usage of diacerein. Interestingly, in subgroup analysis, when the treatment duration was less than 12 weeks, the greater decrease in fasting glycemia and HbA1c showed and less adverse event of gastrointestinal symptoms occurred. The results indicated that, in a certain period of time, diacerein can safely improve the fasting glycemia and HbA1c in the subjects with type 2 diabetes.

Results from our study showed the overall benefit effect on fasting glycemia and HbA1c of diacerein versus placebo. This may be explained by the following reasons. Endocrine dysfunction and inflammation of adipose tissue induce a systemic inflammation and insulin resistance in subjects with obesity, which may result in the development of T2D [25]. And studies have shown that TNF-α and IL-1 participates in the apoptosis of insular β cells, decreasing insulin secretion with the consequent hyperglycemia of T2D [26, 27]. Diacerein is a semi-synthetic anthraquinone derivative with anti-inflammatory effects and its effect on rheumatic diseases had been demonstrated by previous studies [28-32]. Based on in vivo and in vitro experiments in animals and humans, diacerein may be responsible for insulin resistance and glycemic control improvement due to the decrease of some cytokine concentrations such as IL-6, TNF-α, and specially IL-1 [33-37]. In an experimental study in mice with obesity [38], diacerein raised both insulin secretion by reducing pancreatic cell inflammation and insulin sensitivity by increasing insulin signaling in adipose tissue and liver. A randomized, double-blind, placebo-controlled, dose-ranging study of diacerein in patients with T2D found significant reduction in mean HbA1c, demonstrating diacerein may become a treatment for T2DM with a unique mode of action targeting the inflammation pathway associated with both impaired pancreatic cell function and insulin resistance [39].

Furthermore, when the intervention duration of diacerein was longer, the lesser reduction of fasting glycemia and HbA1c achieved. The result of HbA1c was consistent with Cardoso CRL 2017 who found that the greatest improvement in HbA1c occurred at 24 weeks but the improvement attenuated at 36 weeks and 48 weeks [22]. Diabetes disease progression and attenuation of drug potency may contribute to the decrease of diacerein efficacy. With the progression of diabetes, the function of β cell will gradually decrease and insulin resistance and

glycemic control will be worse [40]. This process may limit the effect of diacerein on metabolism. Moreover, the effects of a given dose diminish as treatment goes on, and larger doses must be given to maintain the desired effect. These characteristics may lead to efficacy of diacerein on glycemic management fall with the extension of time. More studies with longer follow-up periods are needed to assess long-term efficacy of diacerein.

In our meta-analysis, diacerein increased the incidence of gastrointestinal adverse events. The result was consistent with the finding of Kongtharvonskul who found diacerein increased approximately 99.6% risk of gastrointestinal adverse events compared with placebo [41]. We found that the shorter time subjects taking diacerein, the lesser gastrointestinal adverse events occurred. This may be associated with an increase in drug accumulation over time that result in an increase in adverse events. Thus, we need to pay more attention to gastrointestinal symptoms during the use of diacerein in the future.

During the meta-analysis, we found that the study of Ramos-Zavala MG 2011 was the source of the heterogeneity. First of all, subjects in the study denied usage of any drugs that could affect metabolism in the previous 6 months and may react relatively better to the drugs than individuals in other studies. In addition, not as a supplement to antidiabetic drugs, diacerein was the only intervention in the study and subjects would not affect by the interaction between drugs. Thirdly, compared with mean 28 weeks in other group, the duration of diacerein was only 8 weeks and the point may happen to be the peak of the drug efficacy, which may present a more significant consequence of diacerein on metabolic conditions. Hence, those patients may be more responsive to diacerein in this study.

Our study had distinguished strengths. This was the first meta-analysis about the effect and safety of diacerein in patients with type 2 diabetes mellitus. Furthermore, the included trials were all RCTs and had no obvious risk of bias. However, some evitable limitations existed in our study. First, the sample size was relatively small, especially 12 patients in one study, that may bias the result. Second, the duration of included studies ranged from 8 weeks to 48 weeks (mean 23 weeks) and the treatment efficacy and safety for longer duration was unknown. Third, because of few eligible trials, we could not estimate the optimal dosage and duration for diacerein aimed at improving metabolism.

In conclusion, although further studies are needed to confirm the optimal approach to the utilization of this treatment in practice, our findings clearly provide support to the use of diacerein in the clinical management of subjects with type 2 diabetes.

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Decai Chen designed the study, wrote and edited the manuscript, contributed to discussion, reviewed and edited the manuscript. Qi Zhang and Junteng Zhou wrote the initial draft of the manuscript, contributed to discussion, and reviewed and edited the manuscript. They contributed equally to this work. Yushu Wang wrote sections of the manuscript, contributed to discussion, and reviewed and edited the manuscript.

Disclosure of conflict of interest

None.

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