


Effect of rosiglitazone on circulating malondialdehyde (MDA) level in diabetes based on a systematic review and meta-analysis of eight clinical trials

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ABSTRACT

Patients with type 2 diabetes have high levels of malondialdehyde (MDA), and clinical data suggest a reducing effect of rosiglitazone (RSG) on the level of MDA in these patients. However, the results of available studies on the level of MDA in RSG-treated patients are not univocal. This meta-analysis aimed to assess the impact of RSG on the level of MDA. We performed a comprehensive search of PubMed, the Institute for Scientific Information Web of Science, Embase, Scopus, and Cochrane Library for related controlled trials until July 2020. Eligible studies were selected based on the inclusion criteria. Extracted data from each study were combined using a random-effects model. Sensitivity and subgroup analyses were conducted to explore potential heterogeneity. Eight trials with 456 subjects met the inclusion criteria. The results significantly showed the reducing effect of RSG on circulating MDA level ($-0.47 \mu\text{mol}/\text{mL}$; 95% CI -0.93 to -0.01 ; $p=0.04$; $I^2=82.1\%$; p heterogeneity= 0.00) in individuals with T2D. No publication bias was observed with Begg's rank correlation ($p=0.71$) and Egger's linear regression ($p=0.52$) tests. Subgroup analyses showed that an intervention dose of 8 mg/day in serum samples was found to have a reducing effect on the level of MDA ($-0.56 \mu\text{mol}/\text{mL}$; 95% CI -0.98 to -0.14 ; $p=0.008$; $I^2=11.4\%$; p heterogeneity= 0.32). Random-effects meta-regression did not show any significant association between the level of MDA and potential confounders including RSG dose, treatment duration, and sex. In conclusion, we found a significant reduction in MDA concentration in subjects with T2D who received a dose of 8 mg of RSG daily.

INTRODUCTION

Type 2 diabetes (T2D) is a global health problem that is closely related to the prevalence of obesity. Individuals with T2D are at high risk of complications including cardiovascular disorders, neuropathies, kidney diseases, and non-alcoholic fatty liver disease.¹ Insulin resistance and impaired insulin secretion are

the most important defects in T2D.¹ Recently, growing evidence indicates the role of oxidative stress in the development of insulin resistance in patients with T2D.² Oxidative stress is caused by free radical formation in diabetes through non-enzymatic glycation of proteins, glucose oxidation, and impaired lipid metabolism.³ Of these, lipid peroxidation due to its detrimental effects on lipid metabolism leads to damage to enzymes and cellular machinery and aggravates insulin resistance.⁴ Therefore, the circulating level of malondialdehyde (MDA) as a well-known lipid peroxidation marker came into focus as a potential sign of oxidative damage in patients with T2D.^{5,6}

Accumulating evidence points out that anti-diabetic drugs can ameliorate oxidative stress, suggesting that they are regarded as anti-oxidative stress approaches. Among these, thiazolidinediones (TZDs), as peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists, are well-studied antidiabetic drugs.⁷ The main function of TZD is to increase glucose uptake by enhancing insulin sensitivity.⁸ TZD also has antioxidant effects that inhibit the activation of the nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase pathway through 5' adenosine monophosphate-activated protein kinase (AMPK) activation. The activation of NAD(P)H oxidase pathway leads to the production of reactive oxygen species (ROS), the onset of lipid peroxidation, and the inactivation of critical metabolic enzymes. On the other hand, hyperglycemia in uncontrolled diabetes itself induces NAD(P)H oxidase pathway^{9,10} in a vicious cycle. Rosiglitazone (RSG) is a member of the TZD family.¹¹ Due to their antioxidative effects, PPAR- γ agonists are recommended in reducing the level of MDA.¹² In this regard, several studies have provided discordant results on the impact of RSG on the circulating level of MDA in patients with T2D. Many studies reported a significant reduction in the level of MDA,¹³⁻¹⁵ whereas others did not show any alteration in the circulating level of MDA following treatment with RSG in patients with



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T2D.¹⁶ Given the discrepancies in the results of previous clinical trials performed so far, the present meta-analysis aimed to evaluate the effect of RSG on the circulating level of MDA in patients with T2D.

METHODS

Search strategy

This study is based on the guidelines presented in 2009 for systematic reviews and meta-analyses (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).¹⁷ To identify randomized controlled trials (RCTs) related to this subject, a search was conducted on Scopus, Web of Science, PubMed, and Cochrane Library databases up to July 2020. The main keywords were selected using MeSH (medical subject headings) with the following query: (Rosiglitazone OR Rosiglitazone Maleate OR Avandia OR BRL 49653) AND (Malondialdehyde OR Malonyldialdehyde OR Malonaldehyde OR Malonylaldehyde OR Propanedial OR Sodium Malondialdehyde) AND (type 2 diabetes OR diabetes, OR diabetes mellitus). In addition, continuous search was performed by searching the bibliographies of the included studies by hand. The wild-card term “*” was used to increase the sensitivity of the search process. The search was limited to human studies.

Selection criteria

RCTs were selected for this study if they were published in English and evaluated the impact of RSG on plasma/serum levels of MDA. Eligible studies were RCTs where the circulating level of MDA was assessed as a primary outcome. Moreover, RCTs were eligible if they included data on adherence to a treatment duration of at least 12 weeks, included patients with T2D >20 years of age, and compared the RSG drug as an intervention with a placebo group. Articles that presented data on MDA levels at baseline and at the end of RSG treatment were also included. Studies were excluded if they did not measure the circulating level of MDA following treatment with RSG. Studies where MDA was not reported in the placebo group, articles using a mixture of RSG with other drugs, and studies that were written in other languages, such as the Taguchi *et al* study,¹⁸ were excluded from the analysis. We also excluded reviews, brief reports, case reports, and letters to editorial. Exclusion of an article due to the latter reason was done if no feedback was received after contacting the author(s).

All stages of study selection were independently reviewed using two types of research (ZM, SH) through comprehensive search using a predefined standard protocol. Studies that did not meet the inclusion criteria were excluded by screening the title and abstract, then the full text of the articles was downloaded for further assessments. The included studies received quality evaluation from two reviewers (NA-D, ZM). In this regard, disagreement between the two reviewers was resolved by a third reviewer through discussion and full consensus at each stage of the review.

Data extraction

Eligible studies were independently reviewed by two investigators (SH, JH), and the following data were extracted using a standardized form: (1) first author's name; (2) year of publication; (3) study location; (4) study design;

(5) number of the study population; (6) sample type; (7) age, gender and body mass index (BMI) of study subjects; (8) baseline and after treatment levels of MDA; and (9) dose and duration of RSG consumption. Where data were presented as a graph, data were extracted using the GetData Graph Digitizer software (<http://getdata-graph-digitizer.com/>) as a number.

Quality assessment

A systematic evaluation of bias in the included studies was performed using the Cochrane criteria.¹⁹ The items used to evaluate each study were as follows: (1) adequacy of sequence generation, (2) allocation concealment, (3) blinding and addressing of dropouts (incomplete outcome data), and (4) selective outcome reporting and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of ‘yes’ indicated a low risk of bias, while ‘no’ indicated a high risk of bias.

Main outcome

The primary outcome was the circulating level of MDA in patients with T2D following treatment with RSG, presented as 95% CI for each study.

Statistical analyses

The overall effect size was calculated using standard mean difference (SMD) and 95% CI. The SMD metric was performed based on similarity in scaling between studies. Observed heterogeneity was assessed using the Cochrane Q test and Higgins I² statistics. The Cochrane Q test and I² statistics revealed significant heterogeneity, so data from each study were combined using a random-effects model. SD of the SMD was calculated using the following formula: $SD = \sqrt{[(SD \text{ pretreatment})^2 + (SD \text{ post-treatment})^2 - (2r \times SD \text{ pretreatment} \times SD \text{ post-treatment})]}$, assuming a correlation coefficient (r) of 0.5. In reporting SEM, SD was estimated using the following formula: $SD = SEM \times \sqrt{n}$, where n is the number of subjects. Net changes in measurements (change scores) were calculated for parallel and cross-over trials, as follows: (measure at end of follow-up in the treatment group – measure at baseline in the treatment group) – (measure at end of follow-up in the control group – measure at baseline in the control group). To avoid double-counting of subjects and consequent unit-of-analysis error in trials with more than one treatment arm, the control group was evenly (where possible) divided. To explore probable publication bias, visual inspection of Begg's funnel plot asymmetry²⁰ and Egger's weighted regression tests²¹ were done. Publication bias was also determined using Duval and Tweedie ‘trim and fill’ and ‘fail-safe N’ methods. Sensitivity analysis was conducted by calculating the pooled treatment effect of RCTs that measured the circulating level of MDA following treatment with RSG after excluding each study one at a time using the leave-one-out method.²² Random-effects meta-regression was performed using unrestricted maximum likelihood method²³ to evaluate the association between the calculated effect size of serum/plasma MDA levels and dose and duration of treatment, BMI, type of sample and age, as well as respective changes in plasma/serum concentrations. Subgroup analysis investigated

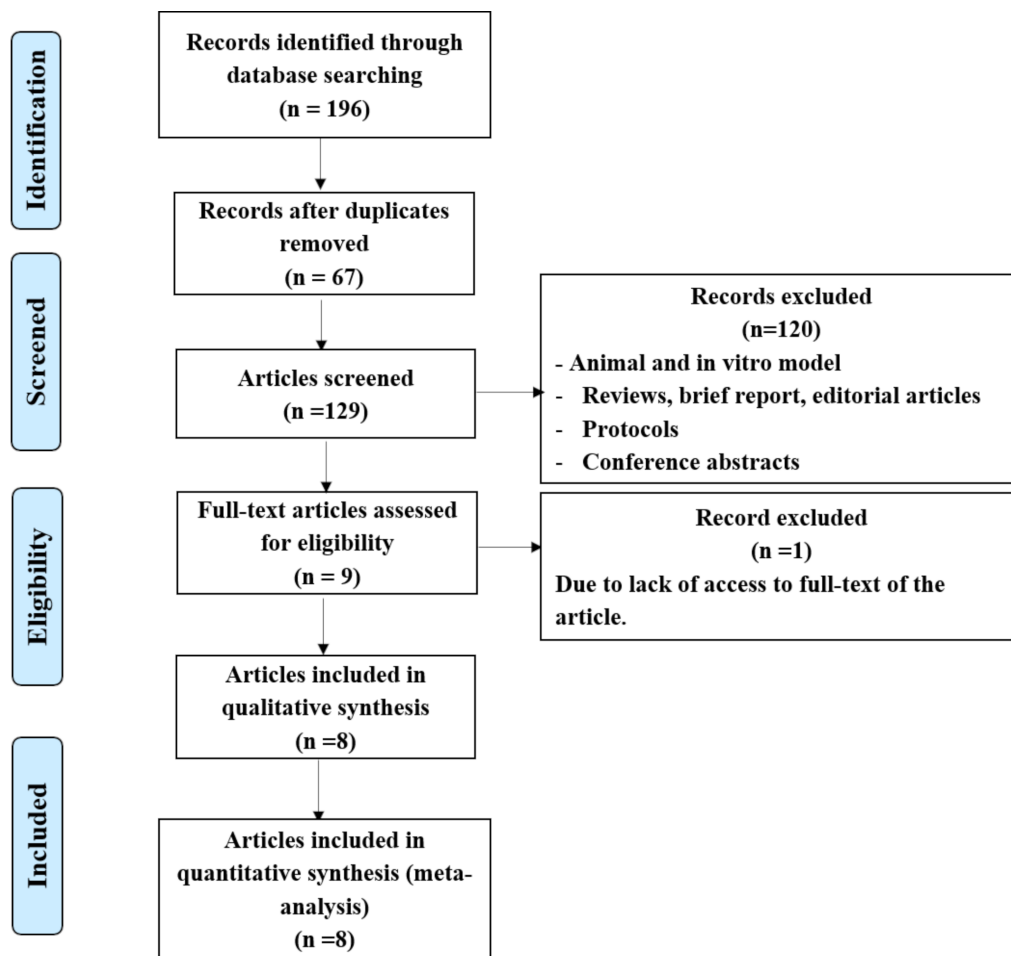


Figure 1 Flow chart of study selection for the systematic review in accordance with the PRISMA guidelines. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

whether the pooled treatment effect differed by the demographic status of the study populations (sample type, RSG dose, treatment duration, study design, and metabolic parameters). All statistical analyses were performed using the Comprehensive Meta-Analysis V.3 software (Biostat, New Jersey). Effect sizes with $p < 0.05$ were considered statistically significant.

RESULTS

Flow of study selection

To determine the impact of RSG on the level of MDA in patients with T2D, we first performed a comprehensive search to identify eligible studies. Of 196 studies identified, 58 were from PubMed, 50 from the Institute for Scientific Information Web of Science, 30 from Embase, 38 from Scopus, and 20 from the Cochrane Library. According to the predefined inclusion and exclusion criteria, 67 duplicate studies, 78 studies on animal and in vitro model, and 42 reviews, brief reports, case series, and editorials were excluded. Another study was also removed due to lack of access to the full text of the article. Eight studies were finally included in the meta-analysis. A summary of the study selection process is illustrated in [figure 1](#).

Key characteristics of included studies

In total, there were eight articles with 227 patients and 229 controls in the current systematic review and meta-analysis. The eight studies were performed in Turkey ($n=3$), China ($n=2$), India ($n=1$), USA ($n=1$) and Germany ($n=1$). The eligible studies presented a mean age of 50 years (23–58 years) and were published between 2005 and 2019. RSG was administered in different dosages among the studies, which ranged from 4 mg to 8 mg once/twice daily. The duration of intervention in the studies ranged from 12 weeks to 48 weeks. Of the eight studies, four reported an outcome in the serum sample, whereas the remaining studies reported outcomes in the plasma sample. Moreover, two studies evaluated the circulating level of MDA in patients with polycystic ovary syndrome (PCOS) and metabolic syndrome, while the remaining exclusively evaluated the MDA level in patients with T2D. The patients with T2D in all studies received antidiabetic drugs before treatment with RSG. All subjects were randomized into two arms. Individuals in the first arm received one tablet of masked placebo daily, while subjects in the second arm received masked RSG 4–8 mg daily. [Table 1](#) shows the demographic and biochemical characteristics of each included study. According to the Cochrane Handbook, five studies were considered to be

Table 1 Baseline characteristics of included studies in the systematic review and meta-analysis

First author	MDA		Sample size (inter)	Mean (cont)	SD (cont)	Sample size (cont)	Dose of RSG (mg/day)	Duration (week)	Type of sample	Age (years)	Disease	M/F (inter)	M/F (cont)	MDA assay
	Mean (inter)	SD (inter)												
Yilmaz ¹⁵	0.004	0.002	25	0.007	0.003	25	4	12	Serum	23.92	PCOS	25F	25F	SPC
von Bibra ¹³	0.006	0.0003	12	0.007	0.0007	12	8	16	Plasma	59	T2D	8/4	8/4	HPLC
Gupta ³¹	0.0006	0.0001	30	0.0006	0.0001	30	8	12	Plasma	50	T2D	30F	30F	SPC
Lazich ¹⁴	0.007	0.002	23	0.007	0.001	20	4	24	Serum	58.7	MS	9/14	14/6	ELISA
Atamer ¹²	0.003	0.001	45	0.005	0.001	50	4	12	Serum	58.7	T2D	25/20	30/20	SPC
Huang ¹⁶	14.3	8.9	40	11.2	4.1	40	4	12	Plasma	50.8	T2D	14/26	15/15	SPC
Li ⁴⁰	0.004	0.009	40	0.006	0.001	40	4	48	Plasma	40.36	T2D	21/19	21/19	SPC
Pasali ⁴¹	0.001	0.0004	12	0.001	0.0003	12	8	24	Serum	53	T2D	6/6	6/6	SPC

Cont, control; F, Female; HPLC, high performance liquid chromatography; Inter, intervention; M, male; MDA, malondialdehyde; MS, metabolic syndrome; PCOS, polycystic ovary syndrome; RSG, rosiglitazone; SPC, spectrophotometry; T2D, type 2 diabetes.

of low to moderate quality and three studies were of high quality. The results of the quality assessment of the included studies are presented in online supplemental table 1.

Overall results

The SMD of the circulating level of MDA was significantly lower in patients with T2D following treatment with RSG ($-0.47 \mu\text{mol/mL}$; 95% CI -0.93 to -0.01 ; $p=0.04$) than in placebo (figure 2). There was a high level of between-study heterogeneity ($I^2=82.1\%$; p heterogeneity=0.00). Sensitivity analyses indicated that the overall effect sizes were not changed when each study of low to moderate quality was in turn removed (pooled effect size ranged between $-0.36 \mu\text{mol/mL}$ and $-0.61 \mu\text{mol/mL}$). The exclusion of a study with a large sample size suggests a lower level of MDA ($-0.36 \mu\text{mol/mL}$; 95% CI -0.82 to 0.09) in patients with T2D after treatment with RSG similar to the overall effect size and also a substantial reduction in the between-study heterogeneity ($I^2=70\%$ vs $I^2=82.1\%$) (online supplemental figure 1).

Publication bias

Significant publication bias across studies was ruled out. On the one hand, the funnel plot of the impact of RSG on the circulating level of MDA was broadly symmetrical. On the other hand, the absence of substantial publication bias was

also underlined by the findings of the Beggs and Mazumdar rank correlation test ($p=0.71$) and Egger’s linear regression ($p=0.52$) (figure 3).

Subgroup analysis

Several a priori determined subgroup analyses were conducted to assess interactions according to dose (4mg/day and 8 mg/day), duration of intervention (≤ 12 weeks and >12 weeks), type of sample (serum and plasma) and gender (female and female plus male (mix)). The subgroup analyses found that RSG did not lower the circulating level of MDA between patients with T2D according to dose of 4mg/day, duration of intervention (≤ 12 weeks and >12 weeks), plasma sample, and gender (female and mix). However, RSG reduced the circulating level of MDA in patients with T2D according to dose of 8 mg/day and serum sample (table 2).

Meta-regression

Random-effects meta-regression evaluating the impact of RSG dose (slope: -0.05 ; 95% CI -0.42 to 0.32 ; $p=0.79$), duration of intervention (slope: 0.008 ; 95% CI -0.02 to 0.04 ; $p=0.63$), BMI (slope: -0.018 ; 95% CI -0.21 to 0.18 ; $p=0.85$), plasma sample (slope: 0.95 ; 95% CI -0.01 to 1.91 ; $p=0.05$), serum sample (slope: -0.07 ; 95% CI -1.08 to 0.93 ; $p=0.88$), and age (slope: 0.008 ; 95% CI

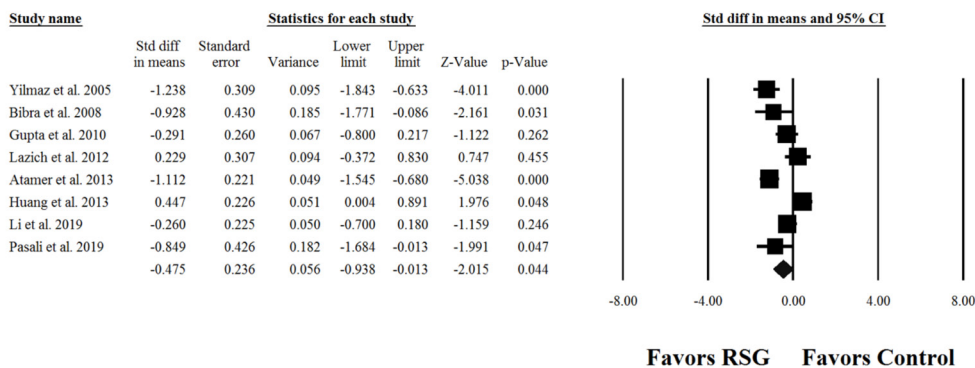


Figure 2 Forest plot evaluating standardized mean difference and 95% CI for the impact of rosiglitazone (RSG) treatment on circulating malondialdehyde level in patients with type 2 diabetes. Meta-analysis was performed using a random-effects model. Std diff, standard difference.

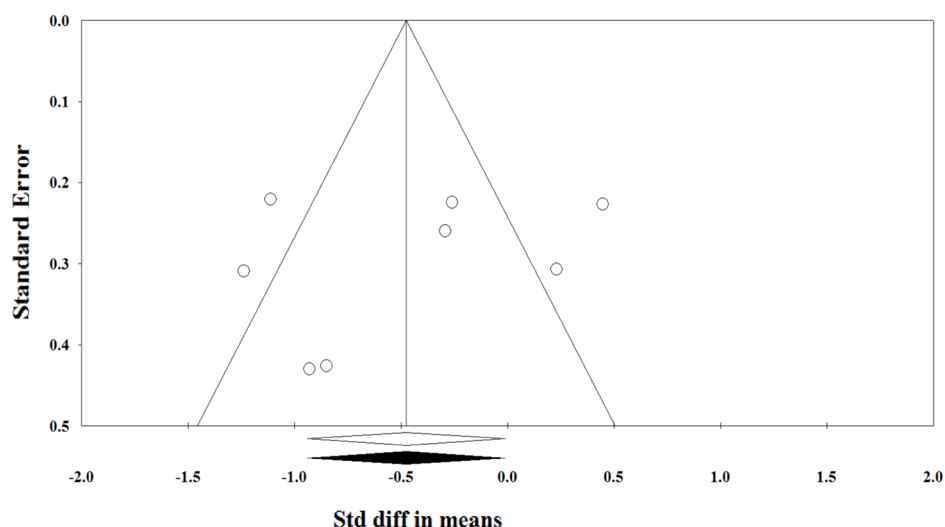


Figure 3 Random-effects funnel plot detailing publication bias in the studies investigating the effect of rosiglitazone treatment on circulating malondialdehyde level in patients with type 2 diabetes after trimming and filling. Circles represent observed published studies. Std diff, standard difference.

−0.03 to 0.04; $p=0.67$) did not show a statistically significant effect (online supplemental figure 2).

DISCUSSION

We performed a systematic review and meta-analysis of eight studies to examine the effect of RSG on the circulating level of MDA in patients with T2D. In the present meta-analysis, we found that treatment with RSG significantly reduced the level of MDA in individuals with T2D. Significant heterogeneity was observed among the included studies. There was no significant publication bias between studies involved in this meta-analysis. Subgroup analyses revealed that the serum levels of MDA under a treatment dose of 8 mg/day of RSG were severely reduced, while other subgroups including 4 mg/day of RSG, plasma sample of MDA level, duration of intervention (≤ 12 weeks and > 12 weeks), and gender (female and male) had no significant

effect on the overall effect size. Subgroup results were further supported by the meta-regression analysis which did not show a significant effect of RSG dose, duration of intervention, sample type, BMI, and age on pooled effect size. In the present study, our results confirmed that dose, as an important factor, can affect the level of MDA in patients with T2D.

TZDs are among the drugs used to treat diabetes.²⁴ RSG is a group of TZDs that have several pharmacological effects. The main effect of RSG is through regulating PPAR- γ , as RSG binds to PPAR- γ with more affinity than other TZDs, leading to improvement in insulin resistance in the muscle and fat tissue.²⁵ This is the main pathway by which RSG affects diabetes. There is also evidence that RSG can improve insulin resistance and ovarian function in PCOS.²⁶ One of the other pharmacological effects of RSG is its effect on oxidative stress, a process that is independent of PPAR

Table 2 Assessment of the impact of rosiglitazone on circulating MDA level in patients with T2D using subgroup analysis

Subgroup	Comparisons (n)	Mean ($\mu\text{mol/mL}$) (95% CI)	Z-value	P value	Test of heterogeneity	
					I^2 (%)	P value
Overall	8	−0.47 (−0.93 to −0.01)	−2.01	0.04	82.1	<0.05
Dose (mg/day)						
4	5	−0.38 (−1.04 to 0.28)	−3.3	0.25	88.9	<0.05
8	3	−0.56 (−0.98 to −0.14)	−2.7	0.008	11.43	0.32
Duration (week)						
≤ 12	4	−0.54 (−1.3 to 0.25)	−3.8	0.18	90.4	<0.05
> 12	4	−0.37 (−0.86 to 0.11)	−1.9	0.13	55.8	0.07
Sample						
Plasma	4	−0.18 (−0.68 to 0.30)	−0.75	0.45	71.7	0.014
Serum	4	0.74 (−1.4 to −0.07)	−5.5	0.03	80.3	0.002
Gender						
Female	2	−0.75 (−1.6 to 0.17)	−3.4	0.11	81.8	0.019
Mix	6	−0.38 (−0.95 to 0.18)	−2.9	0.18	83.9	<0.05

Mix: female plus male.

MDA, malondialdehyde; T2D, type 2 diabetes.

pathway.²⁷ Apart from its role in insulin sensitivity, RSG has been shown to reduce oxidative stress; for instance, pioglitazone reduces lipid peroxidation in an animal model.²⁸ Moreover, TZDs, in particular pioglitazone, reduce triglyceride and low-density lipoprotein cholesterol (LDL-C) levels and increase high-density lipoprotein cholesterol (HDL-C) levels.^{29,30} Several studies have evaluated the impact of RSG on the circulating level of MDA in individuals with T2D.³¹

The exact mechanism for the beneficial effect of RSG on the level of MDA is still unknown; however, mechanisms are emerging indicating that RSG prevents oxidative stress through inhibition of the protein kinase C (PKC) activity.³² Of the major mechanisms is that high glucose in diabetes contributes to oxidative stress and decreases cell survival through an increase in ROS production. High glucose is the major source of ROS production due to increased PKC activity. As a result, hyperglycemia increases the production of diacylglycerol, a potent activator of PKC. Increased activity of NAD(P)H oxidase in a mechanism dependent on PKC activity augments ROS production.¹⁰ Therefore, in this status, the circulating levels of MDA are significantly increased in patients with diabetes. RSG, with its inhibitory effect on PKC activity, could be a possible mechanism responsible for the reduction of the level of MDA in patients with T2D. A study demonstrated that the use of the PPAR- γ inhibitor did not inhibit this RSG effect, indicating that the inhibitory effect of RSG on PKC is probably independent of the PPAR pathway.⁸ Recent studies have also shown that RSG exerts its antioxidant effect possibly by activating AMPK.¹⁰

Another mechanism is that ROS attacks various types of cellular structures and components, including proteins, DNA, RNA, and lipids, which in turn causes cell damage.³³ In this regard, the end-products of lipid oxidation are of great interest in the assessment of oxidative stress. Therefore, unsaturated bonds in polyunsaturated fatty acids (PUFAs), especially arachidonic acid, are highly susceptible to oxidative degradation in the presence of ROS.^{34,35} The reaction of free radicals with unsaturated lipids results in the production of a variety of products. Hydroperoxides are the most important primary products of lipid oxidation. MDA and 4-hydroxynonenal (HNE) are among the most important aldehydes that are produced as secondary lipid oxidation products.³⁴ Specifically, MDA is the most mutagenic product of lipid peroxidation, while 4-HNE is highly toxic.³⁶ MDA is one of the most well-known and reliable markers used to assess oxidative stress in clinical situations, and due to its high reactivity and toxicity MDA has been extensively studied in biomedical research. MDA is made from arachidonic acid and larger PUFAs during enzymatic and non-enzymatic reactions. The non-enzymatic pathway of MDA production is not well understood because it is formed by the free radicals produced by oxidative stress and can react with many biomolecules and cause different pathological states. In the reaction of thromboxane A₂ synthesis from arachidonic acid, MDA is produced as a byproduct which is the enzymatic pathway of MDA synthesis.^{37,38} Therefore, we investigated the effect of RSG on oxidative stress in diabetes based on the MDA marker.

Concerning the considerable between-study heterogeneity, subgroup analyses were performed and showed that RSG was beneficial in reducing the level of MDA in patients

with T2D. It should be noted that RSG has been prohibited due to its adverse effects on the incidence of cardiovascular disease.³⁹ Taken together, findings from this study should be interpreted with caution. Furthermore, further studies on the circulating level of MDA as a primary outcome are needed to establish the favorable impact of RSG on the prevention of oxidative stress. On the other hand, we found no significant effect of a dose of 4 mg/day of RSG and sex variable on the level of MDA in patients with T2D. However, our data support that RSG efficacy is probably independent of low dose, gender, and time of follow-up.

The strengths of our meta-analysis are as follows: first, the literature search was very expansive and comprehensive; second, the quality of studies was relatively moderate to high; third, all studies included in the meta-analysis had an RCT design; and fourth, there was no substantial evidence of potential publication bias in the included studies. On the other hand, this meta-analysis has several limitations. First, we were not able to identify studies unpublished and published in other languages. Moreover, due to the small number of studies, the validation of meta-analysis should be interpreted with caution. We pooled the effect sizes from studies with different population characteristics, such as type of sample and time of follow-up, which potentially might lead to bias. Finally, there was significant heterogeneity among the included studies.

In conclusion, we found that RSG reduced the levels of MDA as an oxidative stress marker under pathological condition in individuals with T2D. Therefore, the use of RSG drugs is recommended to improve oxidative stress in patients with T2D. Strategies for treatment of oxidative stress could focus on the use of RSG in patients with T2D.

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Correction notice Since the Online First publication of this article, the affiliation of Javad Hashemi has been updated from 'Department of Clinical Biochemistry, Faculty of Medicine' to 'Department of Pathobiology and Laboratory Sciences, School of Medicine'.

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