

Effect of Statin Therapy on Diabetes Retinopathy in People With Type 2 Diabetes Mellitus: A Meta-Analysis

Clinical and Applied
Thrombosis/Hemostasis
Volume 27: 1-7
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DOI: 10.1177/10760296211040109
journals.sagepub.com/home/cat



Jun Liu, MD¹ , Yi-Ping Wu, MD¹ , Jun-Juan Qi, MD¹ ,
Zeng-Ping Yue, MD¹ , and Cheng-Dong Hu, MD¹ 

Abstract

Objective: We tried to find the relationship between statin and diabetes retinopathy (DR) in patients with type 2 diabetes mellitus (T2DM). **Methods:** We searched the databases of PubMed, EMBASE, and the Cochrane Library for eligible studies reporting on the relationships between statin use and DR, from inception to September 25, 2020. The terms searched including Diabetes Mellitus, Type 2, Hydroxymethylglutaryl-CoA Reductase Inhibitors, and Diabetic Retinopathy. We expressed the results as the odds ratios (ORs) with 95% confidence intervals (CIs) which were calculated using a random-effects model. **Results:** A total of 6 eligible studies, including 43 826 patients, were included in the meta-analysis. The meta-analysis showed that statin was not associated with elevated risk of DR [OR=0.96 (95% CI: 0.80-1.16), $P=.68$]. Similarly, no differences were found between statin and placebo in participants ≥ 500 [OR=0.98 (95% CI: 0.80-1.21)] or participants < 500 [OR=0.90 (95% CI: 0.49-1.66)]. Further, we conducted a meta-analysis to study the effect of statin therapy on DR in people with type 2 diabetes according to age and found that statin use was associated with a decreased risk of DR in patients with type 2 diabetes 40 years of age or older [OR=0.87 (95% CI: 0.82-0.92)]. **Conclusion:** Our meta-analysis revealed that statin was not associated with elevated risk of DR in patients with T2DM. Moreover, statin use was associated with a lower incidence of DR in patients with type 2 diabetes 40 years of age or older.

Keywords

diabetes retinopathy, statin, type 2 diabetes mellitus

Date received: 24 April 2021; revised: 13 July 2021; accepted: 30 July 2021.

Introduction

In recent years, the prevalence of diabetes mellitus (DM) is high in the world. The most common is type 2 diabetes mellitus (T2DM), which usually occurs in adults. Patients with T2DM are at high risk for macrovascular complications and microvascular complications.¹ The vascular complications of T2DM have always aroused the greatest concern. The macrovascular complications mainly include cerebrovascular disease, cardiovascular disease, and peripheral artery disease, with high morbidity and mortality. As one of the serious microvascular complications of T2DM, DR can cause vision loss in diabetic patients.² The cholesterol control is beneficial in the prevention of macrovascular events^{3,4} and the glucose control is beneficial in the prevention of microvascular events. However, the relationship between DR and dyslipidaemia is not consistent.⁵⁻⁸

Statins (inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase) could effectively reduce the level of serum cholesterol. Statin therapy is effective for the primary prevention of vascular events in patients with DM.⁹ One study indicated that statin therapy can reduce the rate of major vascular events in diabetic patients without diagnosed occlusive arterial disease.¹⁰ Nowadays, statin has been widely used in the primary and secondary prevention of atherosclerotic cardiovascular disease.¹¹ However, some studies indicated that statins may

¹ Handan Central Hospital, Handan, Hebei Province, China

Corresponding Author:

Yi-Ping Wu, Handan Central Hospital, Handan 056001, Hebei Province, China.
Email: wuyphd@163.com



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increase the prevalence of new-onset DMs.¹²⁻¹⁶ Moreover, statin use might increase the level of plasma glucose¹⁷ which can elevate the risk of DR in patients with DM. Intensive therapy slows the progression of DR in patients with insulin-dependent DM.¹⁸ Adhyaru et al¹⁹ have demonstrated the benefits and adverse effects of statin therapy.

The relationship between statin use and microvascular disease in diabetic patients is presently unknown.²⁰⁻²² Moreover, the effect of statin on DR is still debated at present²³⁻²⁷ and has become a concern. Statin use can reduce the risk of DR²⁸⁻³⁰ and postpone the development of retinopathy.^{31,32} It is unclear whether statin use is associated with a higher incidence of DR. Therefore, we conducted this meta-analysis to study the relationship between the use of statin and incidence of DR in patients with T2DM.

Methods

The meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)³³ and Cochrane's Handbook guidelines.³⁴

Search Strategy

A literature search was conducted using the databases of PubMed, EMBASE, and the Cochrane Library for eligible studies reporting on the relationships between statin use and DR, from inception to September 25, 2020. We used a combination of MeSH (medical subject headings) and Entry Terms including "Diabetes Mellitus, Type 2," "Hydroxymethylglutaryl-CoA Reductase Inhibitors," and "Diabetic Retinopathy."

Selection of Studies

The included studies should meet the following inclusion criteria: (1) the studies included type 2 diabetes patients, (2) statin was compared with control (Nonstatin Group), (3) the outcomes of studies should include incidence of DR or progression of DR. Exclusion criteria were as follows: (1) the review articles, case reports, and letters; (2) the studies were not published in English; (3) the studies on unidentified type of diabetes; (4) the studies included the patients undergoing vitrectomy; (5) the studies included the patients who received coadministration of statin and other lipid lowering drugs; and (6) animal experimental studies. Two researchers independently did the search and selection.

Data extraction and quality assessment. The information was collected from the selected studies, including design type, sample size, outcomes, and so on. Newcastle–Ottawa Scale (NOS) was used for assessing the quality of studies (case-control, cohort, and cross-sectional studies) in meta-analysis. The 3 categories for case-control studies as follows: selection (① case definition, ② representativeness, ③ control selection, and ④ control definition), comparability and exposure (① ascertainment of exposure, ② same method of ascertainment for

cases and controls, and ③ nonresponse rate). The 3 categories for cohort studies include: selection (① representativeness of the exposed cohort, ② selection of the nonexposed cohort, ③ ascertainment of exposure, and ④ demonstration that outcome of interest was not present at start of study), comparability and outcomes (① assessment of outcome, ② follow-up long enough for outcomes to occur, and ③ adequacy of follow up of cohorts). The studies included could be awarded 1 star for each item. A maximum of 9 stars can be given for each study.

Statistical Analyses

Meta-analysis of the included studies was conducted to evaluate the effect of statin on DR in people with T2DM. Revman software version 5 was employed to perform a meta-analysis. We expressed the results as the odds ratio (OR) with 95% confidence intervals (CIs) which was calculated using a random-effects model. The I^2 was used to assess the heterogeneity across included studies. The risk of bias was assessed for studies using the NOS. Forest plots were constructed for analysis groups. It was considered as a statistically significant difference when $P < .05$.

Results

Search Results and Patient Characteristics

A total of 1236 studies were identified from the initial search, 121 duplicate studies were removed and 1115 studies remained. After reading the titles and abstracts of the 1115 studies, 978 studies were further excluded. The full text of the remaining 137 studies were retrieved after the original screening. Finally, a total of 6 eligible studies, including 43 826 patients, were included in the meta-analysis. The statin group included 22 056 patients. The nonstatin treatment group included 21 770 patients. The study flow diagram of the screening process is shown in Figure 1. The characteristics of studies and the patients are summarized in Table 1. The quality assessment of the included studies is also summarized in Table 1. Three studies provided information on race characteristics. Two cross-sectional studies, 2 case-control studies, and 1 cohort study were included. Five trials investigated the effects of statin on the presence of DR and 1 trial²⁹ studied the progression of DR.

The Effects of Statin on DR

The included trials investigated the effect of statin on DR in people with T2DM. The Meta-analysis showed that statin was not associated with elevated risk of DR [OR = 0.96 (95% CI: 0.80-1.16), $P = .68$] (Figure 2). Subgroup analysis was performed based on the number of participants ($n \geq 500$ or $n < 500$). Similarly, no difference was found between the studies with different scales ($P = .81$) (Figure 3), and no differences were found between statin and placebo in participants ≥ 500 [OR = 0.98 (95% CI: 0.80-1.21)] or participants < 500 [OR = 0.90 (95% CI: 0.49-1.66)] (Figure 3). One study focused on

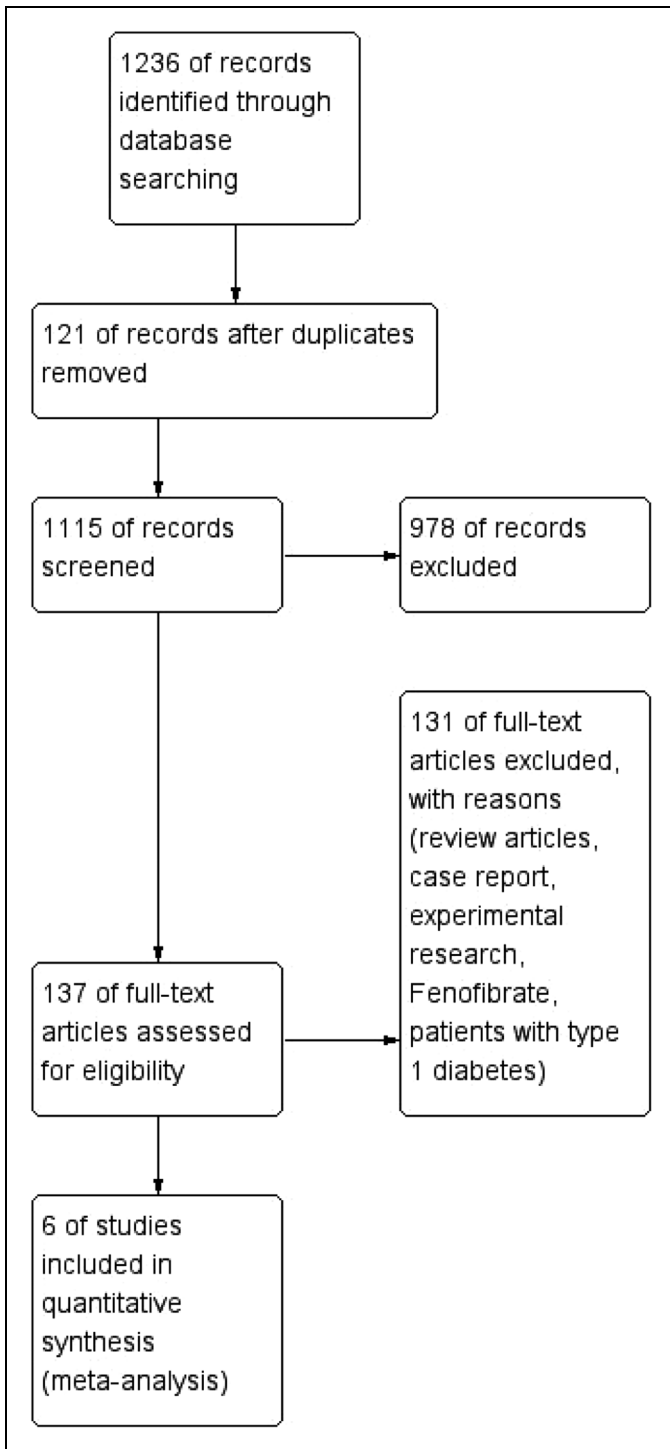


Figure 1. Study flow diagram of the included trials.

the DR progression (≥ 2 steps of DRSS).²⁹ We performed a meta-analysis for the other 5 studies to assess the efficiency of statin on the presence of DR and the result did not show a significant association between the statin use and the presence of DR [OR = 0.95 (95% CI: 0.78-1.15)] (Figure 4). Among the included studies, 3 studies involved diabetic patients with age ≥ 40 years. Further, we conducted a meta-analysis to study the effect of statin

Table 1. Baseline Data of the Included Trials in the Meta-Analysis.

Study, Year (Reference)	Study Design	Statin Group		Nonstatin Group		Mean age (year)		Male sex, No. (%)		Quality Score	Race (%)
		Events, No.	Total patients, No.	Events, No.	Total patients, No.	Statin Group	Nonstatin Group	Statin Group	Nonstatin Group		
Kang et al ²⁸	Cohort study	2004	18 947	2269	18 947	61.5	61.0	8511	8517	8*	Taiwanese patients (100%)
Chung et al ²⁹	Retrospective study	16 (23%)	70	7 (18%)	40	58.1 ± 11.6	52.3 ± 12.2	41 (58.6)	17 (42.5)	8*	NR
Sacks et al ³⁵	Case-control Study	571	2451	631	2434	NR	NR	NR	NR	8*	White/European (41%-51%)
Choi et al ³⁶	Cross-sectional study	23	50	19	46	NR	NR	NR	NR	8*	NR
Larroumet et al ³⁷	Cross-sectional design	124	456	39	224	NR	NR	NR	NR	8*	NR
Walus-Miarka et al ³⁸	Case-control study	25	82	35	79	NR	NR	NR	NR	8*	European Caucasians (100%)

Abbreviation: NR, not reported.

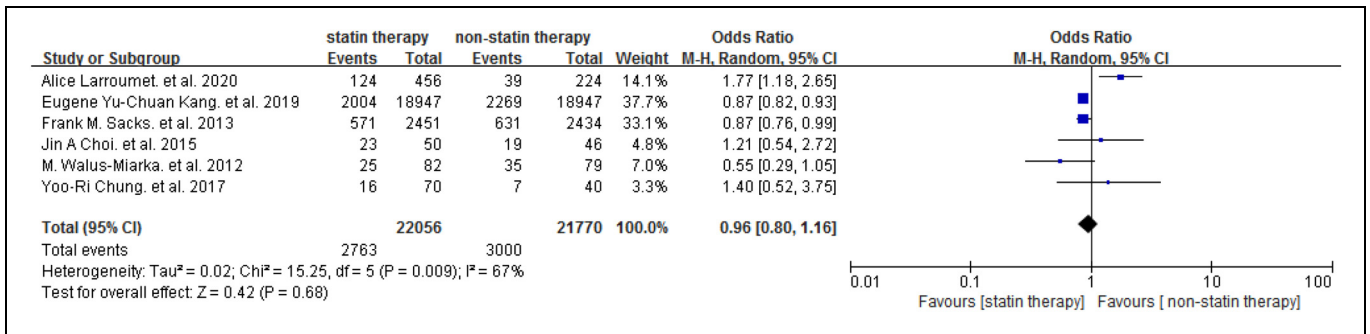


Figure 2. Forest plots for the effect of statin therapy on DR in people with T2DM. Abbreviations: DR, diabetes retinopathy; T2DM, type 2 diabetes mellitus.

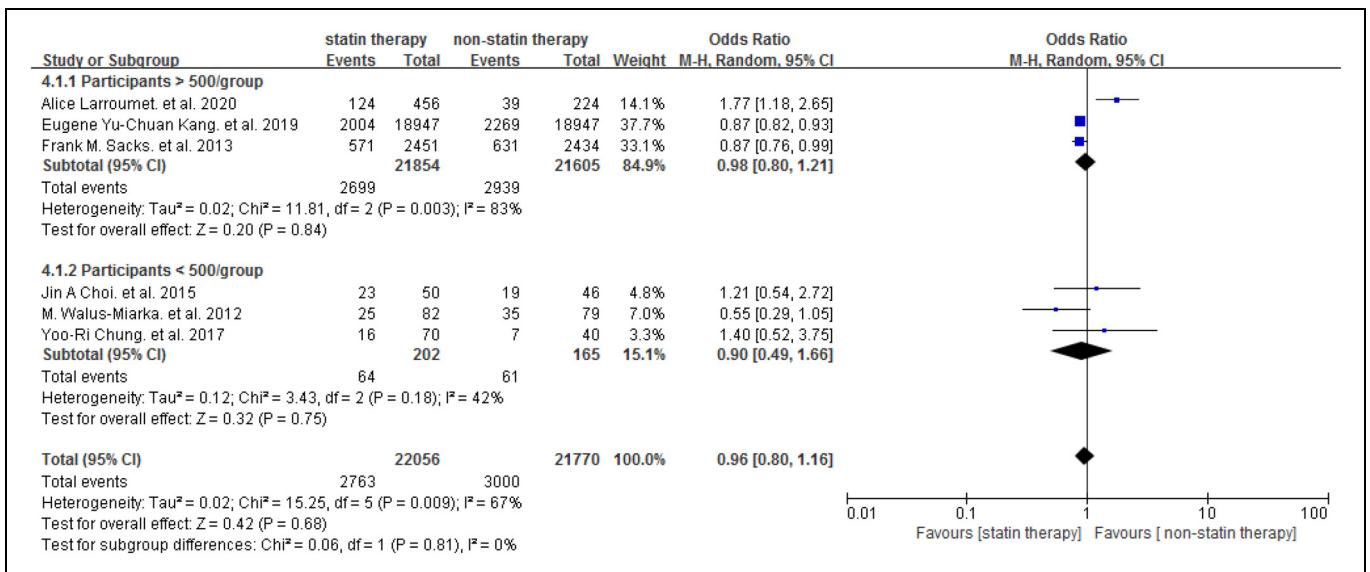


Figure 3. Subgroup analyses effects of statin therapy on DR according to the number of participants. Abbreviation: DR, diabetes retinopathy.

therapy on DR in people with type 2 diabetes according to age and found that statin use was associated with a decreased risk of DR in patients with type 2 diabetes 40 years of age or older [OR = 0.87 (95% CI: 0.82-0.92)] (Figure 5).

Discussion

We made the meta-analysis to estimate the effect of statin on DR and found no significant association between statin therapy and DR in patients with T2DM. In addition, we performed a subgroup analysis according to the number of participants. The analysis found no differences between statin and placebo group too. Besides, we made other subgroups analysis and found that statin use was associated with a decreased risk of DR in patients with T2DM 40 years of age or older. Overall, patients with T2DM who received statin showed no increase in the risk of DR in the statin group compared with the nonstatin group in our study. The results of our study provided additional insights on the safety and limitations of statin therapy.

The effects of statins on DR are uncertain in previous studies. Some studies found that the use of statin was related to a decreased risk of DR.²⁸ One study reported that dyslipidemia treatment was associated with the prevention of diabetic microvascular disease.³⁵ The combination treatment of dyslipidemia and glycemic control can reduce the progression of DR.³⁹ ACCORD-EYE study (Action to Control Cardiovascular Risk in Diabetes-EYE) indicated that Fenofibrate combined with simvastatin in the treatment of DR was more effective compared with simvastatin alone.⁴⁰ Sen et al³⁰ have proposed that simvastatin retards the progression of DR. One cohort study including 37 894 Taiwanese patients indicated that the use of statin was related to a lower risk of DR in individuals with T2DM.²⁸ Moreover, Nielsen et al⁴¹ found a similar result in statin users too. Nevertheless, the studies investigated the relationship between serum lipids and DR reported conflicting results.⁴² Some studies did not support the association between statin and DR.^{24,29} Statin users had no significant difference in the progression of DR when compared with nonusers (23% vs 18%, $P =$

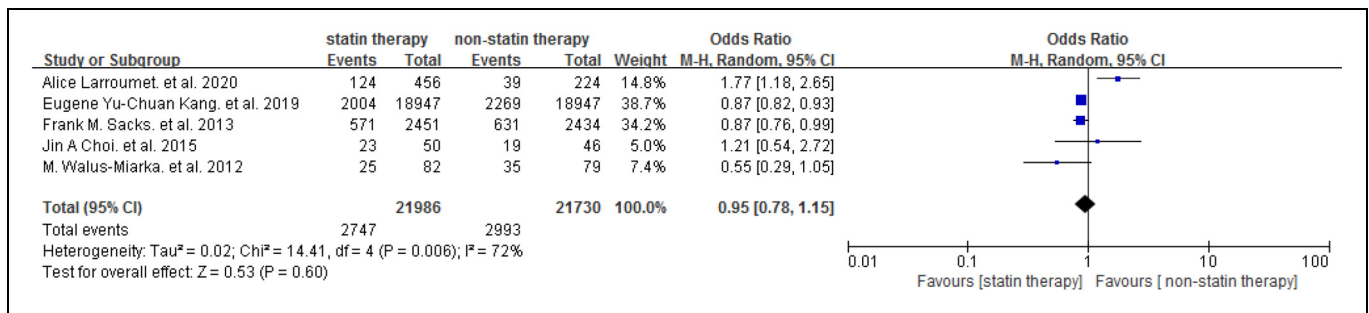


Figure 4. Effect of statin therapy on the presence of DR. Abbreviation: DR, diabetes retinopathy.

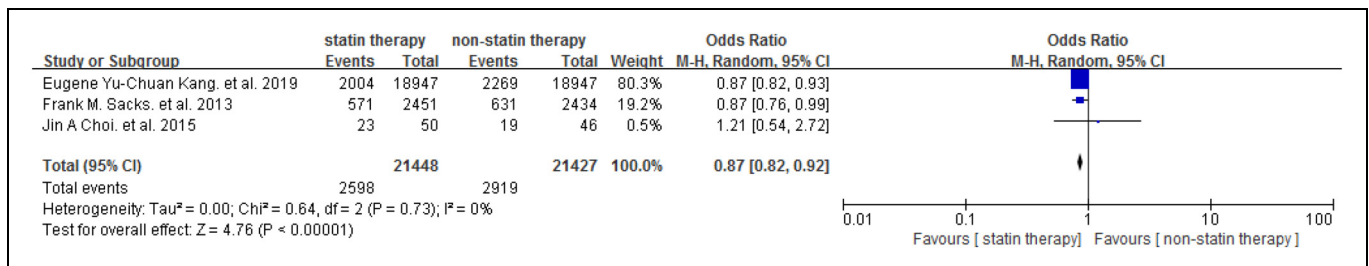


Figure 5. Effect of statin therapy on DR in people with type 2 diabetes 40 years of age or older. Abbreviation: DR, diabetes retinopathy.

.506).²⁹ The statin therapy in the pre-diagnosis of diabetes stage did not increase the risk of microvascular disease.⁴¹ The results of studies before were conflicting. Statin has several nonlipid effects which may contribute to the clinical efficacy and explain the discordant findings in previous studies.

Nowadays, statin was widely used to prevent the macrovascular complications of DM. The underlying disadvantage of statin therapy in patients with DM has attracted more attention. However, there is a lack of studies assessing the effect of statin on DR in patients with T2DM currently. Statin may increase the prevalence of new-onset DMs.¹² The disadvantage of statin may be explained by the complex mechanisms of statin including increased insulin resistance or impaired insulin secretion.⁴³ The insulin resistance in patients with T2DM can lead to the abnormalities in lipoprotein transport.

DR is one of the microvascular complications of diabetes which can lead to vision loss.¹³ Previous study demonstrated that examination of the optic disc in patients with T2DM and albuminuria might be necessary.³⁶ The mechanisms of microvascular damage that occurs during DM are complex. Many studies have been made to understand the pathophysiology of DR. The pathogenetic events in DR include vascular changes, hypoxia, blood–retina barrier disruption.⁴⁴ Ion channels may play a role in the pathophysiology of coronary microvascular dysfunction in patients with DM.⁴⁵ Oxidative Stress can affect ion channel function. The exposure to oxidative stress in diabetic patients may promote lipid peroxidation, leading to the determinism of microvascular dysfunction in DM.⁴⁶ Rapid decline of HbA1c³⁷ and changed fibrin-clot properties³⁸ were associated with DR.

Advanced glycosylation end products (AGEs), protein kinase C (PKC) pathways and renin–angiotensin system (RAS) activation might have important roles in the development of DR.⁴⁴ Besides the consistent risk factors for DR (hyperglycaemia, hypertension, diabetes duration),⁴⁷ dyslipidaemia might be a risk factor. Furthermore, the AGE and protein kinase C (PKC) pathways mentioned above are involved in the lipid levels.⁴⁸ Other associated mechanisms contributing to DR include pro-inflammatory cytokine production and vascular endothelial growth factor (VEGF). Statins have anti-inflammatory effects.⁴⁹ VEGF plays important role in the development of DR. Statins which might influence the concentration of vitreous VEGF in patients with DR.⁵⁰ Our study has several limitations. The main limitation of our meta-analysis is the lack of RCT. The results should be confirmed by high-quality RCT studies in the future. Moreover, some studies had small numbers of participants. In summary, our meta-analysis revealed that statin was not associated with elevated risk of DR in patients with T2DM. Moreover, statin use was associated with a lower incidence of DR in patients with type 2 diabetes 40 years of age or older.






Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Jun Liu  <https://orcid.org/0000-0002-3732-6448>
 Yi-Ping Wu  <https://orcid.org/0000-0003-4946-0182>
 Jun-Juan Qi  <https://orcid.org/0000-0003-1279-6555>
 Zeng-Ping Yue  <https://orcid.org/0000-0002-8472-2443>
 Cheng-Dong Hu  <https://orcid.org/0000-0002-6982-8143>

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