

# The relationship between statins and diabetic retinopathy: A review of literature

Naif Mamdouh Alali<sup>1</sup>, Hani Basher Albalawi<sup>1</sup>, and Hyder Osman Mirghani<sup>2</sup>

1. Ophthalmology Department, Faculty of Medicine, University of Tabuk, Saudi Arabia

2. Department of Medicine, Internal Medicine and Endocrine, Faculty of Medicine, University of Tabuk, Saudi Arabia

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## REVIEW

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### Corresponding Author:

Hyder Osman Mirghani  
Faculty of Medicine, University of Tabuk, PO Box 3378  
Tabuk 51941, Saudi Arabia  
Email: [s.hyder63@hotmail.com](mailto:s.hyder63@hotmail.com)

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## ABSTRACT

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### Background

Treatment with statins is a robust strategy in reducing cardiovascular complications among patients with diabetes mellitus and chronic kidney disease. There is an increasing awareness regarding the association of statins with diabetic retinopathy.

### Aims

The current review aimed to assess the relationship of statins therapy to diabetic retinopathy.

### Methods

The literature in PubMed and Google Scholar was searched for relevant articles from the first available article up to present using the terms statins, simvastatin, atorvastatin, pravastatin, and diabetic retinopathy. Among the 169 articles retrieved, 26 full-texts were assessed for eligibility and only sixteen studies (four from the USA, another four from Europe, six from Asia, and one from Australia and Brazil each) met the inclusion criteria for the systematic review. The author name, year of publication, country, type of study, number of patients, and the duration of the study

were reported.

### Results

The studies reviewed showed that statins reduce the development of diabetic retinopathy, retard the progression of hard exudates and micro-aneurisms, reduce retinopathy and macular oedema.

### Conclusion

Statins prevent and reduce the progression of diabetic retinopathy and macular oedema.

### Key Words

Statins, atorvastatin, simvastatin, pravastatin, diabetic retinopathy

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## What this review adds:

### 1. What is known about this subject?

Statins are recommended to lower the serum cholesterol and low density lipoproteins among patients with diabetes mellitus (a coronary syndrome equivalent). However, impaired glycaemic control was observed. The impact of statins-related deterioration on retinopathy is not fully elucidated.

### 2. What new information is offered in this review?

No association of statin with retinopathy deterioration. In fact, statins improve retinopathy and prevent further deterioration.

### 3. What are the implications for research, policy, or practice?

In addition to its known beneficial effects on macrovascular disease and atherosclerotic plaques stabilization, statins are needed to target the common disabling diabetic retinopathy.

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## Introduction

Diabetes mellitus (DM) is a major health problem. It is

associated with other major cardiovascular risks including hypertension and dyslipidaemias. The prevalence of diabetes mellitus is on the rise worldwide (estimated to reach 366 million by the year 2030) due to increasing obesity and physical inactivity.<sup>1</sup> Diabetes mellitus is a significant cause of retinopathy (a leading cause of blindness among the working age group in the Western World).<sup>2</sup> Statins or 3-Hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors are a class of lipid-lowering drugs with anti-inflammatory, immunomodulatory, and vascular effects. Statins are increasingly used in a variety of medical conditions including diabetes mellitus to reduce macrovascular complications.<sup>3</sup> The association of statins with retinopathy is a matter of controversy (retinopathy has sometimes been associated with statin administration, whether the association is true is to be determined. In addition, the available reviews either searched only one database or cannot draw conclusions giving a strong rationale for further reviews. Thus we conducted this review to assess the relationship of statins with diabetic retinopathy.

## Methods

### Eligibility criteria

Observational studies, case reports and series, experimental studies, reviews and metaanalyses, and randomized controlled trials published in English language and assessing statins relationship to retinopathy were eligible. All the articles from the first available manuscript to 6<sup>th</sup> December 2019 were included.

### Outcomes

The primary outcomes were the incidence and progression of diabetic retinopathy and the secondary outcomes were changes in visual acuity while on statins use.

### Information sources and search methods

A systematic manual search was conducted in PubMed and Google Scholar databases from the first available paper up to the 6<sup>th</sup> of December 2019. The following search terms were applied: Statins, simvastatin, atorvastatin, and diabetic retinopathy with the protean AND or OR, the filter was set to English publications with no time limitation.

A total of 169 studies were identified through the database search. One hundred and thirty-four identified on statins and retinopathy, twenty-three on simvastatin, while thirteen were regarding atorvastatin.

Titles and abstracts were screened independently by two authors and full texts retrieved for the manuscripts found

relevant for the topic. Additional articles were searched and identified through hand searching of the bibliography. The retrieved full-text articles were assessed for eligibility for inclusion and data were extracted by the authors using proforma. Any disagreement in the selection of articles and data was discussed and solved between the researchers. The different phases of the systematic review were reported in Figure 1.

The quality of the observational studies included was assessed according to Ottawa Newcastle Scale (Tables 1 and 2).

## Results

Among these 169 papers, 26 full-text articles were assessed for eligibility: only sixteen studies (four from the USA, four from Europe, six from Asia, one from Australia, and one from Brazil) met the inclusion criteria for the systematic review. The studies included 3,04,373 participants with a mean duration of 42.4 months. Out of the sixteen full texts reviewed, a pilot study reported the improvement of hard exudates and microaneurysms with paravastain use, the results of the four randomized controlled trials were mixed with two showed retardation of progression of diabetic retinopathy while on statins and two observed no differences between drug users and placebo. The two available reviews concluded the benefits of statins on hard exudates and macular oedema, another review and metaanalysis stated the uncertainty due to low quality of the included RCTs, all the four retrospective studies concluded the benefits of statins on prevention and retardation of diabetic retinopathy progression, the same findings were shown by an observational analysis, and experimental study, and eighteen case series, while a case control study showed neutral effects.

## Discussion

A pilot study conducted in the year 1991 in the United States of America<sup>4</sup> showed that statins improved hard exudates and micro-aneurisms, Sen et al.<sup>5</sup> published a randomized controlled trial including 50 patients with six months follow-up showed a non-significant improvement in visual acuity among simvastatin users. However, a significant difference was observed regarding visual acuity deterioration (lesser deterioration among simvastatin users), the findings implies that simvastatin significantly retards the progression of retinopathy. Another RCT was designed to investigate the effects of simvastatin on diabetic retinopathy<sup>6</sup> and found no difference between the drug and placebo groups, but the study aims were broad including other microvascular and macrovascular

complication and was terminated early with only two patients reaching two years of follow-up. A review of clinical trials<sup>7</sup> concluded the improvement of hard exudates with pravastatin, Ozkiris et al.<sup>8</sup> conducted a double-blind placebo-controlled trial and concluded that atorvastatin decreased the mean systolic blood pressure in the ophthalmic and central retinal arteries and hence prevents retinopathy progression, a case-control study from USA<sup>9</sup> included 6,441 patients and followed for five years found no association between statins and diabetic retinopathy, a case-series published in Greece<sup>10</sup> observed the improvement of hard exudated and macular oedema. A study assessed the effects of atorvastatin on diabetic retinopathy found no difference between the drug and the placebo arms<sup>11</sup> Nielsen et al.<sup>12</sup> in their retrospective study found that statins could prevent retinopathy even before the development of diabetes, another retrospective study from South Korea<sup>13</sup> showed that statins decreased macular oedema and retinopathy. An observational analysis from Japan<sup>14</sup> included 69,070 patients followed for three years found that statins decreased diabetic retinopathy, and a review conducted on statins effect on various eye disorders<sup>15</sup> concluded that statins decreased macular oedema and progression of diabetic retinopathy. However, the broad review aims, the search in only one database, and the narrative nature may not give solid evidence regarding the conclusion, another well-designed recent review and metaanalysis concluded the uncertainty regarding the association of statin and diabetic retinopathy. It is important to note that the study included eight randomized controlled trials (three on statins, four on fibrates, and one assessed the combination of statins and fibrates)<sup>16</sup> gave uncertain findings due to low quality of the included trials. An experimental study conducted in Australia<sup>17</sup> showed that Statins may play a role in diabetic retinopathy, while more recent cohorts<sup>3,18</sup> concluded that Statins therapy was associated with a decreased risk of diabetic retinopathy and need for treatments for vision-threatening diabetic retinopathy.

## Conclusion

Statins prevent diabetic retinopathy and macular oedema, and retard the progression of hard exudates and microaneurisms.

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## **PEER REVIEW**

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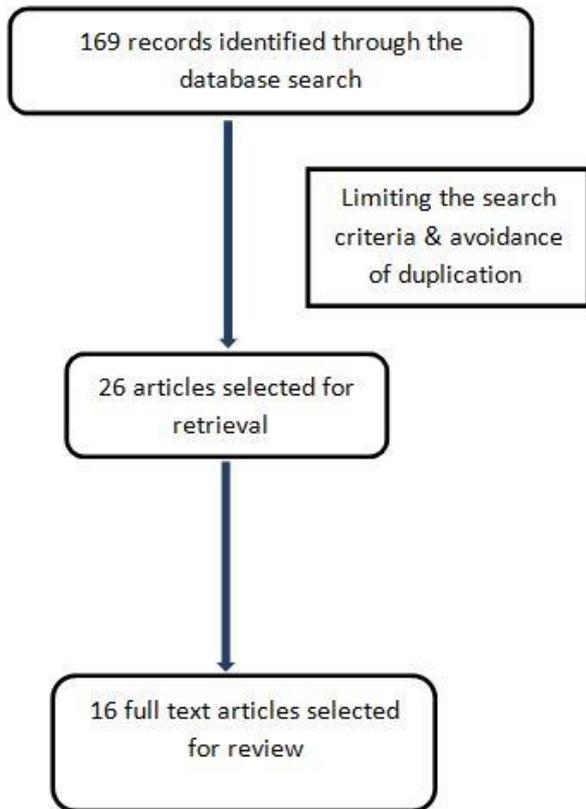
## **CONFLICTS OF INTEREST**

The authors declare that they have no competing interests.

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**Figure 1: The different phases of the literature search**



**Table 1: The relationship between statins and diabetic retinopathy**

Author	Year	Country	Type	Patients	Follow	Result
Gordon et al.	1991	USA	A pilot study	6	1 year	Hard exudates and micro-aneurysms improved
Sen et al.	2002	India	Randomized controlled trial	50	6 months	Simvastatin significantly retards the progression of retinopathy
Baghdasarian et al.	2004	USA	Review of a clinical trial of 6 patients among other studies on DM	6		Improved hard exudates on pravastatin
Ozkiris et al.	2007	Turkey	A double-blind placebo-controlled trial	45	10 weeks	Atorvastatin decreased the mean systolic blood pressure in the ophthalmic and central retinal arteries.
Zhang et al.	2007	USA	Case-control	6441	5 years	No association
Panagiotoglou et al.	2010	Greece	Case series	18	1 year	Atorvastatin reduced hard exudates and ME
Nielsen et al.	2014	Denmark	retrospective	15,679	2.7 years	Retinopathy prevention even before DM
Chung et al.	2017	South Korea	retrospective	110		Decreased ME and retinopathy
Kawasaki et al.	2018	Japan	Observational analysis	69 070	3 years	Decreased retinopathy
Al-Janabi et al.	2018	UK	Review			Decreased macular edema
Mozetic et al.	2019	Brazil	Review and meta-analysis of RCTs			Uncertainty due to low quality

Ooi et al,	2019	Australia	Experimental study			Statins may play a role in diabetic retinopathy
Gurreri et al.	2019		retrospective	479		Statins reduce nonproliferative diabetic retinopathy complications
Kang et al.	2019	Taiwan	A population Registry-based cohort	219359	15 years	Statin therapy was associated with a decreased risk of diabetic retinopathy and need for treatments for vision-threatening diabetic retinopathy

**Table 2: Ottawa Newcastle assessment for the included studies**

Author	Selection	Compatibility	Outcome	Score
Gordon et al.	4	1	3	8
Zhang et al.	4	1	2	7
Nielsen et al.	4	2	2	8
Chung et al.	4	1	2	7
Kawazaki et al.	4	2	2	8
Gurreri et al.	4	1	1	6
Kang et al.	4	2	2	8