Review Article

Association of metformin use with age-related macular degeneration risk

Michael R. Kozlowski [1]

[1] *Arizona College of Optometry, Midwestern University, Glendale, AZ, USA*

ABSTRACT

Background: The association between metformin use and reduced age-related macular degeneration (AMD) risk has been explored. Studies have shown a positive association, no association, or ambiguous results. The aim of this narrative review is to compile these divergent findings, and thereby, better assess the potential of metformin use in reducing the AMD risk.

Methods: Studies were extracted in two ways. First, a standard Google Scholar™ search was performed using the keywords "metformin" AND "macular degeneration" without language or time restrictions. The full texts of relevant articles identified in this search were retrieved and assessed, and articles of peer-reviewed original studies and meta-analyses were included. Second, the reference lists of the included articles were used to identify additional articles that satisfied the search algorithm and included in this review.

Results: Of the 12 studies included in this review, eight showed a positive correlation between metformin use and a reduced AMD risk, while one showed no association. Of the eight positive studies, seven were retrospective. Apart from the design, the studies were also diverse. The number of participants in each study ranged from over 300 to 30 million person-years. The study populations included those with type 2 diabetes mellitus, those with AMD, and those without either. The study locations were the United States, Europe, and Asia. The ambiguous or negative results from four studies could largely be rationalized based on the confounding factor of study design.

Conclusions: Most studies examined in this review demonstrated a positive association between metformin use and a reduced AMD risk. Studies not reporting such an association did not definitively demonstrate its absence. Overall, the studies reviewed herein support further clinical investigation of metformin as a prophylactic and potential treatment modality for AMD. Further randomized clinical trials with reasonably longer follow-up periods are necessary to determine the generalizability of the findings of studies reporting positive results.

KEYWORDS

metformin hydrochloride, type 2 diabetes mellitus, age-related macular degeneration, retinal pigment epithelium, cell senescence, dry AMD, exudative AMD, wet macular degeneration, geographic atrophy, macular degeneration

Correspondence: Michael R. Kozlowski, Midwestern University, Arizona College of Optometry, 19555 North 59th Avenue, Glendale, Arizona 85308. Email: mkozlo@midwestern.edu. ORCID iD: https://orcid.org/0000-0003-1213-7015

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INTRODUCTION

Metformin is the most commonly prescribed oral medication for type 2 diabetes mellitus (T2DM) [1, 2]. Its ability to lower blood glucose levels was first noted over 70 years ago when investigating its use to treat malaria and influenza [1, 2]. It was developed as a drug to treat diabetes in the late 1950s and approved for use in 1958 in the United Kingdom and in 1995 in the United States [1, 2]. It has been used off-label to treat disorders other than T2DM, including prediabetes, metabolic syndrome, polycystic ovarian syndrome, certain cancers, cardiovascular disease, degenerative skeletal diseases, liver disease, kidney disease, obesity, and some types of dementia [1-4]. A common risk factor for many of these disorders is age.

However, the mechanism underlying the clinical activity of metformin is poorly understood. The clinical effects of metformin may be mediated at the biochemical level through inhibition of mitochondrial complex I, activation of AMP-activated protein kinases, inhibition of fructose-1,6-biphosphatase by AMP, and increased glucagon-like peptide-1 secretion [3, 5] and at the phenomenological level through inhibition of cell senescence [6-11].

Cell senescence is a natural process accompanied by the loss of mitotic potential and changes in cell structure and physiology [12-15]. It changes the cell morphology, lysosomal activity, gene expression, protein synthesis, and secretory phenotype [12-15]. It is thought to perform adaptive functions, including tumor suppression [12, 15, 16], but can also interfere with the functioning of tissues that contain senescent cells [12, 13, 15, 16]. This disruption in normal functioning is thought to contribute to the pathology of several age-related disorders, including T2DM [12, 13, 15, 16]. Therefore, the ability of metformin to inhibit cell senescence may be the key mechanism underlying its clinical efficacy.

Metformin is currently undergoing phase-2 clinical trials for age-related macular degeneration (AMD) [17]. Similar to T2DM, AMD pathogenesis may involve cell senescence, particularly senescence of the retinal pigment epithelium (RPE) cell layer [18, 19]. Metformin seems to inhibit the senescence of RPE cells [19, 20], suggesting a mechanistic basis for its use in treating AMD. However, the incidence of AMD may be lower in patients exposed to metformin for other medical reasons [21-28].

In this narrative review, we explore studies on the relationship between metformin use and AMD risk. The reviewed studies were divided into three categories: "positive," if they demonstrated a statistically significant association between metformin use and a reduced risk for any form of AMD; "negative," if they revealed no evidence of an association between metformin use and the AMD risk; and "ambiguous," if they did not fit into either of these categories.

METHODS

Studies were extracted using two methods. First, a standard Google Scholar™ search was performed using the keywords "metformin" AND "macular degeneration" without language or time restrictions. The full texts of relevant articles identified in this search were retrieved and assessed, and articles of peer-reviewed original studies and meta-analyses were included. Second, the reference lists of the selected articles were used to identify additional articles that satisfied the search algorithm and included in this review.

RESULTS

Of the 12 studies included in this review, eight, one, and three were in the "positive" [21-28], "negative" [29], and "ambiguous" categories, respectively [30-32]. The "ambiguous" or "negative" results from the four studies could largely be rationalized based on the confounding factors in their study designs. Table 1 summarizes the main characteristics of the twelve included articles, classified into three categories. The three categories are discussed in detail below.

DISCUSSION

Positive association between metformin use and reduced AMD risk

Eight studies demonstrated the ability of metformin to reduce AMD incidence (Table 1) [21-28]. Of these, seven were retrospective [21-27]. Apart from the design, the studies were diverse. The number of participants in each study ranged from over 300 million to over 30 million person-years. The study populations included those with T2DM [23, 24, 26, 27], those with AMD [21, 22, 25], and those without either [28]. The study locations were the United States [21, 22, 25, 26], Europe [28], and Asia [23, 24, 27].

Table 1. Summary of included studies on the effect of metformin use on the AMD risk

Author (year)	Age (years)	Study design	Number of participants	Effect of metformin use
Positive association between metformin use and reduced AMD risk				
Starr et al. (2023) [25]	76*	Retrospective population-based study comparing AMD, no AMD, and cataract.	504 in each group	Increased metformin use in patients without AMD.
Tseng et al. (2023) [27]	50 – 79*	Retrospective cohort study involving patients with T2DM and comparing metformin and no metformin use.	13 300 in each group	Reduced risk of all AMD types and not wet AMD alone, with dose-dependence.
Jiang et al. (2022) [24]	≥ 50	Retrospective study involving patients with T2DM and comparing metformin and no metformin use.	Metformin = 209 No metformin = 115	Reduced risk of all AMD types and not wet AMD alone.
Vergroesen et al. (2022) [28]	≥ 45	Prospective population-based cohort study (1 – 21 years of follow-up) involving three cohorts categorized by age and not by disease status.	11 260	Reduced AMD risk at baseline, with no reduced lifetime risk.
Blitzer et al. (2021) [21]	> 55	Retrospective case–control study comparing patients with newly diagnosed AMD and matched controls.	AMD = 312 404 Control = 31 343 467**	Reduced AMD risk, with dose-dependence.
Stewart et al. (2020) [26]	≥ 60	Cross-sectional retrospective study involving patients with T2DM.	3120	Reduced AMD risk.
Brown et al. (2019) [22]	> 55	Retrospective case–control study comparing AMD and no AMD.	AMD = 1947 No AMD = 5841	Reduced AMD risk.
Chen et al. (2019) [23]	> 50	Population-based, retrospective cohort study involving patients with T2DM comparing metformin and no metformin use.	Metformin = 42 544 No metformin = 22 681	Reduced AMD risk, with dose-dependence.
No association between metformin use and AMD risk				
Lee et al. (2019) [29]	≥ 65	Nested case–control study involving patients with AMD or cardiovascular disease comparing all current medications (statins, metformin, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers).	26 108	No association of metformin use with the AMD risk.
Ambiguous results				
Domalpally et al. (2023) [30]	69	Cross-sectional study in the follow-up phase of a randomized clinical trial involving patients at risk for T2DM enrolled from the Diabetes Prevention Program.	Metformin = 546 Lifestyle = 513 Placebo = 428	Metformin reduced AMD prevalence by 14% but without statistical significance.
Gokhale et al. (2023) [31]	≥ 40	Population-based retrospective open cohort study involving patients with T2DM comparing metformin and other anti-T2DM medications.	117 668	No greater association of metformin with AMD compared to the other medications.
Eton et al. (2022) [32]	> 55	Retrospective cohort study involving patients with T2DM without AMD.	1 007 226	Metformin reduced the AMD risk with prior use but increased it with current use.

Abbreviations: AMD, age-related macular degeneration; T2DM, type 2 diabetes mellitus. Note: *mean age or age range; ** person-years.

Although all of these studies revealed that metformin decreased the AMD risk, some secondary findings differed. For example, one study revealed that metformin was associated with a reduced AMD risk in the population at baseline but not throughout life (cumulative incidence at age 85 years), as assessed during 1–21 years of follow-up [28]. In addition, two studies revealed that metformin was more effective in reducing the risk of dry AMD compared to late-stage or wet AMD [24, 26].

Negative association between metformin use and reduced AMD risk

One study reported no reduction in the AMD risk after metformin use (Table 1) [29]. This retrospective, nested case–control study included over 26 000 patients with AMD or cardiovascular disease. However, only some participants were treated with metformin alone (4%), whereas most (70%) were treated with other drugs or drug combinations [29]. This feature of the study design may have made it difficult to determine the effects of metformin.

Ambiguous results

Three studies yielded ambiguous results (Table 1) [30-32]. One study examined data from participants in the Diabetes Prevention Program [30]. This program compared the effects of treatment with metformin, healthy lifestyle changes, and placebo on the rate of diabetes development in at-risk participants. A comparison of the AMD risk among the three groups showed no effect of metformin use [30]. However, this analysis did not consider that some patients from each non-metformin treatment group were eventually administered metformin. A secondary analysis comparing metformin use with no metformin use across all groups revealed a 14% decrease in AMD incidence among patients using metformin but without statistical significance [30].

Another study involving patients with T2DM and no history of AMD revealed that prior use of metformin was effective in reducing the AMD risk, whereas current use was associated with a slightly increased risk [32]. This study examined only the development of dry AMD over a study period as short as 2 years. The duration of metformin use may have been limited for some patients, and some cases of AMD (i.e., wet AMD) may have been missed. Another study compared the effect of metformin use on the AMD risk with that of other antidiabetic drugs [31]. Although metformin did not lower the risk compared to other antidiabetic drugs, this may be because some other antidiabetic drugs share the ability of metformin to lower the AMD risk, possibly by inhibiting cell senescence [7-9, 11, 28, 33-39].

A limitation of this narrative review is the use of a single database, as using more databases could yield more reliable and comprehensive results with additional studies to review. However, this review outlines the key findings of original peer-reviewed studies on the association between metformin use and AMD risk. The present data support further clinical investigations of metformin as a prophylactic and potential treatment modality for AMD. A final assessment of its effectiveness awaits the results of these studies, at least one of which is currently underway [17, 40].

CONCLUSIONS

Over the past 4 years, many studies have explored the potential link between metformin use and AMD risk, 12 of which were included in this review. Most of the included studies showed that metformin use reduced AMD risk. These studies were diverse in size, patient selection criteria, and geographical area, suggesting that the effects were both robust and general. Three additional studies yielded ambiguous results. Two of these studies provided some support for the anti-AMD activity of metformin; however, their experimental designs may have limited their ability to fully assess the effects of metformin. The third ambiguous study did not directly address this question because it compared metformin to other antidiabetic medications, some of which may share anti-AMD effects. One study reported a negative result; however, this study examined the effects of many drugs and drug combinations on the AMD risk, with metformin being only marginally represented. This may have obscured the effects of metformin. Further randomized clinical trials with reasonably longer follow-up periods are necessary to determine the generalizability of the findings of the studies reporting positive results.

ETHICAL DECLARATIONS

Ethical approval: This study was a narrative review, and no ethical approval was required.
Conflict of interests: None

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