Chapter

# Potential Protective Effects of Metformin on Ocular Complications in Patients with Type 2 Diabetes

*Jasna Kusturica, Aida Kulo, Maida Rakanović-Todić, Lejla Burnazović-Ristić and Sanita Maleškić*

## Abstract

Diabetes mellitus (DM) as a chronic condition is a growing global problem. Its numerous complications, including ocular diseases, affect patients' quality and length of life. Metformin is an effective, safe, and inexpensive first-line pharmacotherapy for type 2 diabetes (T2D). The current evidence indicates metformin's multiple sites of action and multiple molecular mechanisms leading to its beneficial impact on metabolism, inflammation, oxidative stress, aging, as well as to its cardiovascular, neurological, bone, and antiproliferative properties. These impacts are the result of its acting on adenosine monophosphate-activated protein kinase (AMPK)-dependent and AMPK-independent pathways. Limited data suggest the protective role of metformin on microvascular ocular complications, including retinopathy, glaucoma, and age-related macular degeneration in patients with T2D. However, to confirm its mentioned protective and therapeutic effects, more large, randomized, double-blind, and placebo-controlled clinical studies are needed.

**Keywords:** type 2 diabetes, metformin, molecular mechanisms, ocular complications

## 1. Introduction

Diabetes mellitus (DM) is a chronic systemic disease accompanied by impaired metabolism of carbohydrates, proteins, and fats. The American Diabetes Association (ADA) [1] distinguishes two basic types of diabetes mellitus, type 1 (T1D) and type 2 (T2D), while, in addition, gestational diabetes and specific forms of the disease are also recognized. The main pathophysiologic events in DM are insulin deficiency and insulin resistance. The most significant event is insulin resistance that develops in target tissues of action of insulin (muscle, fat tissues, and liver). In T1D, autoimmune destruction of β cells of the pancreatic islets (Langerhans islets) leads to deficient production and absolute insulin deficiency, while in T2D, insulin secretion is considered insufficient to overcome insulin resistance in peripheral tissues (relative insulin deficiency).

T1D is commonly diagnosed in childhood and early adolescence, affects men and women equally, and shows the highest prevalence in the white race. T2D occurs in older life, while an increase in incidence is associated with poorer socioeconomic

status, and an increase in risks is associated with lower economic income, education levels, and unemployment. Overall, DM prevalence is expected to increase to 10.1% in the coming decades [2]. The global trend of the increasing prevalence of both types of DM implies a significant influence of environmental factors on the development of the disease.

The polygenic inheritance of DM has been suggested, with different gene variants that contribute to the overall risk of disease [3, 4]. The risk of developing the disease in the offspring is higher if one parent has T2D (~40%) and T1D (~5%). Gene variants that associate with type 1 and type 2 diseases have a different genetic basis. A limited number of specific gene variants characterize a small subset of patients with Maturity-onset diabetes of the young, a monogenic disease with autosomal dominant transmission [4].

A fundamental pathogenic event in the etiology of T1D is an aberrant immune response and production of autoantibodies to β cells. In children and adolescents with T1D, the polyendocrine autoimmune syndrome has also been described, which involves the expression of autoimmune activity against more than one endocrine organ. T1D is associated with the incidence of autoimmune thyroiditis, celiac and autoimmune gastric disease, and other rare autoimmune conditions [5, 6]. Molecular mimicry and viral infections have been investigated the longest, while recently the focus of research is covering deficiencies in immunoregulation that have been identified in patients with T1D [4]. The interaction of genetic and environmental factors may be important for triggering autoimmune events and the onset of T1D [3]. Association was established between the occurrence of T1D and the consumption of foods rich in nitrates or nitrites, low serum vitamin D levels, or early exposure to enteroviral and other infections. The timing of the introduction of cereals and gluten into the diet and alterations of the gut microbiome were suggested to affect the β-cell autoimmune response with autoantibody production [7]. Consistently, a pattern of assimilation of the local incidence rate of T1D has been observed in persons who migrated from lower geographical areas to a higher incidence area [3].

The increase in T2D prevalence has been particularly linked to obesity, sedentary lifestyles, and unhealthy diets. One of the major risk factors for T2D is obesity. Insulin resistance is thought to develop with increasing fat deposition in the liver and muscle. Visceral obesity contributes to the development of insulin resistance and possibly independently contributes to the development of T2D [8]. In prediabetes and early-stage T2D, partial reversibility of insulin secretion disorders has been observed after the restriction in the high-calorie intake and weight loss [9].

Three symptoms characterize the early onset of DM, i.e., hyperglycemia, polyuria, and increased thirst. The recommended diagnostic criteria and therapeutic monitoring of DM are based on impaired fasting glucose levels, impaired glucose tolerance test, and measuring glycosylated hemoglobin Type A1C (HbA1C). HbA1C is an indicator of long-term glycemic control (over the period of past 2–3 months), as it reflects the average level of glucose to which the erythrocytes were exposed to. In the treatment of DM, special attention is given to a balanced diet and physical activity. Administrations of exogenous insulin and insulin analogs are the first-line treatments for T1D. Insulin therapy requires an individualized approach and involves maintaining blood glucose levels as close as possible to reference levels while avoiding hypoglycemia, which is the most significant side effect of this treatment. Glycemia regulation in T2D is being attempted by oral antidiabetic agents, and if adequate control of the disease cannot be established, insulin therapy is initiated. Antidiabetics usually work by increasing the secretion of insulin from the pancreatic β cells or by reducing the insulin resistance. Also, drugs have been developed both to reduce the postprandial glycemia by slowing and reducing the

absorption of food from the gut and to reduce the production and release of glucose from the liver.

Complications of the disease significantly influence the quality of life of patients with DM. Acute complications of diabetes are metabolic and, in their extreme form, include diabetic ketoacidosis and nonketotic hyperosmolar coma. While those acute complications can directly endanger the patient's life, late chronic complications are significant due to the impact on the quality of life and morbidity and mortality associated with the disease itself. Both, acute and chronic complications are in inverse onset with the degree of metabolic control of the disease [4]. HbA1C level showed association with risks of cardiovascular disease [10] and is considered to be associated with microvascular disease [11].

## 2. Chronic complications of the disease

Chronic DM complications can be a cause of cardiovascular events, renal failure, blindness, or lower limb amputation. They are classified as macrovascular and microvascular. Coronary disease and myocardial infarction arise as macrovascular complications of DM. It is estimated that 80% of patients with T2D develop cardiovascular complications [12]. Microvascular complications of DM include diabetic retinopathy (DR), nephropathy, and neuropathy. Retinal capillary endothelial cells, mesangial cells of the renal glomeruli, glial cells, and Schwann cells of the peripheral nerves are particularly exposed as they lack the ability to inhibit glucose transport to the cell under hyperglycemia conditions [13].

The impact of glycemic control on the development of microvascular complications of T2D has been documented in large prospective studies [12, 14–16]. The DISCOVER study was conducted in 38 countries and included 16,000 patients with T2D, with an average disease duration of 4.1 years [12]. The results of this study indicated that the prevalences of microvascular and macrovascular complications were 18.8 and 12.7%, respectively. The most common microvascular complications included peripheral neuropathy (7.7%), chronic kidney disease (5.0%), and albuminuria (4.3%). Coronary artery disease (8.2%), heart failure (3.3%), and stroke (2.2%) were the most commonly reported macrovascular complications. An association was observed for the following factors of risk: age, male gender, diabetes duration, and history of hypoglycemia.

In the development of diabetic neuropathy, the changes in cellular metabolism that result from hyperglycemia and dyslipidemia are leading to oxidative stress as a leading causative factor [17]. Hyperglycemia also exerts a negative effect on the β cells themselves, due to the increased formation of reactive oxygen species (ROS). β cells have reduced amounts of catalase enzyme and superoxide dismutase that metabolize ROS under normal conditions, and an increased amount of ROS activates proapoptotic nuclear factor kappa B (NF-κB).

Several mechanisms underlie the onset of microvascular complications, and their common feature is the formation of excess oxygen radicals that cause DNA damage. In hyperglycemia, an accumulation of advanced glycation end (AGE) product and increases in the activity of the hexosamine biosynthesis pathway, polyol pathway, and protein kinase C (PKC) are described [13, 17, 18]. High plasma glucose concentrations cause glycation of amine groups in proteins, and consequently, AGE is formed. AGE causes changes in the signaling pathway of macrophages or vascular endothelial cells with the release of various cytokines and increases the expression of vascular endothelial growth factor (VEGF), which causes increased vascular permeability and retinal angiogenesis [19]. Also, AGE-mediated ROS generation is considered as a pathogenesis factor [17].

In addition, hyperglycemia increases the activity of the hexosamine pathway, the synthesis of diacylglycerol (DAG), and the activity of aldose reductase within the polyol pathway. Fructose-6-phosphate synthesis of glucosamine-6-phosphate is the first step in the hexosamine biosynthesis pathway. Activation of the hexosamine pathway increases the formation of uridine diphosphate N-acetylglucosamine, which is a substrate donor and catalyzes the binding of monosaccharide GlcNAc to serine and threonine residues of cytosolic and nuclear proteins, including the transcription factor NF-κB. DAG activates PKC isoforms, while basal membrane thickening, increased permeability, coagulation and contractility abnormalities, increased angiogenesis, and cardiomyopathy are all considered to be related to PKC activation. Increased activity of the polyol pathway leads to increased sorbitol formation. When converting glucose to sorbitol, nicotinamide adenine dinucleotide phosphate is consumed, and the production of reduced glutathione as a key antioxidant in the cell is reduced. All these cause the cell to be more susceptible to oxidative stress. Finally, the interaction of metabolic and vascular disorders leads to impaired cellular function and, over the long term, can mediate cell damage and apoptosis.

### 2.1 Ocular complications of DM

Ocular complications of DM include DR, glaucoma, and cataracts.

The most common ocular complication is DR. Its occurrence is associated with patient age, duration of DM, and hyperglycemia [20]. The contribution of inflammation-mediated pathways and angiogenesis to the progression of DR has been documented [21, 22]. One of the first clinical features of DR is proliferation of endothelial cells and forming of the microaneurysms in retinal capillaries [23]. Capillary damage of ischemia gradually leads to neovascularization. Newly formed capillaries are prone to microhemorrhages. The VEGF signaling is considered to have a significant role in the regulation of neovascularization in retina and pathogenesis of DR [23–25]. Recent advances in treatment of DR include developments in anti-VEGF therapy, which is associated with significant reductions in vision loss due to DR [23].

VEGF levels could be influenced by oxidative stress and formation of ROS, and it has been suggested that exposition of retinal cells to $H_2O_2$ might be important in stimulation of VEGF-dependent angiogenesis. Imbalance of VEGF isoforms in retinal cells has been observed *in vivo* [24]. Nevertheless, altered expression of VEGF in retinal pigment epithelial (RPE) cells of normoglycemic and diabetic mice was not observed, whereas expression of antiangiogenic VEGF165b isoform was significantly reduced in diabetic retina. Authors suggested that both hyperglycemia and oxidative stress contribute to the changes in balance of pro- and antiangiogenic factors in the retina.

Along with DR, ocular complications of DM include glaucoma and cataracts. Although age is the most significant risk factor in glaucoma development, DM has been confirmed as an etiological factor for neovascular glaucoma, while there are controversial opinions regarding open-angle glaucoma (OAG) and angle-closure glaucoma (ACG) [26]. The association of T2D and cataract has been demonstrated [26, 27], and assumed underlying mechanisms are compiled of increased oxidative stress, activation of the polyol pathway leading to an increase in the osmotic stress, and glycation of lens proteins [26, 28].

## 3. Method

We performed a short review to assess and discuss potential protective effects of metformin on ocular complications in patients with T2D.

## 4. Metformin: protective effects on ocular complications

Apart from glycemic control, metformin has shown to have antiinflammatory, antiangiogenic, and calorie restriction-related antiaging activity. Limited data suggest the protective role of metformin on microvascular ocular complications in patients with T2D. The list of studies regarding the link between metformin and ocular involvements in diabetes is presented in **Table 1**.

### 4.1 Link between metformin and VEGF-A

Changed levels of not only VEGF-A, one of the most potent members of angiogenic factor family, but also of its isoforms such as VEGF120, VEGF164, and VEGF188 are results of hyperglycemia and oxidative stress in mice [24, 25]. Previous studies have shown that angiogenesis and neovascularization in the eyes of diabetic patients, including DR, are result of increased level of VEGFs [29, 30]. Metformin was shown to mediate the reduction of the VEGF-A expression and angiogenic inhibitors in CD34+ cells under the state of hyperglycemia-hypoxia [31]. Other preliminary study reports that compared to significantly increased plasma VEGF levels in patients treated with pioglitazone, no change in VEGF levels was detected in patients treated with metformin [32]. It is interesting that change of VEGF-A during metformin therapy is independent of metformin-associated effects regarding BMI, HbA1C levels, and waist circumference of fat percentage. Even when the blood glucose and HbA1C levels were not in the recommended range, patients treated with metformin had a lower incidence of ocular complications than patients in the nonmetformin group [33].

### 4.2 Protective effect on diabetic retinopathy

The beneficial effects of metformin were detected in patients with DR [25, 33]. It was documented that 45.5% of patients from the nonmetformin group developed DR compared to 27.3% of patients from the group treated with metformin [34]. However, metformin protective effects on DR are not purely clear. Several studies investigated its effects on vascular endothelium of retina, mainly focusing on pathological background and features of angiogenesis and inflammation. There is evidence that metformin could potently protect endothelial cells via antiangiogenic, antiinflammatory, and antioxidant mechanisms [35, 36].

Han et al. [37] in their *in vitro* study found that metformin directly inhibits angiogenesis of human retinal vascular endothelial cells (hRVECs) and has prevented tumor necrosis factor alpha (TNFα)-induced upregulation of multiple inflammatory cytokines in hRVECs.

Retinal degenerations are characterized by a progressive loss of photoreceptors or their support cells, the retinal pigmented epithelium (RPE). Xu et al. [38] used metformin to determine whether stimulation of the adenosine monophosphate-activated protein kinase (AMPK) pathway protects the photoreceptors and the RPE from retinal degeneration (**Table 1**). Metformin was able to protect the photoreceptors from light damage, delay rod, and cone degeneration in the Rd10 model and to increase the resistance of the RPE to the injury. Also, authors concluded that metformin's mechanism of protection was associated with increased mitochondrial biogenesis and reduced oxidative stress.

The long-term oral metformin was associated with significantly reduced severity of DR in patients with T2D [39]. It could be explained by metformin-induced restoration of energy balance in the retina through activation of AMPK [25]. AMPK

| Authors, Year | Study title | Study design | Study outcome | Ref. |
|---|---|---|---|---|
| Brown EE et al., 2019 | The Common Antidiabetic Drug Metformin Reduces Odds of Developing Age-Related Macular Degeneration | Retrospective case-control study with medical records from patients >55 years. Three controls were matched for every AMD case, defined by Int. Class. of Diseases, 9th Revision code, based on Charlson Comorbidity Index. | Patients treated with metformin had decreased odds of developing AMD suggesting its therapeutic role in development or progression of AMD in patients at risk. | [47] |
| Chen YY et al., 2019 | Association Between Metformin and a Lower Risk of Age-Related Macular Degeneration in Patients with Type 2 Diabetes | Population-based retrospective cohort study with 68,205 patients with T2D. | Metformin use, especially in higher doses, was associated with significantly lower risk of development of AMD. | [48] |
| Li Y et al., 2018 | Association of Metformin Treatment with Reduced Severity of Diabetic Retinopathy in Type 2 Diabetic Patients | Retrospective chart review study with 335 patients with DR and with T2D ≥15 years. The severity of DR was determined by Early Treatment Diabetic Retinopathy Study scale. | Long-term use of metformin was independently associated with significant lower rate of severe nonproliferative DR or proliferative DR in patients with T2D ≥15 years. | [41] |
| Han J et al., 2018 | Metformin Suppresses Retinal Angiogenesis and Inflammation In Vitro and In Vivo | Metformin effects and mechanism were tested in vitro in hRVEC culture and in vivo in vldlr−/− mice. | Metformin showed potent antiangiogenic and antiinflammatory effects on hRVECs, reduced retinal neovascularization in vldlr−/− mice, and suppressed leukostasis in STZ-induced diabetic mice, suggesting its potential to target key pathogenic components in DR. | [37] |
| Xu L et al., 2018 | Stimulation of AMPK Prevents Degeneration of Photoreceptors and the Retinal Pigment Epithelium | In vivo study with metformin tested in three different mouse models of retinal degeneration: a light-induced degenerative model, the Pde6brd10 inherited retinal degeneration model, and a model of sodium iodate-induced RPE and retinal injury, as well as in AMPK retinal knockout mice. | By stimulation of AMPK metformin protected photoreceptors and the RPE in three different mouse models of retinal degeneration, including acute bright light damage, Pde6brd10 inherited retinitis pigmentosa, and sodium iodate-induced RPE injury. Local expression of AMPK catalytic subunit α2 was required for those effects. | [38] |
| Maleskic S et al., 2017 | Metformin Use Associated with Protective Effects for Ocular Complications in Patients with Type 2 Diabetes – Observational Study | Observational study with medical records from 234 patients with T2D (190 patients using metformin and 44 using other oral antihyperglycemic agents). | Metformin use was associated with fewer ocular complications with decreased odds of both glaucoma and DR compared to other oral antihyperglycemic agents. | [33] |

| Authors, Year | Study title | Study design | Study outcome | Ref. |
|---|---|---|---|---|
| Yi QY et al., 2016 | Metformin Inhibits the Development of Diabetic Retinopathy through Inducing Alternative Splicing of VEGF-A | Metformin effects on the development of DR were tested in STZ-induced diabetic model in mice. | Metformin inhibited VEGF signaling by inducing VEGF-A mRNA splicing to VEGF120 isoform, creating a potential for new treatment option for DR. | [25] |
| Simão S et al., 2016 | Oxidative Stress Modulates the Expression of VEGF Isoforms in the Diabetic Retina | Retinal tissue and D407 RPE cells from wild-type and Ins2Akita mouse model of diabetes were used as experimental models. | Both hyperglycemia and oxidative stress disrupted the equilibrium between pro- and antiangiogenic factors in the retina. Hyperglycemia contributed to deregulation of the expression of VEGF proteins and the production of ROS in RPE cells. Pathological H2O2 levels downregulated the VEGF165b. | [24] |
| Lin H-C et al., 2015 | Association of Geroprotective Effects of Metformin and Risk of Open-Angle Glaucoma in Persons with Diabetes Mellitus | Retrospective cohort study with patients with T2D aged ≥40 years and with no preexisting record of OAG. | Metformin use was associated with reduction in risk of developing OAG. Proposed mechanisms involved improved glycemic control or effects involving neurogenesis, inflammatory systems, or longevity pathways. | [43] |
| Richards JE et al., 2014 | Targeting aging: Geroprotective Medication Metformin Reduces Risk of Adult-onset Open-angle Glaucoma | Longitudinal data from a large database were used, and patients with diabetes, aged ≥40 with no preexisting OAG, were monitored for incident OAG. | Metformin use was associated with reduced risk of OAG, on a dose-dependent manner. Proposed mechanisms involved neurogenesis, longevity pathways, and/or reduced inflammation. | [46] |

*AMD: Age-Related Macular Degeneration; DR: Diabetic Retinopathy; hRVEC: human retinal vascular endothelial cell; vldlr-/-mice: very-low-density lipoprotein receptor knockout mutant mouse; STZ: streptozotocin; AMPK: adenosine monophosphate-activated protein kinase; RPE: retinal pigmented epithelium; VEGF-A: vascular endothelial cell growth factor A; OAG: Open-Angle Glaucoma; POAG: primary open-angle glaucoma.*

**Table 1.**
*List of studies regarding the link between metformin and ocular involvements in diabetes.*

activation was suggested to be protective for the tissues that are undergoing metabolic stress. However, the regulation on endothelial inflammatory and angiogenic responses by metformin also has been shown through both AMPK-dependent and AMPK-independent mechanisms [37, 40].

According to a retrospective study [41], there is a correlation between the long-term metformin treatment and reduced severity of DR in patients with T2D regardless of their HbA1c level, gender, race or treatment with sulfonylurea or insulin.

In summary, metformin might be used for the purpose of reducing DR progression in patients with long history of T2D.

### 4.3 Protective effect on glaucoma

Glaucoma is a type of neuropathy, and association with DM was identified – it could cause optic neuropathy [42]. The thicker central cornea in patients with DM than in healthy subjects could be a cause of higher intraocular pressure in those patients [26]. A retrospective cohort study showed that metformin use is associated with reduced risk of developing open-angle glaucoma and suggested that metformin could have an impact on glaucoma risk on multiple levels including glycemic control and calorie restriction (CR) [43]. As previous studies suggested that age-related tissue changes significantly contribute to glaucoma development [44], the antiaging effect of metformin as a CR mimetic drug could delay the progression of tissue damage [45].

Risk reduction of glaucoma was shown to be dose-dependent for metformin and independent of glycemic control in the population with DM [46]. In the observational study, patients treated with metformin had a lower prevalence of glaucoma than patients treated with other oral antidiabetic medications, 3.2 vs. 11.4%, respectively [33].

### 4.4 Protective effect on age-related macular degeneration

Recently, the first studies on this topic indicated an association between metformin use and the reduction of age-related macular degeneration (AMD) development [47, 48]. Those authors assumed metformin's protective role in development or progression of AMD based on both its antiinflammatory and antioxidative properties and on AMD pathogenesis. Namely, besides environmental and genetic factors, AMD pathogenesis involves inflammation and oxidative stress, which can lead to choroidal neovascularization and geographic atrophy with potential loss of vision [47–50].

In study Chen et al., both the incidence of AMD (3.4 vs. 6.6%) and cumulative hazard for AMD were significantly lower among metformin users than nonusers. Lower hazard ratios for AMD were shown to be associated with higher dose of metformin and longer duration of therapy, and they remained even after adjustment for the patients' age, gender, and comorbidities [48].

Similar results were found in the study by Brown et al., where decreased odds of developing AMD, except for metformin, were not associated with dipeptidyl peptidase 4 inhibitors, selective serotonin reuptake inhibitors, tetracyclic antidepressants, and statins [47].

Almost 8.4 million people worldwide are affected by AMD [51]. It is the most common cause of vision impairment in the developed countries, and the third one, after uncorrected refractive errors and cataract, globally [52–54]. Estimated blindness prevalence related to AMD is 8.7% [55]. However, it is projected that due to the extended life expectancy, the number of people with AMD will increase [52–54]. Current AMD therapy with anti-VEGF drugs is costly, i.e., the cost of an injection of anti-VEGF is up to £800, and usually eight injections per year are recommended [51]. Therefore, as metformin is well-known cheap drug, its potentially protective effect on AMD is promising, especially for countries with limited health care resources.

## 5. Conclusion

Metformin is effective, well-tolerated, and inexpensive first-line pharmacotherapy for T2D. Its additional potential protective effects on ocular complications

in patients with T2D may have a major beneficial impact on the disease course and quality and length of their life. Well-designed randomized controlled clinical trials should be conducted to evaluate the effects of metformin either on the prevention of ocular complication or on the therapy of already developed ocular complications in patients with T2D.

## Conflict of interest

The authors declare no conflict of interest.



## Author details

Jasna Kusturica*, Aida Kulo, Maida Rakanović-Todić, Lejla Burnazović-Ristić and Sanita Maleškić
Institute of Pharmacology, Clinical Pharmacology and Toxicology, Medical Faculty, University of Sarajevo, Sarajevo, Bosnia and Herzegovina

*Address all correspondence to: jasna.kusturica@mf.unsa.ba

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