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Review article

An update on ocular effects of antidiabetic medications

Elham Sadeghi [a], Elham Rahmanipour [b], Nicola Valsecchi [a,c,d], Saloni Kapoor [a], Maria Vittoria Cicinelli [e], Jay Chhablani [a,*]

[a] University of Pittsburgh, School of Medicine, PA, USA
[b] Immunology Research Center, Mashhad University of Medical Science, Mashhad, Iran
[c] Ophthalmology Unit, Dipartimento di Scienze Mediche e Chirurgiche, Alma Mater Studiorum University of Bologna, Bologna, Italy
[d] IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[e] San Raffaele Scientific Institute, Milano, Italy

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ABSTRACT

The global increase in the prevalence of type 2 diabetes has led to the development and implementation of new classes of antidiabetic medications, introducing advanced therapeutic options for the management of the disease. These new medications, though primarily designed to regulate blood glucose levels, also have applications in weight management, potentially transforming the current approaches to diabetes treatment. Newer medications, however, have ophthalmic side effects with controversies in trials and real-life data. We comprehensively assessed the ocular benefits and adverse effects of traditional and newer-generation anti-diabetic drugs. Our primary focus is on how these newer medications affect the stage of diabetic retinopathy. Additionally, we explore the associations between these medications and other ocular conditions, including age-related macular degeneration, glaucoma, orbital conditions, and diseases impacting the ocular surface. Furthermore, we provide contextual background by discussing the ocular effects of traditional anti-diabetic drugs.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic condition characterized by hyperglycemia caused by abnormalities in insulin secretion, action, or both. This condition leads to microvascular and macrovascular complications such as retinopathy, nephropathy, neuropathy, and cardiovascular disease. [52] In the eye, DM is associated with retinopathy (DR), neuropathic keratitis, cataract formation, and glaucoma. [9,45,155] DR is one of the most common causes of blindness worldwide and is expected to affect approximately 160 million people by 2045. [130] It is classified into 2 groups: nonproliferative DR (NPDR), which presents with microaneurysms, vascular leakage, exudates, and capillary occlusion, and proliferative (PDR), which involves the formation of new vessels. [130] Diabetic retinopathy currently has no cure; the available treatments aim to slow its progression and minimize vision loss from complications like diabetic macular edema (DME). These treatments include strict blood sugar control, retinal laser therapy, and intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents. [1]

Several medications are available for controlling blood sugar levels, with different mechanisms of action. These include increasing insulin release, enhancing insulin sensitivity, decreasing gluconeogenesis, and reducing glucose absorption from the kidney or small bowel. [59] Recent advancements in pharmacotherapy for diabetes have introduced a wide range of new medications, each with distinct mechanisms of action and metabolic effects. [125] These include novel insulin formulations, sodium-glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors [40,157] (see Fig. 1). While these medications significantly enhance glycemic control and offer systemic benefits, their effects on the ocular system, particularly in the progression or prevention of DR, are currently under investigation, and multiple theories are suggested. [8,136] One possible cause for the progression of DR could be the reduction in intravascular osmotic pressure due to the rapid lowering of HbA1c levels. This reduction creates an osmotic gradient between the extracellular and intracellular compartments, leading to the movement of water from areas of high to low osmotic pressure, which mainly

* Correspondence to: Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.
E-mail addresses: Elham.sadeghi@rocketmail.com, el.sadeghi91@gmail.com (E. Sadeghi), Elhamrahmanipour@gmail.com (E. Rahmanipour), Nicola.valsecchi2@studio.unibo.it (N. Valsecchi), kapoors2@upmc.edu (S. Kapoor), cicinelli.mariavittoria@hsr.it (M.V. Cicinelli), Jay.Chhablani@gmail.com, chhablanijk2@upmc.edu (J. Chhablani).

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affects small blood vessels in the eye.[36,60] Another potential explanation is the synergistic hypothesis, which posits that the combined action of insulin and VEGF on retinal blood vessels triggers vascular proliferation, thereby exacerbating DR. [60] Other mechanisms include the breakdown of the blood-retinal barrier following intensive insulin therapy [103], and the upregulation of VEGF by tight glycemic control in a hypoxic environment. [49]

Besides the effects on DR, these agents may also provide protective benefits against dry eye, glaucoma, and other retinal diseases; however, they may exacerbate certain ocular conditions affecting the anterior and posterior segments and the orbit. [111]

We comprehensively review antidiabetic medications, including their mechanisms of action, systemic effects, side effects, and, most importantly, how these medications affect the risk, progression, and management of DR and other ocular diseases. The adverse effects are classified according to their impact on various eye segments, such as the orbit, ocular surface, anterior segment, posterior segment, and optic nerve.

2. Drugs classification

We present an overview of the methods of action, positive advantages, and ocular side effects connected with different types of antidiabetic medications. The adverse effects are classified according to their impact on various eye segments, such as the orbit, ocular surface, anterior segment, posterior segment (including findings from optical coherence tomography [OCT]) and optic nerve. See Table 1.

DR Diabetic retinopathy; *AMD* Age-related macular degeneration; *DME* Diabetic macular edema; *RVO* Retinal vessel occlusion; *T2DM* Type 2 diabetes mellitus; *PCO* Posterior capsular opacity; *RP* Retinitis pigmentosa; *PDR* Proliferative diabetic retinopathy; *DPP-4* Dipeptidyl Peptidase-4; *GLP-1* Glucagon-like Peptide-1; *GIP* Glucose-dependent insulinotropic polypeptide; *NVG* Neovascular glaucoma; *SGLT2* Sodium-dependent Glucose Co-transporter 2; *ATP* Adenosine triphosphate; *AMP* Adenosine monophosphate; *K* potassium; *PPARγ* Peroxisome proliferator-activated receptor γ; *CNV* Choroidal neovascularization; *TED* Thyroid eye disease.

2.1. Traditional medications

2.1.1. Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors such as acarbose and miglitol are oral anti-diabetic drugs that work by inhibiting alpha-glucosidase enzymes in the brush borders of the small intestine. This inhibition leads to slower digestion of carbohydrates and a more gradual absorption of glucose, effectively managing postprandial hyperglycemia by reducing rapid glucose spikes after meals. [51,110]

Regarding ocular effects, most studies focused on their impact on glycemic control and lowering the chances of DR. [23] Three animal studies found that acarbose treatment can reduce or prevent diabetic changes in the retina by improving glycemic control, preventing basement membrane thickening, and improving retinal arteries' blood flow. [16,126,143] Also, reducing aldose reductase activity and increasing glutathione levels and lenticular protein may help prevent diabetic cataract formation in diabetic rats. [21] This class of drug has not been associated with any ocular side effects.

2.1.2. Biguanides

Biguanides, notably metformin, have been extensively used for many years to treat type 2 diabetes mellitus (T2DM). [131] Metformin's popularity and widespread use derive from its efficacy, safety profile, and systemic effects, such as weight maintenance and cardiovascular health. [139] Metformin reduces hepatic glucose production (gluconeogenesis) and enhances insulin sensitivity, leading to higher glucose uptake and utilization in peripheral tissues. Unlike other antidiabetic drugs, this medicine does not stimulate insulin secretion, so it does not cause hypoglycemia. [149]

Metformin does not directly affect the eye or vision; however, its critical function in systemic glucose management may indirectly benefit ocular health by lowering the risk and progression of DR. [111] Some studies investigated the potential of metformin for preventing the onset and progression of DR due to its anti-inflammatory and anti-angiogenesis properties. These effects are attributed to an increase in thrombospondin-1 levels and a reduction in plasminogen activator inhibitor-1 activity, which enhances fibrinolytic activity. [138] Additionally, metformin has been found to enhance the effectiveness of

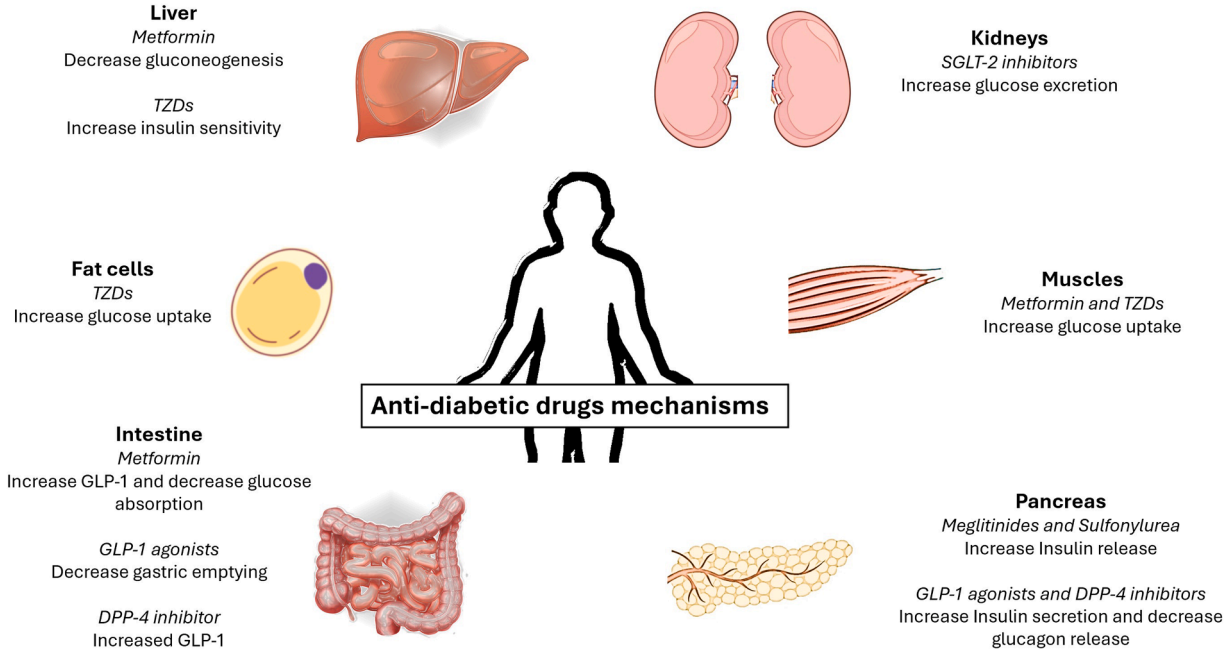

Fig. 1. Anti-diabetic drugs' mechanisms. Glucagon-like peptide 1 (GLP-1), Thiazolidinediones (TZDs), Dipeptidyl peptidase 4 (DPP-4), Sodium-glucose cotransporter 2 (SGLT-2).

Table 1
Mechanisms, systemic and ocular effects of anti-diabetic drugs.

Drugs	Mechanisms of effect	Ocular benefits	Ocular side effects
Traditional medications			
Alpha-Glucosidase Inhibitors – Acarbose – Miglitol – Voglibose	Inhibition of alpha-glucosidase enzymes in the small intestine	– Protective effect on DR – Preventive diabetic cataract development	No reported side effect
Biguanides – Metformin	Activation of AMP-activated protein kinase	– Protective effect on DR and DME – Decreasing the risk of RVO in diabetic patients – Preventive effect in AMD – Preventive effect in RP – Controlling uveitis – Preventive diabetic cataract development – Decrease PCO after cataract surgery – Protecting bleb failure in glaucoma filtration surgery – Decrease the risk of glaucoma – Controlling corneal neovascularization – Corneal burn ulcer healing – Decrease glaucoma in patients with T2DM	No reported side effect
Insulin	Cellular glucose absorption, preventing gluconeogenesis	– Long-term controlling DR – Corneal epithelial healing in diabetic keratopathy and dry eye diseases	– Early worsening of DR – Temporary refractive changes
Thiazolidinediones (TZDs) – Pioglitazone – Rosiglitazone	activating PPARγ and improving insulin sensitivity	– Controlling DR – Neuroprotective effect in glaucoma – Decrease incidence and progression of AMD – Preventive effect on diabetic dry eye – Preventive effect on corneal neovascularization – Preventive effect on conjunctival scarring	– Early worsening of DR or DME – Exacerbation of TED
SulfonylureasFirst generation: – Tolbutamide – Chlorpropamide Second generation: – Glibenclamide – Glipizide – Glyburide – Glimepiride	Close ATP-sensitive K-channels in the beta-cell plasma membrane and stimulate insulin production	– Controlling DR – Decreasing the risk of glaucoma	– No reported side effect
Newer-generation medications			
DPP−4 Inhibitors – Sitagliptin – Vildagliptin – Linagliptin – Saxagliptin – Alogliptin – Evogliptin – Gemigliptin	Inhibiting the DPP−4, stopping the degradation of GLP−1 and GIP incretin hormones, and stimulating the insulin release	– Protective effect on DR – Anti-angiogenesis effect – Neuroprotection – Preventive diabetic cataract development – Maintaining bleb function after glaucoma filtering surgery in NVG	– Early worsening of DR – Ocular cicatricial pemphigoid
GLP−1 Agonists – Semaglutide (Ozempic®) – Exenatide – Liraglutide – Dulaglutide – Albiglutide – Lixisenatide	Increasing glucose-dependent insulin secretion, inhibiting glucagon release, and delaying stomach emptying	– Long-term controlling DR – Decreasing diabetic dry eye – Decreasing the risk of glaucoma	- Early worsening of DR - Nonarteritic Anterior Ischemic Optic Neuropathy
Both GIP and GLP−1 Agonist – Tirzepatide (Mounjaro®)	Increasing glucose-dependent insulin secretion, Inhibiting glucagon release, and delaying stomach emptying	– Long-term controlling DR	– Early worsening of DR
SGLT2 Inhibitors – Canagliflozin – Dapagliflozin – Empagliflozin – Ertugliflozin	Inhibit the SGLT2 protein in the kidneys and decrease the absorption of glucose	– Controlling DR – Decreasing the risk of glaucoma – Decreasing diabetic dry eye	– Progression to PDR – Increased risk of RVO

anti-VEGF injections in treating DME, thereby improving control over DME and enhancing visual acuity. [118]

A population-based cohort of retinal vessel occlusion (RVO) patients showed that older age, hypertension, and DR were the risk factors. Metformin was protective against RVO in patients with DM. [77]

Metformin may offer protection against retinitis pigmentosa by reducing light-induced retinal degeneration and apoptosis, suppressing the activation of microglia and Müller cells, improving retinal blood capillaries, and providing neuroprotective effects. [28] It could also suppress ocular inflammation in rats by reducing leukocyte infiltration and cytokine secretion and inhibiting inflammatory proteins and transcription factors. [62]

Further research has explored metformin's role in reducing age-related macular degeneration (AMD) incidence and progression. A large study found that metformin may reduce the risk of developing geographic atrophy by 12 %. [89] Another study showed that metformin had a protective effect against AMD in non-diabetic cases. [2] A recent study reported that cumulative doses below 1080 g over 24 months significantly reduced the likelihood of neovascular AMD, especially in patients without DR. [64]

Metformin is suggested to reduce the risk of open-angle glaucoma (OAG) by 25 % in diabetic patients through improved glycemic control and modulation of neurogenesis and inflammatory systems. Each additional gram of metformin is associated with a 0.16 % reduction in OAG risk. [76] The molecular mechanisms involved are believed to relate to fibrotic signaling pathways, mitochondrial bioenergetics, and NAD oxidation. [53] Metformin's antiinflammatory and antifibrotic properties might also prevent the formation of scarring in the filtrating blebs following glaucoma filtration surgery. [75]

Innovative applications of metformin include the development of metformin-loaded silk fibroin microparticles as a topical therapy for corneal neovascularization, which is showing promise in animal studies. [102] For instance, rabbit models of corneal burn ulcers treated with metformin exhibited decreased corneal edema and inflammation, enhanced epithelial repair, and improved collagen structure in the cornea, leading to better healing outcomes. [6]

Finally, metformin has been found to increase glutathione levels in the lens, which may confer protection against diabetic cataract. [144] It also appears to downregulate the epithelial-to-mesenchymal transition in residual cells, potentially protecting against posterior capsular opacification after cataract surgery. [98]

2.1.3. Exogenous insulin

Insulin regulates blood glucose by promoting glucose uptake in muscle and fat cells and inhibiting hepatic glucose production, thereby directly lowering blood sugar levels. [87] Long-term benefits of insulin therapy include a significant slowdown in the progression of DR, especially in individuals with PDR or severe NPDR, primarily through effective blood sugar control. [69]

The presence of insulin in tears and insulin receptors on the ocular surface highlights its role in managing ocular surface diseases. [109] Topical insulin has been used to promote corneal epithelial proliferation and migration, treating diabetic keratopathy through the induction of Akt signaling. [100] Animal studies, such as those by Chen and coworkers[17] and Módulo and coworkers[88], demonstrate its efficacy in accelerating corneal wound healing in diabetic rats by promoting nerve regeneration, increasing substance P and calcitonin gene-related peptide levels, and preventing lipofuscin-like inclusions in the lacrimal gland associated with diabetic dry eye syndrome. [88] Burgos-Blasco and coworkers also noted the beneficial effects of off-label topical insulin in treating dry eye disease with epithelial damage. [15] The exact mechanisms of insulin's effect on diabetic keratopathy are not fully understood, but it is attributed to increased cell proliferation. [109]

Despite these benefits, insulin therapy may have adverse effects. Initiating insulin therapy might achieve strict glycemic control, but could cause fluctuations in blood glucose levels, potentially worsening DR temporarily. [69] Studies by Polak and coworkers and Jingi and coworkersfound that exogenous insulin could increase ophthalmic artery and choroid blood flow without affecting retinal blood flow [101] and might synergize with VEGF from the ischemic retina [60], thereby exacerbating DR. Moreover, topical insulin treatment has been linked to increased retinal acellular capillaries and significant vascular damage [67] and may decrease retinal blood flow in diabetic eyes, contributing to retinal hypoxia, capillary vasodilation, and increased edema through blood-retinal barrier breakdown. [103]

Additionally, insulin treatment may cause short-term changes to the ocular surface and focusing capability, impacting lens and cornea thickness and resulting in transient hyperopia and hazy vision. [115,140]

2.1.4. Thiazolidinediones

Thiazolidinediones (TZDs), commonly referred to as glitazones, target peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear receptor that regulates fatty acid storage, insulin sensitivity, and adipogenesis. These medications enhance insulin sensitivity and reduce blood glucose levels without stimulating insulin production. [108] Pioglitazone is the most commonly used TZD, mainly because it improves glycemic control and has beneficial effects on lipid profiles. Rosiglitazone usage has diminished due to concerns about its cardiovascular risks. [7]

The impact of TZDs on DR and DME remains controversial. Some studies have linked TZD use with an increased risk of DME, [32,55,90] which may be attributed to increased plasma volume from reduced renal sodium excretion. [99] Conversely, findings from the ACCORD trial showed no association between TZD use and the incidence or progression of DME or DR [4] and visual acuity outcomes. [41] Additional research, such as that by Shen and coworkers, suggests that rosiglitazone might delay the onset of PDR due to its antiangiogenic properties. A study by Shani and coworkers reported that rosiglitazone had been linked to increased rates of intensive eye treatments such as laser therapy and vitrectomy. Still, it could be related to slightly higher HbA1c levels observed in users than controls. [116] Other studies indicate that TZDs may reduce the progression to PDR and lessen visual acuity loss [97,119]; however, some community-based studies have reported increased rates of laser treatment and vitrectomy following long-term use of this class of drug. [116]

PPAR-γ agonists, including TZDs, have demonstrated neuroprotective and antioxidant activities. [5] Animal studies have shown that pioglitazone can protect retinal ganglion cells and prevent axonal degeneration in glaucoma. [151] Additionally, pioglitazone may manage PDR effectively by preventing fibrotic changes in retinal pigment epithelial cells through the inhibition of TGF-β pathways [46] and may reduce inflammation in exudative AMD [132] and uveitis. [95]

The role of TZDs in thyroid eye disease (TED) is mixed. Some evidence suggests that while PPAR γ exacerbates TED, its anti-inflammatory and anti-fibrotic effects could be protective. [44,84,121] In vitro and animal model studies have also shown that PPAR-γ agonists can reduce inflammation [86] and have therapeutic effects on ocular conditions like dry eye [91], corneal inflammation [92], [29] and neovascularization, highlighting their potential utility in reducing scarring following pterygium or glaucoma filtering surgery. [142,153]

2.1.5. Sulfonylureas

Sulfonylureas have played a vital role in managing T2DM since their introduction in the 1950s. These medications primarily enhance blood glucose control by stimulating insulin production from pancreatic beta cells and closing ATP-sensitive K channels in the beta-cell plasma membrane. [156] Second-generation sulfonylureas, such as glibenclamide, glipizide, glyburide, and glimepiride, are favored due to their enhanced efficacy, reduced risk of hypoglycemia, and more convenient dosing schedules compared to first-generation agents like tolbutamide and chlorpropamide. [120,156]

The landmark UKPDS study, which involved 3867 individuals newly diagnosed with T2DM, demonstrated that intensive glucose regulation

using insulin or sulfonylureas could reduce the risk of DR, [57] later confirmed by Berdugo and coworkers. [11] Notably, gliclazide has been shown to prevent retinal leukostasis and directly improve retinal microvascular abnormalities independent of its blood sugar control effects. [66] On the other hand, Tang and coworkers reported a higher risk of DR with sulfonylureas compared to placebo and SGLT2 inhibitors. [128]

The SUR1 receptor binds glibenclamide and is present in rodents and human retinas. The interaction between glibenclamide and the receptor might prevent cell death and help maintain visual function. [10] Moreover, sulfonylureas have been suggested to possess ocular hypotensive properties and direct neuroprotective actions on retinal ganglion cells, potentially offering a protective effect against glaucoma. [19] Nonetheless, this class of drugs has also been associated with higher intraocular pressure in the general population, indicating a need for cautious evaluation of their ocular effects.[50]

2.2. Newer-generation medications

2.2.1. Dipeptidyl peptidase-4 Inhibitors

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) drugs are a class of oral hypoglycemic medication for T2DM delaying the breakdown of glucagon-like peptide-1 (GLP-1), enhancing insulin sensitivity in peripheral tissues. [3,27,145] This mechanism helps improve fasting and postprandial blood glucose levels without directly stimulating insulin secretion, thus reducing the risk of hypoglycemia. [113] Their neutral effect on body weight makes them a preferred choice for patients concerned about weight gain from diabetes treatment. [112]

Recent studies have demonstrated the ocular benefits of DPP-4 inhibitors. For instance, Seo and coworkers found that evogliptin could inhibit abnormal angiogenesis in a mouse model with PDR by suppressing VEGF production. [114] In an animal study, Kolibabka and coworkers observed the anti-VEGF effects of linagliptin in oxygen-induced retinopathy, independent of GLP-1R signaling. [68] Linagliptin has also been shown to attenuate local inflammation by reducing monocyte attachment to vascular endothelial cells in invitro culture and decreasing the generation of inflammatory interleukins and reactive oxygen species. [74] Additionally, sitagliptin has been noted to prevent redistribution of occludin and claudin-5 caused by diabetes, [39] prevent blood-retina barrier breakdown, [38] and provide neuroprotection by preserving crucial presynaptic proteins in diabetic rats. [106,107] The topical application of sitagliptin and saxagliptin has effectively prevented various retinal abnormalities in early-stage DR. [12]

Gemigliptin may prevent retinal pericytes' apoptosis and vascular leakage due to high blood sugar and treat retinal neovascularization in oxygen-induced retinopathy by reducing overexpression of plasminogen activator inhibitor-1. [61]

Recently, DPP-4 inhibitors have been shown to maintain the filtering bleb in diabetic eyes post-trabeculectomy for neovascular glaucoma by inducing anti-fibrotic changes by inhibiting transforming growth factor-beta (TGF-β)/Smad signaling. [146]

Despite these benefits, concerns have been raised about the potential for DPP-4 inhibitors to exacerbate DR, especially in the initial treatment period. [56] In both *in vitro* and *in vivo* models, DPP-4 inhibitors have been associated with increased vascular leakage mediated through the SDF-1α/CXCR4/Src/VE-cadherin signaling pathways. [71] Large-scale epidemiological studies suggest a potential initial increased risk of DR when starting treatment with DPP-4 inhibitors, compared to other anti-diabetic drugs; however, no overall increased risk of DR has been observed over the long term. [65]

There have also been numerous reports of systemic bullous pemphigoid [129] and a notable case of ocular cicatricial pemphigoid associated with DPP-4 inhibitor use, [83] emphasizing the need for careful monitoring of patients in this medication class.

2.2.2. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dual-action GLP-1 and glucose-dependent insulinotropic polypeptide agonists

GLP-1RAs, such as semaglutide, represent a revolutionizing class of treatments for T2DM. These drugs mimic endogenous GLP-1 by enhancing glucose-dependent insulin secretion, reducing glucagon release, slowing stomach emptying, and decreasing appetite, thereby facilitating weight loss. [81] Their additional advantages include a lower risk of hypoglycemia, once-weekly dosing, and protective effects on cardiovascular and renal health. [13,18,33,35,42,105,150] Conversely, glucose-dependent insulinotropic polypeptide (GIP) receptor agonists are a newer class of anti-diabetic drugs that augment insulin secretion by activating pancreatic GIP receptors. [70]

Tirzepatide, which combines the actions of GLP-1 and GIP receptor agonists, has shown significant efficacy in reducing blood glucose levels.[85]

GLP-1 and its receptor, GLP-1R, are expressed in the human retina. [48,104] In a study by Hernandez and coworkers, topical administration of a GLP-1R agonist demonstrated a remarkable effect against neuronal damage by modulating glutamate levels and enhancing survival signaling pathways, holding promise for treating neurodegeneration in early DR. [48] A study by Zhai and coworkers indicated that exendin-4, a GLP-1R agonist, restored the patency of retina capillaries under ischemic reperfusion conditions. [152] GLP-1R agonists can help manage DR by decreasing nerve cell damage and glial cell activation, protecting the blood-retinal barrier, and providing anti-oxidative and anti-inflammatory effects. [94,96]

Large-scale studies and clinical trials have yielded mixed results regarding the risk of diabetic retinopathy (DR) associated with GLP-1RA use. While some studies suggest a reduced risk compared to insulin, [26] others report an increased risk of DR progression, especially in the early stages of treatment. The first case of DR worsening with Exenatide was reported in 2009. [14] Additionally, Kapoor and coworkers found that albiglutide increased the risk of early-stage DR. [63] Given the potential risk of DR progression, large-scale clinical trials, such as those by Yoshida and coworkers, recommend avoiding these drugs in patients with known DR or those at high risk for developing DR. [147] The PIONEER 6 study indicated that oral semaglutide caused a 0.8 % increase in DR rates, even though patients with PDR were excluded. [54] The SUSTAIN 6 trial further showed that various DR presentations, including vitreous hemorrhage, need for anti-VEGF injections or photocoagulation, and blindness, were significantly higher in patients treated with Semaglutide. [82] The ongoing FOCUS study, a 5-year case-control study comparing the effects of semaglutide to placebo on DR, will publish its results in 2026. [93] Treatment with GLP-1R agonists can lead to more significant progression to PDR and a higher risk of DME compared to treatments with SGLT-2 inhibitors. [134] Notably, a remarkable deterioration of PDR and DME was observed after just 4 months of GLP-1R agonist treatment. [14] Several factors contribute to the progression of diabetic DR despite improved glycemic control, including prolonged diabetes duration, presence of DR at onset, degree of HbA1c reduction and rapid glycemic improvement, and higher initial HbA1c levels. [133]

Despite previous evidence that significant HbA1c reduction is associated with transient worsening of DR, [22,43] extensive retrospective clinical cohort studies and meta-analyses reported that GLP-1R agonists are not linked to an increased risk of DR. [37,128] In a retrospective analysis, 80 % of diabetic patients treated with GLP-1R agonists for ten months showed improved DR despite an initial transient worsening associated with rapid glycemic improvement; [133] however, with semaglutide treatment, around 10–20 % of patients' DR and ME deteriorate; that rate is larger among those who already have advanced DR and DME. [111] Continued treatment leads to long-term benefits in managing retinopathy. [124]

A recent retrospective cohort study by Hathaway and coworkers suggested an association between semaglutide and nonarteritic anterior ischemic optic neuropathy (NAION). In the 710 patients with T2DM, there were 17 cases of NAION among patients prescribed semaglutide,

compared to 6 cases in the non-GLP-1RA antidiabetes cohort. Among 979 patients who were overweight or obese, 20 NAION events occurred in the semaglutide group, while 3 events were reported in the non-GLP-1RA cohort. [47]

In three separate studies, the incidence of DR associated with tirzepatide, which acts on GLP-1 and GIP receptors, remained below 2 %. This indicates that the risk of developing DR or related conditions does not increase when compared to therapies that only target the GLP-1R. [24,34,80]

In a retrospective cohort study conducted by Sterling and coworkers, it was found that diabetic patients treated with GLP-1R agonists had a lower risk of new glaucoma diagnosis compared to those using other anti-diabetic medications. [122] Another retrospective cohort study by Chuang demonstrates that GLP-1R agonist is associated with a lower incidence of OAG in patients with T2DM. [20] GLP-1 receptor agonists are typically known to maintain vascular integrity and suppress inflammation, which can contribute to the risk of developing OAG. [141]

As GLP-1 and GIP receptor agonists evolve, clinicians must carefully monitor their effects, particularly in patients with pre-existing retinal conditions, to ensure optimal outcomes and prevent potential complications that could impact vision.

2.2.3. *Sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors*

Sodium-glucose co-transporter 2 (SGLT2) inhibitors represent a novel class of oral medication for T2DM that works by inhibiting SGLT2 in the proximal tubules of the kidney. This action prevents glucose reabsorption from the urine into the bloodstream, promoting glucose excretion without affecting insulin secretion. [25,111] A recent experimental study reported their role in reducing the microvascular complications that can result in nephropathy, retinopathy, and neuropathy. [127]

The direct impacts of SGLT2 inhibitors on ocular health have not been extensively studied, yet their role in overall diabetes management could potentially lower the risk of developing DR. [135] Studies, including post-hoc analyses and meta-analyses, suggest a protective effect against DR, although there have been reports of increased risk of vitreous hemorrhage with specific drugs like canagliflozin. [31,58,73,137,154]. The mechanisms behind this side effect remain unclear.

In comparative studies, Lin and coworkers showed that patients treated with SGLT2 inhibitors had a lower rate of PDR and fewer vitreoretinal interventions than those receiving GLP-1R agonists, possibly due to a smaller decline in HbA1c. [78] [128] Fernandes and coworkers reported that dapagliflozin might protect against gradual retinal thinning in diabetic patients, which is a benefit of reduced hypoxia and inflammatory/oxidative stress. [30] A human case study highlighted the beneficial effects of SGLT2 inhibitors on recovery from DME after 16 weeks of treatment with Ipragliflozin, [148] while animal studies demonstrated protective effects against diabetic cataract progression and retinal functional abnormalities as detected by electroretinogram. [127]

Recent epidemiological evidence is mixed regarding the risk of RVO. One study reported an increased risk with SGLT2 inhibitors in comparison to other glucose-lowering drugs, especially in older individuals and those with lower renal function. [72] Another study found that SGLT2 inhibitor users had lower rates of RVO and related complications than DPP-4 inhibitor users. [79]

Furthermore, recent research suggests that SGLT2 inhibitors may offer a reduced risk of glaucoma, [117] and dry eye disease in patients treated with SGLT2 inhibitors compared to other medications, likely due to their anti-inflammatory properties. [123]

Overall, while SGLT2 inhibitors present promising benefits for diabetes management, their comprehensive impact, especially concerning ocular health, warrants careful consideration and further research to understand their therapeutic potential and limitations fully.

3. Conclusion

We provide a comprehensive overview of antidiabetic medications, detailing their mechanisms of action, systemic and ocular effects, and potential side effects and emphasize the impact of these drugs on DR and its progression, along with other ocular disease. This review highlights that, while antidiabetic medications are crucial for managing DR over the long term, certain drugs, including newer ones like DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors, may initially worsen DR and DME. Notably, recent applications of medicines such as GLP-1R agonist (Ozempic®) and dual action GIP-1 and GLP-1 agonist (Mounjaro®) extend beyond diabetes management to include antiobesity treatments. We emphasize the importance of closer follow-up in patients who recently started new-generation drugs; however, conflicting reports on their side effects underscore the necessity for more extensive and prolonged research. Additionally, we note that some antidiabetic drugs offer protective benefits against other eye conditions like AMD, glaucoma, cataracts, and diseases affecting the ocular surface, attributed to their antiinflammatory and neuroprotective properties, particularly in newer drug generations. We also discuss how different segments of the eye might exhibit side effects from these medications, with specific examples including ocular cicatricial pemphigoid from DPP-4 inhibitors, RVO from SGLT2 inhibitors, and TED from thiazolidinediones. We conclude by emphasizing the need for additional studies to comprehensively explore the diverse impacts of anti-diabetic medications on eye health.

4. Future directions

Anti-diabetic medications, increasingly used for various purposes like weight management, necessitate a shift towards in-depth and enduring research to elucidate their impact on eye health. It's essential to evaluate the long-term effects of these drugs during clinical trials to gain a clearer picture. The emergence of novel anti-diabetic categories, such as twincretins, places a spotlight on their potential implications for DR and other eye-related conditions. The research aims to cultivate a detailed comprehension of the interaction between these drugs and eye health, with a focus on DR. Considering the noninvasive imaging and AI-based early detection of DR may help to support the identification of ocular side effects in routine clinical practice among primary care physicians, and non-ophthalmic practices. Detecting adverse outcomes is crucial for refining treatment approaches for diabetic patients, ensuring their overall and ocular health is maintained.

Method

A PubMed and Google Scholar literature search was conducted in May 2024, focusing on recent studies. We used only the English language articles. We used "anti-diabetic," "Hyperglycemia," "Diabetic retinopathy," "Retina," "Macular edema," "Microvascular," "Lens," "Cornea," "Orbit," and "Glaucoma" keywords. Then we added each class of anti-diabetic drugs into our search, including Alpha-Glucosidase Inhibitors, Biguanides, DPP-4 Inhibitor, insulin, GLP-1 Agonists, GIP Receptor Agonists, SGLT2 Inhibitors, Sulfonylureas, and Thiazolidinediones. The author utilized AI assistance from Microsoft Copilot for English language editing support.

Ethical approval

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CRediT authorship contribution statement

Chhablani Jay: Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology,

Conceptualization. **Cicinelli Maria Vittoria:** Writing – review & editing. **Kapoor Saloni:** Writing – review & editing. **Valsecchi Nicola:** Writing – review & editing. **Rahmanipour Elham:** Writing – original draft, Methodology. **Sadeghi Elham:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Conceptualization.

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

References

1. Afarid M, Sadeghi E, Johari M, Namvar E, Sanie-Jahromi F. Evaluation of the effect of garlic tablet as a complementary treatment for patients with diabetic retinopathy. *J Diabetes Res*. 2022;2022, 6620661.
2. Aggarwal S, Moir J, Hyman MJ, et al. Metformin use and age-related macular degeneration in patients without diabetes. *JAMA Ophthalmol*. 2024;142:53–57.
3. Alsamghan AS, Alwabli AS, Abadi M, et al. From sequence analysis of DPP-4 to molecular docking based searching of its inhibitors. *Bioinformation*. 2020.
4. Ambrosius WT, Danis RP, Goff Jr DC, et al. Lack of association between thiazolidinediones and macular edema in type 2 diabetes: the ACCORD eye substudy. *Arch Ophthalmol*. 2010;128:312–318.
5. Aoun P, Simpkins JW, Agarwal N. Role of PPAR-γ ligands in neuroprotection against glutamate-induced cytotoxicity in retinal ganglion cells. *Invest Ophthalmol Vis Sci*. 2003;44:2999–3004.
6. Asghari A, Hashemzadeh Homaioni B, Mortazavi P, Jahandideh A. Experimental study of the effect of metformin on corneal burn ulcer healing in rabbit. *Vet Res Biol Prod*. 2016;29:110–117.
7. Atamer Y, Atamer A, Can AS, et al. Effects of rosiglitazone on serum paraoxonase activity and metabolic parameters in patients with type 2 diabetes mellitus. *Braz J Med Biol Res*. 2013.
8. Bain SC, Klufas MA, Ho A, Matthews DR. Worsening of diabetic retinopathy with rapid improvement in systemic glucose control: a review. *Diabetes, Obes Metab*. 2019;21:454–466.
9. Becker C, Schneider C, Aballéa S, et al. Cataract in patients with diabetes mellitus—incidence rates in the UK and risk factors. *Eye*. 2018;32:1028–1035.
10. Berdugo M, Delaunay K, Naud M-C, et al. The antidiabetic drug glibenclamide exerts direct retinal neuroprotection. *Transl Res*. 2021;229:83–99.
11. Berdugo M, Delaunay K, Lebon C, et al. Long-term oral treatment with non-hypoglycemic dose of glibenclamide reduces diabetic retinopathy damage in the goto-kakizakirat model. *Pharmaceutics*. 2021;13:1095.
12. Bogdanov P, Ramos H, Valeri M, et al. Minimum effective dose of DPP-4 inhibitors for treating early stages of diabetic retinopathy in an experimental model. *Biomedicines*. 2022;10.
13. Boyle JG, Livingstone R, Petrie JR. Cardiovascular benefits of GLP-1 agonists in type 2 diabetes: a comparative review. *Clin Sci*. 2018.
14. Brooks AM, Lissett CA. A dramatic deterioration in diabetic retinopathy with improvement in glycated haemoglobin (HbA(1c)) on exenatide treatment. *Diabet Med*. 2009;26:190.
15. Burgos-Blasco B, Diaz-Valle D, Rego-Lorca D, et al. Topical insulin, a novel corneal epithelial regeneration agent in dry eye disease. *Eur J Ophthalmol*. 2023;34:719–725.
16. Chakrabarti S, Cherian PV, Sima AA. The effect of acarbose on diabetes-and age-related basement membrane thickening in retinal capillaries of the BBW-rat. *Diabetes Res Clin Pract*. 1993;20:123–128.
17. Chen S, Li Y, Song W, et al. Insulin eye drops improve corneal wound healing in STZ-induced diabetic mice by regulating corneal inflammation and neuropeptide release. *BMC Ophthalmol*. 2024;24:155.
18. Chong K. Recent Advances in the Treatment of Type 2 Diabetes Mellitus Using New Drug Therapies. *Kaohsiung J Med Sci*. 2024.
19. Chowdhury UR, Dosa PI, Fautsch MP. ATP sensitive potassium channel openers: a new class of ocular hypotensive agents. *Exp Eye Res*. 2017;158:85–93.
20. Chuang CC, Wang K, Chang CK, et al. Prescription of glucagon-like peptide 1 agonists and risk of subsequent open-angle glaucoma in individuals with type 2 diabetes mellitus. *Int J Med Sci*. 2024;21:540–546.
21. Cohen-Melamed E, Nyska A, Pollack A, Madar Z. Aldose reductase (EC 1.1. 1.21) activity and reduced-glutathione content in lenses of diabetic sand rats (Psammomys obesus) fed with acarbose. *Br J Nutr*. 1995;74:607–615.
22. Control D. Group CTR: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977–986.
23. Creutzfeldt W. Effects of the alpha-glucosidase inhibitor acarbose on the development of long-term complications in diabetic animals: pathophysiological and therapeutic implications. *Diabetes Metab Res Rev*. 1999;15:289–296.
24. Dahl D, Onishi Y, Norwood P, et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial. *Jama*. 2022;327:534–545.
25. Davidson JA, Kuritzky L. Sodium glucose co-transporter 2 inhibitors and their mechanism for improving glycemia in patients with type 2 diabetes. *Postgrad Med*. 2014.
26. Douros A, Filion KB, Yin H, et al. Glucagon-like peptide 1 receptor agonists and the risk of incident diabetic retinopathy. *Diabetes Care*. 2018;41:2330–2338.
27. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368:1696–1705.
28. Eltony SA, Mohaseb HS, Ahmed AA, Sayed MM. Can metformin modulate the retinal degenerative changes in a rat model of retinitis pigmentosa? *Tissue Cell*. 2022;76, 101786.
29. Fan F, Li Y, Duan X, et al. Rosiglitazone attenuates activation of human Tenon's fibroblasts induced by transforming growth factor-β1. *Graefe'S Arch Clin Exp Ophthalmol*. 2012;250:1213–1220.
30. Fernandes VHR, Chaves FRP, Soares AAS, et al. Dapagliflozin increases retinal thickness in type 2 diabetic patients as compared with glibenclamide: a randomized controlled trial. *Diabetes Metab*. 2021;47, 101280.
31. Fitchett D, Inzucchi SE, Cannon CP, et al. Empagliflozin reduced mortality and hospitalization for heart failure across the spectrum of cardiovascular risk in the EMPA-REG OUTCOME trial. *Circulation*. 2019;139:1384–1395.
32. Fong DS, Contreras R. Glitazone use associated with diabetic macular edema. e581 *Am J Ophthalmol*. 2009;147:583–586.
33. Forst T, Weber MM, Pfützner A. Cardiovascular benefits of GLP-1-basedtherapies in patients with diabetes mellitus type 2: effects on endothelial and vascular dysfunction beyond glycemic control. *Exp Diabetes Res*. 2012.
34. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med*. 2021;385:503–515.
35. Fujita H, Morii T, Fujishima H, et al. The protective roles of GLP-1R signaling in diabetic nephropathy: possible mechanism and therapeutic potential. *Kidney Int*. 2014;85:579–589.
36. Funatsu H, Yamashita H, Ohashi Y, Ishigaki T. Effect of rapid glycemic control on progression of diabetic retinopathy. *Jpn J Ophthalmol*. 1992;36:356–367.
37. Gaborit B, Julla JB, Besbes S, et al. Glucagon-like Peptide 1 receptor agonists, diabetic retinopathy and angiogenesis: the angiosafe type 2 diabetes study. *J Clin Endocrinol Metab*. 2020;105.
38. Gonçalves A, Marques C, Leal E, et al. Dipeptidyl peptidase-IV inhibition prevents blood–retinal barrier breakdown, inflammation and neuronal cell death in the retina of type 1 diabetic rats. *Biochim Et Biophys Acta (BBA)-Mol Basis Dis*. 2014;1842:1454–1463.
39. Gonçalves A, Leal E, Paiva A, et al. Protective effects of the dipeptidyl peptidase IV inhibitor sitagliptin in the blood–retinal barrier in a type 2 diabetes animal model. *Diabetes, Obes Metab*. 2012;14:454–463.
40. Gorde VD, Rachh PR. Review on teneligliptin: a novel antihyperglycemic agent. *J Drug Deliv Ther*. 2019.
41. Gower EW, Lovato JF, Ambrosius WT, et al. Lack of longitudinal association between thiazolidinediones and incidence and progression of diabetic eye disease: the ACCORD eye study. *Am J Ophthalmol*. 2018;187:138–147.
42. Grossman SS. Pathophysiological and pharmacological rationale for the use of exenatide once weekly in patients with type 2 diabetes. *Adv Ther*. 2014;31:247–263.
43. Group UPDS. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837–853.
44. Guo N, Woeller CF, Feldon SE, Phipps RP. Peroxisome proliferator-activated receptor γ ligands inhibit transforming growth factor-β-induced, hyaluronan-dependent, T cell adhesion to orbital fibroblasts. *J Biol Chem*. 2011;286:18856–18867.
45. Han SB, Yang HK, Hyon JY. Influence of diabetes mellitus on anterior segment of the eye. *Clin Interv Aging*. 2019:53–63.
46. Hatanaka H, Koizumi N, Okumura N, et al. Epithelial-mesenchymal transition-like phenotypic changes of retinal pigment epithelium induced by TGF-β are prevented by PPAR-γ agonists. *Invest Ophthalmol Vis Sci*. 2012;53:6955–6963.
47. Hathaway JT, Shah MP, Hathaway DB, et al. Risk of nonarteritic anterior ischemic optic neuropathy in patients prescribed semaglutide. *JAMA Ophthalmol*. 2024.
48. Hernández C, Bogdanov P, Corraliza L, et al. Topical administration of GLP-1 receptor agonists prevents retinal neurodegeneration in experimental diabetes. *Diabetes*. 2015.
49. Hernández C, Zapata MA, Losada E, et al. Effect of intensive insulin therapy on macular biometrics, plasma VEGF and its soluble receptor in newly diagnosed diabetic patients. *Diabetes/Metab Res Rev*. 2010;26:386–392.
50. Ho H, Shi Y, Chua J, et al. Association of systemic medication use with intraocular pressure in a multiethnic asian population: the singapore epidemiology of eye diseases study. *JAMA Ophthalmol*. 2017;135:196–202.
51. Hossain U, Das A, Ghosh S, Sil PC. An overview on the role of bioactive α-glucosidase inhibitors in ameliorating diabetic complications. *Food Chem Toxicol*. 2020.
52. Hou C, Carter B, Hewitt J, Francisa T, Mayor S. Do mobile phone applications improve glycemic control (HbA1c) in the self-management of diabetes? A systematic review, meta-analysis, and GRADE of 14 randomized trials. *Diabetes Care*. 2016.
53. Hurley DJ, Irnaten M, O'Brien C. Metformin and glaucoma—review of anti-fibrotic processes and bioenergetics. *Cells*. 2021;10:2131.
54. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381:841–851.

55. Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. *Arch Intern Med*. 2012;172:1005–1011.
56. Igweokpala S, Sule NO, Douros A, Yu OHY, Filion KB. Incretin-based drugs and the risk of diabetic retinopathy among individuals with type 2 diabetes: a systematic review and meta-analysis of observational studies. *Diabetes, Obes Metab*. 2024;26:721–731.
57. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). The Lancet; 1998 352 p.837-853, .
58. Inzucchi S, Wanner C, Hehnke U, et al. Composite retinopathy outcome in patients treated with empagliflozin versus placebo in the EMPA-REG OUTCOME trial. P 066 *Diabetol und Stoffwechs*. 2019;14.
59. J Meneses M, M Silva B, Sousa M, et al. Antidiabetic drugs: mechanisms of action and potential outcomes on cellular metabolism. *Curr Pharm Des*. 2015;21:3606–3620.
60. Jingi AM, Tankeu AT, Ateba NA, Noubiap JJ. Mechanism of worsening diabetic retinopathy with rapid lowering of blood glucose: the synergistic hypothesis. *BMC Endocr Disord*. 2017;17:1–4.
61. Jung E, Kim J, Kim C-S, Kim S-H, Cho M-H. Gemigliptin, a dipeptidyl peptidase-4 inhibitor, inhibits retinal pericyte injury in db/db mice and retinal neovascularization in mice with ischemic retinopathy. *Biochim Et Biophys Acta (BBA) - Mol Basis Dis*. 2015;1852:2618–2629.
62. Kalariya NM, Shoeb M, Ansari NH, Srivastava SK, Ramana KV. Antidiabetic drug metformin suppresses endotoxin-induced uveitis in rats. *Invest Ophthalmol Vis Sci*. 2012;53:3431–3440.
63. Kapoor I, Sarvepalli SM, D'Alessio D, Grewal DS, Hadziahmetovic M. GLP-1 receptor agonists and diabetic retinopathy: a meta-analysis of randomized clinical trials. *Surv Ophthalmol*. 2023;68:1071–1083.
64. Khanna S, Shaw L, Hyman MJ, et al. Association of metformin use with risk of newly onset neovascular age-related macular degeneration development. *RETINA*. 2024;44.
65. Kim N, Choi J, Choi K, et al. Dipeptidyl peptidase-4 inhibitor use and risk of diabetic retinopathy: a population-based study. *Diabetes Metab*. 2018;44:361–367.
66. Kinoshita N, Kakehashi A, Inoda S, et al. Effective and selective prevention of retinal leukostasis in streptozotocin-induced diabetic rats using gliclazide. *Diabetologia*. 2002;45:735–739.
67. Koevary SB, Nussey J, Kern TS. Long-term, topical insulin administration increases the severity of retinal vascular pathology in streptozotocin-induced diabetic rats. *Optom - J Am Optom Assoc*. 2007;78:574–581.
68. Kolibabka M, Dietrich N, Klein T, Hammes H-P. Anti-angiogenic effects of the DPP-4 inhibitor linagliptin via inhibition of VEGFR signalling in the mouse model of oxygen-induced retinopathy. *Diabetologia*. 2018;61:2412–2421.
69. Lam PY, Chow SC, Lam WC, Chow LLW, Fung N. Management of patients with newly diagnosed diabetic mellitus: ophthalmologic outcomes in intensive versus conventional glycemic control. *Clin Ophthalmol*. 2021.
70. Lamont BJ, Drucker DJ. Differential antidiabetic efficacy of incretin agonists versus DPP-4 inhibition in high fat–fed mice. *Diabetes*. 2008.
71. Lee C-S, Kim YG, Cho H-J, et al. Dipeptidyl peptidase-4 inhibitor increases vascular leakage in retina through VE-cadherin phosphorylation. *Sci Rep*. 2016;6, 29393.
72. Lee M-K, Kim B, Han K, et al. Sodium–glucose cotransporter 2 inhibitors and risk of retinal vein occlusion among patients with type 2 diabetes: a propensity score–matched cohort study. *Diabetes Care*. 2021;44:2419–2426.
73. Li C, Zhou Z, Neuen BL, et al. Sodium-glucose co-transporter-2 inhibition and ocular outcomes in patients with type 2 diabetes: a systematic review and meta-analysis. *Diabetes, Obes Metab*. 2021;23:252–257.
74. Li H, Zhang J, Lin L, Xu L. Vascular protection of DPP-4 inhibitors in retinal endothelial cells in in vitro culture. *Int Immunopharmacol*. 2019;66:162–168.
75. Li X, Leng Y, Jiang Q, et al. Eye drops of metformin prevents fibrosis after glaucoma filtration surgery in rats via activating AMPK/Nrf2 signaling pathway. *Front Pharmacol*. 2020;11:1038.
76. Lin H-C, Stein JD, Nan B, et al. Association of geroprotective effects of metformin and risk of open-angle glaucoma in persons with diabetes mellitus. *JAMA Ophthalmol*. 2015;133:915–923.
77. Lin T-C, Hwang D-K, Hsu C-C, et al. Protective effect of metformin against retinal vein occlusions in diabetes mellitus–a nationwide population-based study. *PLoS One*. 2017;12, e0188136.
78. Lin TY, Kang EY, Shao SC, et al. Risk of diabetic retinopathy between sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists. *Diabetes Metab J*. 2023;47:394–404.
79. Lin TY, Kang EY, Shao SC, et al. Association of sodium-glucose cotransporter-2 inhibitors and the risk of retinal vascular occlusion: a real-world retrospective cohort study in Taiwan. *Diabetes Metab Res Rev*. 2024;40, e3773.
80. Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet*. 2021;398:583–598.
81. Mabilleau G, Gobron B, Bouvard B, Chappard D. Incretin-based therapy for the treatment of bone fragility in diabetes mellitus. *Peptides*. 2018.
82. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834–1844.
83. Matsumoto A, Fukuoka H, Yoneda A, Yokoi N, Sotozono C. Ocular cicatricial pemphigoid following Dipeptidyl Peptidase-4 inhibitor use: a case report. *Am J Ophthalmol Case Rep*. 2023;32, 101957.
84. Mimura LY, Villares SM, Monteiro ML, Guazzelli IC, Bloise W. Peroxisome proliferator-activated receptor-γ gene expression in orbital adipose/connective tissues is increased during the active stage of graves' ophthalmopathy. *Thyroid*. 2003;13:845–850.
85. Min T, Bain SC. The role of tirzepatide, dual GIP and GLP-1 receptor agonist, in the management of type 2 diabetes: the SURPASS clinical trials. *Diabetes Ther*. 2020.
86. Miralles E, Kamma-Lorger CS, Domènech Ò, et al. Assessment of efficacy and safety using PPAR-γ agonist-loaded nanocarriers for inflammatory eye diseases. *Int J Mol Sci*. 2022;23:11184.
87. Modi KD, Gadge P, Jain P, et al. Clinical challenges with excipients in insulin formulations and role of concentrated insulin. *Int J Basic Clin Pharmacol*. 2019.
88. Módulo CM, Jorge AG, Dias AC, et al. Influence of insulin treatment on the lacrimal gland and ocular surface of diabetic rats. *Endocrine*. 2009;36:161–168.
89. Moir J, Hyman MJ, Gonnah R, et al. The Association between metformin use and new-onset ICD coding of geographic atrophy, 23 *Invest Ophthalmol Vis Sci*. 2024;65:23.
90. Motola D, Piccinni C, Biagi C, et al. Cardiovascular, ocular and bone adverse reactions associated with thiazolidinediones: a disproportionality analysis of the US FDA adverse event reporting system database. *Drug Saf*. 2012;35:315–323.
91. Mu PY, Chu CC, Yu D, Shao Y, Zhao SZ. PPARγ: the dominant regulator among PPARs in dry eye lacrimal gland and diabetic lacrimal gland. *Int J Ophthalmol*. 2020;13:860–869.
92. Nakano Y, Arima T, Tobita Y, et al. Combination of peroxisome proliferator-activated receptor (PPAR) alpha and gamma agonists prevents corneal inflammation and neovascularization in a rat alkali burn model. *Int J Mol Sci*. 2020;21:5093.
93. Novo Nordisk A. *S. A research study to look at how semaglutide compared to placebo affects diabetic eye disease in people with type 2 diabetes (FOCUS);[about 9 screens]. ClinicalTrials. gov*. Bethesda, MD: National Library of Medicine (US); 2000.
94. Oezer K, Kolibabka M, Gassenhuber J, et al. The effect of GLP-1 receptor agonist lixisenatide on experimental diabetic retinopathy. *Acta Diabetol*. 2023;60:1551–1565.
95. Okunuki Y, Usui Y, Nakagawa H, et al. Peroxisome proliferator-activated receptor-γ agonist pioglitazone suppresses experimental autoimmune uveitis. *Exp Eye Res*. 2013;116:291–297.
96. Pang B, Zhou H, Kuang H. The potential benefits of glucagon-like peptide-1 receptor agonists for diabetic retinopathy. *Peptides*. 2018;100:123–126.
97. Panigrahy D, Singer S, Shen LQ, et al. PPARγ ligands inhibit primary tumor growth and metastasis by inhibiting angiogenesis. *J Clin Investig*. 2002;110:923–932.
98. Patnaik JL, Christopher KL, Pedler MG, et al. The protective effect of metformin use on early Nd: YAG laser capsulotomy, 24 *Invest Ophthalmol Vis Sci*. 2021;62:24.
99. Perkovich BT, Meyers SM. Systemic factors affecting diabetic macular edema. *Am J Ophthalmol*. 1988;105:211–212.
100. Peterson C, Chandler HL. Insulin facilitates corneal wound healing in the diabetic environment through the RTK-PI3K/Akt/mTOR axis in vitro. *Mol Cell Endocrinol*. 2022;548, 111611.
101. Polak K, Dallinger S, Polska E, et al. Effects of insulin on retinal and pulsatile choroidal blood flow in humans. *Arch Ophthalmol*. 2000;118:55–59.
102. Polat HK, Aytekin E, Karakuyu NF, et al. Harnessing silk fibroin microparticles for metformin delivery: a novel approach to treating corneal neovascularization. *J Drug Deliv Sci Technol*. 2024;96, 105625.
103. Poulaki V, Qin W, Joussen AM, et al. Acute intensive insulin therapy exacerbates diabetic blood-retinal barrier breakdown via hypoxia-inducible factor-1α and VEGF. *J Clin Investig*. 2002;109:805–815.
104. Puddu A, Sanguineti R, Montecucco F, Viviani GL. Retinal pigment epithelial cells express a functional receptor for glucagon-like peptide-1 (GLP-1). *Mediat Inflamm*. 2013;2013, 975032.
105. Qin J, Song L. Glucagon-Like Peptide-1 (GLP-1) receptor agonists and cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of double-blind, randomized, placebo-controlled clinical trials. *BMC Endocr Disord*. 2022.
106. Ramos H, Bogdanov P, Sabater D, et al. Neuromodulation Induced by sitagliptin: a new strategy for treating diabetic retinopathy. *Biomedicines*. 2021;9.
107. Ramos H, Bogdanov P, Simó R, Deàs-Just A, Hernández C. Transcriptomic analysis reveals that retinal neuromodulation is a relevant mechanism in the neuroprotective effect of sitagliptin in an experimental model of diabetic retinopathy. *Int J Mol Sci*. 2022;24.
108. Rizos CV, Kei A, Elisaf M. The current role of thiazolidinediones in diabetes management. *Arch Toxicol*. 2016.
109. Rocha EM, Cunha DA, Carneiro EM, et al. Identification of insulin in the tear film and insulin receptor and IGF-I receptor on the human ocular surface. *Invest Ophthalmol Vis Sci*. 2002;43:963–967.
110. Sarhat ER, Abbas MQ, Aljader GH, et al. Biochemical study on the hypoglycemic effects of extracted phenolic compounds from grape seeds in streptozotocin -induced diabetic rats. *Indian J Forensic Med Toxicol*. 2021.
111. Saw M, Wong VW, Ho IV, Liew G. New anti-hyperglycaemic agents for type 2 diabetes and their effects on diabetic retinopathy. *Eye*. 2019.
112. Scheen A. DPP-4 inhibitors in the management of type 2 diabetes: a critical review of head-to-head trials. *Diabetes Metab*. 2012.
113. Scheen A, Charpentier G, Östgren CJ, Hellqvist Å, Gause-Nilsson I. Efficacy and Safety of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin in adult patients with type 2 diabetes mellitus. *Diabetes/Metab Res Rev*. 2010.
114. Seo SW, Kim M-K, Kim R-I, et al. Evogliptin, a dipeptidyl peptidase-4 inhibitor, attenuates pathological retinal angiogenesis by suppressing vascular endothelial growth factor-induced Arf6 activation. *Exp Mol Med*. 2020.
115. Seven E, Yıldız S, Tekin S, et al. Effect of insulin therapy on ocular biometric parameters in diabetic patients. *J Ocul Pharmacol Ther*. 2019;36:102–108.

116. Shani M, Feldman L, Kaiserman I, et al. Is Rosiglitazone use associated with an increase in intensive eye treatment in diabetic patients? A community based study. *Eur J Gen Pract*. 2011;17:205–209.
117. Shao S-C, Su Y-C, Lai EC-C, et al. Association between sodium glucose co-transporter 2 inhibitors and incident glaucoma in patients with type 2 diabetes: a multi-institutional cohort study in Taiwan. *Diabetes Metab*. 2022;48, 101318.
118. Shao Y, Wang M, Zhu Y, Li X, Liu J. Association of metformin treatment with enhanced effect of anti-VEGF agents in diabetic macular edema patients. *Acta Diabetol*. 2022:1–7.
119. Shen LQ, Child A, Weber GM, Folkman J, Aiello LP. Rosiglitazone and delayed onset of proliferative diabetic retinopathy. *Arch Ophthalmol*. 2008;126:793–799.
120. Sola D, Rossi L, Schianca GPC, et al. State of the art paper sulfonylureas and their use in clinical practice. *Arch Med Sci*. 2015.
121. Starkey K, Heufelder A, Baker G, et al. Peroxisome proliferator-activated receptor-γ in thyroid eye disease: contraindication for thiazolidinedione use? *J Clin Endocrinol Metab*. 2003;88:55–59.
122. Sterling J, Hua P, Dunaief JL, Cui QN, VanderBeek BL. Glucagon-like peptide 1 receptor agonist use is associated with reduced risk for glaucoma. *Br J Ophthalmol*. 2023;107:215–220.
123. Su Y-C, Hung J-H, Chang K-C, et al. Comparison of sodium-glucose cotransporter 2 inhibitors vs glucagonlike peptide-1 receptor agonists and incidence of dry eye disease in patients with type 2 diabetes in Taiwan. e2232584 *JAMA Netw Open*. 2022;5, e2232584.
124. SureVision: Ozempic Use and Worsening Diabetic Retinopathy: SureVision, Vol. 2024, 2024.
125. Syafira M, Rahardjo SS, Murti B. Meta-analysis the effect of pharmaceutical care on blood glucose level in type 2 diabetes mellitus patients. *J Health Policy Manag*. 2022.
126. Takagi C, King GL, Clermont AC, et al. Reversal of abnormal retinal hemodynamics in diabetic rats by acarbose, an α-glucosidase inhibitor. *Curr eye Res*. 1995;14:741–749.
127. Takakura S, Toyoshi T, Hayashizaki Y, Takasu T. Effect of ipragliflozin, an SGLT2 inhibitor, on progression of diabetic microvascular complications in spontaneously diabetic Torii fatty rats. *Life Sci*. 2016;147:125–131.
128. Tang H, Li G, Zhao Y, et al. Comparisons of diabetic retinopathy events associated with glucose-lowering drugs in patients with type 2 diabetes mellitus: a network meta-analysis. *Diabetes, Obes Metab*. 2018;20:1262–1279.
129. Tasanen K, Varpuluoma O, Nishie W. Dipeptidyl peptidase-4 inhibitor-associated bullous pemphigoid. *Front Immunol*. 2019;10, 463593.
130. Teo ZL, Tham Y-C, Yu M, et al. Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. *Ophthalmology*. 2021;128:1580–1591.
131. Top WMC, Kooy A, Stehouwer CD. Metformin: a narrative review of its potential benefits for cardiovascular disease, cancer and dementia. *Pharmaceuticals*. 2022.
132. Vallée A, Lecarpentier Y, Guillevin R, Vallée J-N. PPARγ agonists: Potential treatments for exudative age-related macular degeneration. *Life Sci*. 2017;188:123–130.
133. Varadhan L, Humphreys T, Walker AB, Varughese GI. The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. *Diabetes Res Clin Pr*. 2014;103:e37–e39.
134. Wai KM, Mishra K, Koo E, et al. Impact of GLP-1 Agonists and SGLT-2 inhibitors on diabetic retinopathy progression: an aggregated electronic health record data study. *Am J Ophthalmol*. 2024.
135. Wakisaka M, Nagao T. Sodium glucose cotransporter 2 in mesangial cells and retinal pericytes and its implications for diabetic nephropathy and retinopathy. *Glycobiology*. 2017.
136. Wang L, Wang W, Kaelber DC, Xu R, Berger NA. GLP-1 receptor agonists and colorectal cancer risk in drug-naive patients with type 2 diabetes, with and without overweight/obesity. *Jama Oncol*. 2024.
137. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323–334.
138. Wasana PWD, Hasriadi, Muangnoi C, et al. Curcumin and metformin synergistically modulate peripheral and central immune mechanisms of pain. *Sci Rep*. 2022.
139. Wiwanitkit V. Metformin high dosage and bleeding episode: a clinical case study. *Indian J Endocrinol Metab*. 2011.
140. Wong C, Lee MH, Yaow CYL, et al. Glucagon-like peptide-1 receptor agonists for non-alcoholic fatty liver disease in type 2 diabetes: a meta-analysis. *Front Endocrinol*. 2021;12, 609110.
141. WuDunn D, Takusagawa HL, Sit AJ, et al. OCT angiography for the diagnosis of glaucoma: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2021;128:1222–1235.
142. Yang XX, Chen J, Zhou Q, et al. Troglitazone induced apoptosis of human pterygium fibroblasts through a mitochondrial-dependent pathway. *Int J Ophthalmol*. 2011;4:143–146.
143. Yang Y-S, Danis RP, Peterson RG, Dolan PL, Wu Y-Q. Acarbose partially inhibits microvascular retinopathy in the zucker diabetic fatty rat (ZDF/GmiTM-fa). *J Ocul Pharmacol Ther*. 2000;16:471–479.
144. Yarat A, Yanardağ R, Tunali T, et al. Effects of glibornuride versus metformin on eye lenses and skin in experimental diabetes. *Arzneimittelforschung*. 2006;56:541–546.
145. Yaribeygi H, Sathyapalan T, Sahebkar A. Molecular Mechanisms by Which GLP-1 RA and DPP-4i Induce Insulin Sensitivity. *Life Sci*. 2019.
146. Yoshida M, Kokubun T, Sato K, et al. DPP-4 inhibitors attenuate fibrosis after glaucoma filtering surgery by suppressing the TGF-β/Smad signaling pathway. -2 *Invest Ophthalmol Vis Sci*. 2023;64:2.
147. Yoshida Y, Joshi P, Barri S, et al. Progression of retinopathy with glucagon-like peptide-1 receptor agonists with cardiovascular benefits in type 2 diabetes – A systematic review and meta-analysis. *J Diabetes its Complicat*. 2022;36, 108255.
148. Yoshizumi H, Ejima T, Nagao T, Wakisaka M. Recovery from diabetic macular edema in a diabetic patient after minimal dose of a sodium glucose co-transporter 2 inhibitor. *Am J Case Rep*. 2018.
149. Yousef F, Yousef N, Mansour O, Herbali J. Metformin: a unique herbal origin medication. *Glob J Med Res*. 2017;17.
150. Yu JH, Park SY, Kim NH, Seo JA. GLP-1 receptor agonists in diabetic kidney disease: current evidence and future directions. *Kidney Res Clin Pract*. 2022;41:136.
151. Zeng H, Dumitrescu AV, Wadkins D, et al. Systemic treatment with pioglitazone reverses vision loss in preclinical glaucoma models. *Biomolecules*. 2022;12:281.
152. Zhai R, Xu H, Hu F, et al. Exendin-4, a GLP-1 receptor agonist regulates retinal capillary tone and restores microvascular patency after ischaemia–reperfusion injury. *Br J Pharmacol*. 2020;177:3389–3402.
153. Zhang S, Gu H, Hu N. Role of peroxisome proliferator-activated receptor γ in ocular diseases. *J Ophthalmol*. 2015;2015, 275435.
154. Zhou B, Shi Y, Fu R, et al. Relationship between SGLT-2i and ocular diseases in patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Front Endocrinol*. 2022;13, 907340.
155. Zhou M, Wang W, Huang W, Zhang X. Diabetes mellitus as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. *PLoS One*. 2014;9, e102972.
156. Zimmerman BR. Sulfonylureas. *Endocrinol Metab Clin North Am*. 1997.
157. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015.