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The Role of Optometry in Managing Visual Impairment in Patients with Diabetes: Prevention and Treatment Options

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Abstract

Diabetic retinopathy (DR) is a leading cause of vision loss globally, affecting both the working-age population and the elderly. DR progresses from mild non-proliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME). Risk factors include prolonged diabetes duration, hyperglycemia, hypertension, and dyslipidemia. DR pathogenesis involves inflammatory, oxidative stress, angiogenesis, and apoptosis pathways. Diagnosis is based on characteristic retinal changes observed during ophthalmoscopy, with additional imaging modalities like fluorescein angiography and optical coherence tomography. Prevention strategies focus on strict glycemic control, while the impact of managing dyslipidemia and hypertension remains inconclusive. Treatment options include laser photocoagulation, anti-vascular endothelial growth factor (VEGF) therapy, and intravitreal steroids. Pars plana vitrectomy is indicated for advanced cases with vitreous hemorrhage or tractional retinal detachment. Fenofibrate, pemafibrate, finerenone, and semaglutide have shown potential in managing DR. Lifestyle modifications, such as a balanced diet, physical activity, and smoking cessation, are crucial adjuncts to medical interventions. Pregnant women with diabetes require close monitoring due to the increased risk of DR progression. Traditional medicine and acupuncture may offer complementary approaches, but further research is needed. A multidisciplinary approach involving ophthalmologists, endocrinologists, and primary care physicians is essential for the optimal management of DR and the preservation of vision in diabetic patients.

Keywords: Diabetic retinopathy (DR), diabetic macular edema (DME), proliferative diabetic retinopathy (PDR), nonproliferative diabetic retinopathy (NPDR), anti-VEGF therapy, laser photocoagulation.

Introduction

Diabetes mellitus (DM) is a globally expanding condition, contributing significantly to increased morbidity rates (Shaw et al., 2010). DM impacts various organs, and its effects can be categorized into macrovascular complications involving large blood vessels (e.g., cardiovascular disease, stroke) and microvascular complications involving smaller vessels (e.g., retinopathy, kidney disorders). Diabetic retinopathy (DR), a result of small vessel involvement, stands as one of the leading causes of blindness globally, affecting both the working-age population and the elderly. If untreated, DR progresses from mild non-proliferative diabetic retinopathy (NPDR) to moderate and severe NPDR, eventually leading to proliferative diabetic retinopathy (PDR), characterized by neovascularization. As DR advances, retinal exudates and edema emerge, particularly around the macula, resulting in diabetic macular edema (DME). DR is prevalent among diabetic patients, with only 5–10% developing advanced PDR and DME [6, 7]. However, the risk of developing DR is as high as 50–

60% in individuals with type 2 diabetes mellitus (T2DM) and up to 90% in those with type 1 diabetes mellitus (T1DM).

Blood pressure exerts an additive effect on DR by increasing its risk and accelerating its progression (Emdin et al., 2015). Elevated vascular pressure exacerbates retinal vessel leakage. Meta-analyses of diabetic landmark trials reveal that a 10 mmHg reduction in blood pressure decreases the risk of DR by 13%. Microalbuminuria, or the presence of trace amounts of protein in the urine, serves as an early marker of kidney damage and is associated with an elevated risk of DR when coupled with dyslipidemia (abnormal lipid levels). Numerous intervention studies underscore that managing multiple risk factors—hyperglycemia, hypertension, dyslipidemia, and microalbuminuria—can mitigate DR onset and progression. This review explores the mechanisms underlying the pathogenesis and classification of DR, along with its management strategies.

Epidemiology

Prevalence and Incidence of Diabetic Retinopathy

In 2021, diabetes mellitus affected 537 million individuals worldwide, with projections suggesting an increase to 784 million by 2045. As diabetes cases rise and life expectancy improves among diabetics, the number of individuals suffering from DR and associated vision impairment is also escalating globally. Long-term studies, such as the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), provide substantial data on the prevalence of DR, DME, and DR in individuals with T1DM and T2DM. The WESDR study noted that approximately 70% of individuals with diabetes develop DR within a decade of diagnosis, with two-thirds of these cases progressing to advanced stages of DR; 20% develop PDR or DME. Diabetic macular edema has emerged as the predominant cause of vision loss, surpassing PDR in diabetes mellitus. In the US National Health and Nutrition Examination Survey, DME was observed to occur at twice the rate of PDR among diabetic individuals. Many studies and systemic reviews summarize regional and global prevalence estimates of DR (Leasher et al., 2016).

Risk Factors for Diabetic Retinopathy

Several factors contribute to the development of DR, including hypertension, elevated plasma glucose, and prolonged diabetes duration. However, hyperglycemia and hypertension alone do not fully account for the timing and progression of DR. Studies indicate that some patients with uncontrolled glucose levels or hypertension do not develop DR, while others with well-controlled levels present with advanced DR highlighting the influence of additional factors. DR prevalence is higher in T1DM than T2DM, with retinopathy evidence observed in 25% of individuals after five years, increasing to 60% and 80% after ten and fifteen years, respectively. Factors like puberty and pregnancy are notably associated with DR in T1DM. Gestational DM may exacerbate DR due to fluctuating glucose levels, alongside other factors like hypertension, preeclampsia, and hypervolemia. Lipid profile alterations also mediate DR, though studies yield inconsistent results regarding total cholesterol and triglycerides (Lim & Wong, 2012). However, other lipid-related factors, such as apolipoproteins A and B, have been identified as significant risk contributors [42, 43]. Additional systemic risk factors include renal involvement, obesity, anemia, and systemic inflammation markers. Ocular risk factors involve prior cataract surgeries, which increase the likelihood of advanced DR and DME, while myopic refractive error appears protective against DR (Man et al., 2012). Genetic predisposition also plays a role, with heritability estimates of 25–50% in T1DM-associated PDR cases. Genome-wide association studies (GWAS) have identified novel genetic markers, including WDR72, HLA-B, GAP43/RP11-326J18.1, and AL713866.1, linked to DR in T2DM individuals.

Pathogenesis of Diabetic Retinopathy

The complications of diabetes are closely linked to disease duration and glycemic control. Extensive research has shed light on molecular pathways involved in DR pathogenesis, such as the polyol and hexosamine pathways, de novo diacylglycerol formation mediated by protein kinase C, and the generation of advanced glycation end-products (AGEs). Emerging evidence suggests that neuronal degeneration, inflammation, and activation of the renin-angiotensin system (RAS) significantly contribute to DR development.

The progression of DR is gradual and categorized into four stages:

1. Retinal damage with undetectable microvascular changes during ophthalmoscopy.
2. Mild-to-moderate non-proliferative diabetic retinopathy (NPDR), with or without diabetic macular edema (DME).
3. Severe NPDR.
4. Proliferative diabetic retinopathy (PDR) and advanced DR stages.

Role of Signaling Pathways

Diabetic retinopathy represents a chronic inflammatory condition mediated by a range of inflammatory mediators and signaling pathways. This condition involves a complex interplay of inflammation, oxidative stress, angiogenesis, and apoptosis pathways (Li et al., 2023). The inflammatory signaling pathways implicated include the nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and toll-like receptor 4 (TLR4) pathways. These pathways are activated under conditions of oxidative stress, leading to the transcription

of kinases that produce inflammatory mediators (Perrone et al., 2014). The activation of these cascades triggers the inflammatory responses characteristic of diabetic retinopathy.

Angiogenesis observed in proliferative diabetic retinopathy (PDR) is mediated by the stimulation of the VEGF/VEGFR2 and HIF-1α/VEGF signaling pathways, both induced under hypoxic conditions [61, 65, 67]. Chronic hyperglycemia leads to complications through four major metabolic pathways: advanced glycation end products (AGEs), the polyol pathway, the protein kinase C (PKC) pathway, and the hexosamine pathway. These pathways converge to generate reactive oxygen species (ROS), causing oxidative stress. The oxidative stress is further mediated by two key pathways: the Nrf2/HO-1 and STAT3 signaling pathways.

Damage to the Retina with Invisible Microvascular Changes

Elevated blood glucose levels and associated metabolic disturbances result in neuronal degeneration and early dysfunction of small retinal vessels. This dysfunction affects neurovascular coupling, a process linking neuronal activity to blood flow and metabolism, enabling the retina to adjust blood flow according to neuronal and metabolic demands [68]. Retinal neurodegeneration involves two processes: neural apoptosis and reactive gliosis. In diabetes, extracellular glutamate accumulates while the production of neuroprotective agents becomes dysregulated.

Normally, the retina secretes neuroprotective factors such as pigment epithelium-derived factor (PEDF), somatostatin, interstitial retinol-binding protein, and various neurotrophins. However, diabetes reduces the production of these protective agents, impairing resistance against neurotoxic markers of neurodegeneration. Nevertheless, not all neuroprotective markers are downregulated. For instance, VEGF and erythropoietin levels are elevated in diabetic retinas. VEGF, upregulated during early neurodegeneration, is influenced by glutamate accumulation, decreased PEDF levels, and reduced somatostatin, contributing to the dysfunction of small retinal vessels.

Mild to Moderate NPDR and DME

The earliest histopathological changes in retinal vessels during NPDR involve pericyte loss due to disrupted tight junctions, followed by endothelial cell loss. Pericytes, which exhibit contractile properties via smooth muscle actin, regulate vascular tone. Their loss leads to weakened vessel walls and microaneurysm formation. Additionally, pericytes synthesize transforming growth factor β (TGF-β), essential for endothelial cell maintenance; its reduction exacerbates endothelial damage.

These microvascular changes, including basement membrane thickening and tight junction disruption, cause leakage of blood contents (proteins and plasma constituents) into the interstitial space. Aging and hypertension, common comorbidities in diabetes, further enhance the secretion of pro-inflammatory mediators in the retina (Xu et al., 2009). Elevated inflammatory factors contribute to a chronic inflammatory state in diabetic retinas, activating white blood cells, promoting endothelial adhesion, and disrupting the blood-retinal barrier, thereby increasing vascular permeability.

Severe NPDR

As NPDR advances to severe stages (severe NPDR or pre-proliferative DR), there is extensive endothelial destruction and imbalance in vasoactive mediators. Vasoconstrictors such as endothelin and thromboxane A2 are overproduced, while nitric oxide (NO) levels increase due to advanced glycation end products (AGEs) in diabetic retinas. This results in a predominance of vasoconstriction, inducing retinal hypoxia. Disease progression leads to widespread endothelial cell loss, and retinal capillaries acquire thickened basement membranes, increasing their susceptibility to thrombosis. Thrombosis, caused by platelet-fibrin plugs or white blood cells, contributes to capillary obstruction and hypoxia, characteristic of pre-proliferative DR. Angiopoietin-1 receptor (TIE2) also plays a role in angiogenesis at this stage.

On ophthalmoscopy, a hallmark of advanced non-proliferative DR is the presence of cotton wool spots, formed due to stagnation of axoplasmic flow in areas of retinal ischemia or infarction. Intraretinal microvascular abnormalities (IRMA), representing abnormal vascular branching or dilation near ischemic regions, may also develop. Furthermore, retinal veins become tortuous and unevenly dilated, a condition termed venous beading.

9. Proliferative Diabetic Retinopathy (PDR)

Proliferative diabetic retinopathy (PDR) and its complications represent the advanced stage of diabetic retinopathy (DR). The primary clinical distinctions between NPDR and PDR include severe visual impairment, shadows or curtains across the visual field (due to retinal hemorrhages or detachments), ocular pain (from glaucoma), and floaters (due to vitreous hemorrhage). In contrast to NPDR, which may initially present asymptomatically or with minimal symptoms like blurry or distorted vision, PDR typically exhibits advanced symptoms such as difficulty with reading and driving. The key pathogenetic factor transitioning NPDR to PDR is profound hypoxia, which disrupts the balance between angiogenic factors (e.g., vascular endothelial growth factor [VEGF]) and anti-angiogenic factors (e.g., pigment epithelium-derived factor [PEDF]), resulting in the formation of new blood vessels, a hallmark of PDR.

The initial step in neovascularization involves leukocyte-mediated release of proteases that degrade the basement membrane. This degradation, along with the secretion of angiogenic mediators like VEGF under hypoxic conditions, leads to endothelial cell migration and proliferation, ultimately causing neovascularization.

The newly formed blood vessels are fragile, compromising vascular integrity and predisposing to ruptures. These vessels may proliferate into the vitreous cavity and undergo fibrovascularization, resulting in fibrous tissue contraction. This process progresses to advanced diabetic retinopathy with tractional retinal detachment (TRD) and severe visual impairment (Simó et al., 2006).

Non-proliferative diabetic retinopathy progresses to PDR. The terminal stages of DR, including retinal detachment and vitreous hemorrhage, pose significant threats to vision.

10. Diagnosis

Diabetic retinopathy is primarily identified in diabetic individuals through characteristic small vessel alterations observed during retinal examinations. The diagnostic process involves direct and indirect ophthalmoscopy, as well as slit-lamp biomicroscopy. It is crucial to rule out other retinal diseases, as similar retinal changes may occur in individuals without diabetes and could be associated with systemic conditions like hypertension or anemia(Grosso et al., 2011).

11. Classification of Diabetic Retinopathy

11.1. Non-Proliferative Diabetic Retinopathy (NPDR)

The earliest lesion in NPDR is the development of microaneurysms, which are capillary outpouchings. Initially asymptomatic, they may rupture over time, leading to intraretinal hemorrhages such as dot and blot hemorrhages. Fluorescein angiography reveals leakage from these lesions, contributing to macular edema.

Progressive signs of NPDR include superficial and deep retinal hemorrhages (flame-shaped and dot-blot hemorrhages, respectively), lipid exudates, venous abnormalities (e.g., venous beading), and intraretinal microvascular abnormalities (IRMA). IRMAs represent dilated or abnormally branching capillaries in ischemic regions, visible as widened capillaries during fundoscopy.

11.2. Proliferative Diabetic Retinopathy (PDR)

The transition to PDR occurs when widespread retinal capillary non-perfusion leads to ischemia, triggering neovascularization at the optic disc (NVD), elsewhere on the retina (NVE), or in the iris (NVI). Neovascularization attempts to counteract ischemia and is evident as NVD, NVE, and NVI.

Neovascularization is associated with subhyaloid and vitreous hemorrhages, which subsequently form fibrous membranes and bands on the retina. These fibrotic changes can lead to TRD or tractional macular edema, both of which severely impair vision. Advanced DR complications include neovascular glaucoma, which arises from neovascularization extending from the pupil to the anterior chamber angle, obstructing aqueous humor outflow. If untreated, this condition may result in painful blindness and phthisis of the eye.

11.3. Diabetic Macular Edema (DME)

DME diagnosis involves slit-lamp biomicroscopy using a contact lens to identify macular thickening, exudates, and cystic changes. Fundus fluorescein angiography (FFA) may reveal capillary leakage, while optical coherence tomography (OCT) provides qualitative and quantitative macular assessment, playing a critical role in DME diagnosis and management.

DME can be categorized as focal, diffuse, or ischemic. Focal DME arises from capillary leakage, often with hard exudates consisting of lipoprotein deposits. Diffuse DME results from generalized capillary dysfunction and blood-retinal barrier breakdown. Ischemic DME, caused by small vessel blockages, appears as hypofluorescent areas on FFA(Zhang et al., 2014).

Previously, clinically significant macular edema (CSME) was defined based on fundoscopic findings but is now largely diagnosed using OCT. The three fundoscopic criteria for CSME are:

1. Retinal thickening at or within 500 μm of the fovea.
2. Hard exudates at or within 500 μm of the fovea, with adjacent retinal thickening.
3. Retinal thickening exceeding one disc diameter (1500 μm) within one disc diameter of the fovea.

Prevention

Risk factors contributing to the development and progression of diabetic retinopathy include hyperglycemia, dyslipidemia, and hypertension. While strict glycemic control is unequivocally essential in halting the progression of diabetic retinopathy, evidence regarding the role of targeting dyslipidemia and hypertension remains inconclusive.

Hyperglycemia

Maintaining strict glycemic control is pivotal in reducing the risk of diabetic retinopathy development or progression. The Diabetes Control and Complications Trial established a robust correlation between mean HbA1c levels and the risk of diabetic retinopathy. Specifically, a 10% reduction in HbA1c was associated with a 39% decrease in the likelihood of disease progression. Long-term follow-up studies confirmed that stringent blood glucose regulation significantly diminished the progression of severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and clinically significant macular edema.

Dyslipidemia

Elevated levels of serum cholesterol and triglycerides have been identified as risk factors for diabetic retinopathy. However, studies evaluating the impact of statin and fibrate therapy on diabetic retinopathy outcomes have yielded mixed results. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial

demonstrated that intensive glycemic control combined with fenofibrate, and simvastatin therapy reduced the progression of diabetic retinopathy compared to simvastatin with placebo after four years(ACCORD Study Group; ACCORD Eye Study Group, Chew et al., 2010). Similarly, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study reported a reduced need for laser therapy in diabetic retinopathy patients treated with fenofibrate(Keech et al., 2005). Additional research indicates that statin therapy may reduce the risk and incidence of diabetic retinopathy 5. (Liu et al., 2021), though some studies failed to confirm a protective effect (Mozetic et al., 2019). Despite this uncertainty, the benefits of lipid control and statin therapy in reducing cardiovascular disease events and mortality in diabetes patients are well-established (American Diabetes Association, 2021).

Blood Pressure

The impact of blood pressure management on diabetic retinopathy prevention has been investigated extensively. A Cochrane review concluded that while intensive blood pressure control reduced the risk of developing diabetic retinopathy, it did not significantly alter the progression of existing disease when compared to less stringent blood pressure management strategies (Do et al., 2023).

GLP-1 Receptor Agonists, Rapid HbA1c Reduction, and Retinopathy

While glycemic control through pharmacologic therapies is a cornerstone of diabetes management, the role of glucagon-like peptide-1 (GLP-1) receptor agonists in diabetic retinopathy risk remains ambiguous. Certain trials and meta-analyses have reported an increased risk of diabetic retinopathy with GLP-1 receptor agonists 11. (Marso et al., 2016), while others found no significant association (Gerstein et al., 2019). Notably, trials reporting an elevated risk frequently studied semaglutide, while those showing no difference evaluated other GLP-1 receptor agonists. The heightened risk associated with these agents appears to be transient, typically manifesting within three months to three years of initiation (Bain et al., 2019). Conversely, the retinopathy improvements linked to glycemic control persist for a longer duration, spanning three to five years or more (Bethel et al., 2021).

A plausible explanation for this transient risk is the rapid reduction in HbA1c associated with intensive diabetes management, rather than a direct effect of GLP-1 receptor agonists (Poonoosamy et al., 2023). For instance, the Diabetes Control and Complications Trial noted that patients undergoing intensive insulin therapy experienced a greater risk of early retinopathy worsening compared to those receiving conventional treatment. Similar findings were reported in a retrospective case-control study, where large reductions in HbA1c were linked to retinopathy worsening in patients with uncontrolled type 2 diabetes (Shurter et al., 2013). Further research is needed to elucidate the relationship between significant HbA1c reductions and retinopathy, particularly in the context of various glucose-lowering treatments, including bariatric surgery.

Despite potential risks, GLP-1 receptor agonists offer notable benefits, including weight loss, cardiovascular risk reduction, and lower risk of hypoglycemia and kidney complications in diabetes management (Marso et al., 2016). When initiating GLP-1 receptor agonists, physicians should carefully weigh the benefits against the potential for retinopathy progression, especially in patients with a history of the condition. Assessing retinopathy status with an ophthalmologist is essential prior to starting these medications. Rapid reductions in HbA1c should also be monitored closely to minimize risks, with target HbA1c levels maintained at 7% or below.

In cases where retinopathy progression is observed following the initiation of GLP-1 receptor agonists or other rapid glucose-lowering treatments, patients should undergo immediate ophthalmologic evaluation to assess severity and determine appropriate interventions. These may include observation, discontinuation of medications, anti-vascular endothelial growth factor (VEGF) injections, intravitreal corticosteroid injections, or surgery, depending on the complications observed. Comprehensive studies with extended follow-up periods and primary endpoints focused on retinopathy risk are crucial to optimizing treatment strategies for patients with diabetes and diabetic retinopathy.

12. Management

12.1. Laser Photocoagulation

Laser photocoagulation remains a patient-centered treatment for DR and DME. Based on the ETDR study, involving 3711 participants, national guidelines were established to guide its application. Currently, a double-frequency Nd:YAG laser emitting a wavelength of 532 nm is used with a slit-lamp microscope and contact lens for precise treatment. In cases with lens or corneal opacities, alternative approaches, such as 810 nm diode lasers or cataract extraction before laser therapy, are considered.

For PDR, panretinal photocoagulation (PRP) stabilizes peripheral retinal oxygenation, reducing hemorrhage risks and preventing membrane formation. PRP involves approximately 2500 laser spots across the peripheral retina, excluding the central macula. CSME is treated with focal laser therapy targeting microaneurysms near the macular center using laser spots sized 100-200 μm.

12.2. Anti-VEGF Therapy in Diabetic Retinopathy

Anti-VEGF therapy, notably with agents like ranibizumab, has demonstrated improved vision outcomes compared to PRP in PDR patients. Clinical trials suggest anti-VEGF therapy improves diabetic retinopathy severity scale (DRSS) scores and reduces the risk of vitrectomy and DME (Sun et al., 2019).

However, anti-VEGF efficacy requires patient compliance due to frequent ophthalmologist visits. In non-compliant patients, the risks may outweigh the benefits, underscoring the need for individualized treatment approaches based on cost and compliance(Obeid et al., 2019).

12.3. Anti-VEGF Therapy in DME

Anti-VEGF agents have shown promising results in central foveal DME treatment, as demonstrated in multicenter studies. Combination therapies with anti-VEGF agents and lasers, such as those highlighted in the RESTORE, RISE, and RIDE studies, provide superior outcomes compared to laser monotherapy.

VISTA and VIVID trials indicate aflibercept may offer advantages in moderate to severe DME over other anti-VEGF agents; however, these differences diminish in mild cases. To mitigate the short action duration of anti-VEGF agents and the associated need for repeated injections, combining anti-VEGF therapy with focal/grid laser therapy is recommended.

Reported adverse effects of anti-VEGF injections include increased intraocular pressure, infectious endophthalmitis, and cataracts. Rare cases of TRD have also been linked to intravitreal injections.

12.4. Steroid Treatment

Intravitreal steroids are recommended for patients who are noncompliant with anti-VEGF treatments or those who experience systemic complications from these agents. Steroid treatment is suitable for pseudophakic patients with visual acuity (VA) less than 6/12, those with stationary intraretinal fluid levels, and patients who have undergone initial vitrectomy. Indications also include the presence of massive hard exudates and hyperreflective dots observed on OCT imaging. However, there is no recommendation for steroid monotherapy in this context.

12.5. Role in DME

Steroids function by inhibiting mediators that promote inflammation and are suggested for cases where edema is widespread across the macula. To mitigate the adverse effects associated with systemic steroids, topical administration is the most favored route. Steroids can be delivered directly into the vitreous, subtenon space, or as implants. Before the advent of anti-VEGF agents, intravitreal triamcinolone acetonide played a significant role in the management of diabetic macular edema (DME). Studies have demonstrated improved visual outcomes following a single dose of intravitreal triamcinolone; however, due to its short duration of action, repeated dosing is required (Kim et al., 2015). Additionally, combination therapy involving bevacizumab and intravitreal triamcinolone showed similar results to bevacizumab monotherapy, though the combination may facilitate faster visual recovery.

Triamcinolone can also be administered via subtenon injection (subtenon triamcinolone acetonide injection, STTA), which has shown efficacy in treating DME. However, due to the short-lived effects of STTA, recurrent injections are necessary. To reduce injection frequency, combination therapy with STTA and anti-VEGF agents is advised. A study comparing combination therapy with anti-VEGF monotherapy for refractory DME showed that combined therapy provided superior visual outcomes. However, intravitreal triamcinolone acetonide (IVTA) proved more effective than STTA for shorter-duration DME, though STTA was associated with fewer intraocular pressure-related side effects (Qi et al., 2012). Another study demonstrated that the combination of STTA and bevacizumab reduced central macular thickness and decreased the need for frequent anti-VEGF injections in refractory DME cases. Therefore, STTA is beneficial in cases of DME refractory to anti-VEGFs, especially in patients at risk of steroid responsiveness.

Another steroid delivery method is the dexamethasone (DEX) implant. Clinical trials have shown promising outcomes for the DEX implant in managing DME unresponsive to intravitreal anti-VEGFs. One study involving 16 eyes reported a reduction in central macular thickness (CMT) following a single dose of the DEX implant. However, combination therapy with the DEX implant and anti-VEGFs did not demonstrate superior results compared to anti-VEGF monotherapy. In contrast, the intravitreal fluocinolone acetonide implant offers a longer half-life and has shown prolonged effects in DME refractory to anti-VEGF therapy in several trials.

13. SURGICAL TREATMENT

13.1. Role in Diabetic Retinopathy

Pars plana vitrectomy (PPV) is indicated for patients with nonresolving vitreous hemorrhage and retinal detachment due to traction. This procedure involves the removal of the vitreous, repositioning of the retina, filling the vitreous cavity with an alternative fluid, and performing endophotocoagulation. Advancements such as microincision vitrectomy and wide-angle viewing systems have improved surgical outcomes, making these techniques more effective and less invasive. These newer approaches are suitable for the early stages of tractional macular detachment in advanced diabetic retinopathy and demonstrate enhanced outcomes when combined with initial anti-VEGF treatment. However, the prognosis post-PPV is less favorable in cases of advanced diabetic retinopathy, macular detachment, or recurrent vitreous hemorrhage following surgery. Additionally, cataract formation is a potential complication after vitrectomy.

13.2. Role in DME

Vitrectomy shows better visual outcomes for DME patients with associated vitreomacular traction. For cases unresponsive to laser photocoagulation, intravitreal anti-VEGFs, and steroids, PPV becomes a last-resort

treatment option. During the procedure, the epiretinal membrane formed due to fibroblast proliferation is peeled off, and the posterior vitreous layer is induced to detach. While intravitreal triamcinolone showed macular thickness reduction one-year post-treatment compared to vitrectomy, no significant difference in visual outcomes was noted between the two therapies (Doi et al., 2012). Furthermore, macular thickness reduction was observed six months post-PPV compared to laser treatment, although visual acuity remained unchanged. These treatment strategies underscore the importance of controlling plasma glucose levels to manage diabetic retinopathy effectively.

14. OTHER AGENTS USED IN THE TREATMENT OF DR

14.1. Fenofibrate

Fenofibrate is a peroxisome proliferator-activated receptor-alpha (PPARα) agonist, part of the nuclear receptor family. It functions by increasing transporter molecules for free fatty acids, thus lowering their levels in the bloodstream. Additionally, fenofibrate promotes the formation of apolipoproteins and HDL cholesterol. It is primarily used to manage metabolic syndrome, commonly associated with diabetes mellitus, as demonstrated in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study. The FIELD study indicated a reduced need for laser photocoagulation in cases of diabetic macular edema (DME) with advanced diabetic retinopathy. Similarly, the ACCORD study showed that combining fenofibrate with statins halted the progression of diabetic retinopathy more effectively than statins alone.

14.2. Pemafibrate

Pemafibrate is a selective PPARα modulator. Experimental studies on mice have shown that pemafibrate administration decreases triglyceride levels and vasoconstriction-associated eicosanoids (Suto et al., 2021). It also improves endothelial dysfunction in diabetic mice. Clinical trials demonstrated that pemafibrate improves glycemic control, cellular metabolism, and PPARα gene expression in the liver, while increasing fibroblast growth factor 21 levels, which contributes to preventing diabetic retinopathy. Another study revealed that oral pemafibrate downregulated MCP-1 and VCAM-1, halting retinal inflammation in diabetic rats. It also elevated thrombomodulin levels, thereby reducing leukostasis in retinal vessels caused by diabetes.

14.3. Finerenone

Finerenone is a nonsteroidal mineralocorticoid receptor antagonist recently approved for delaying chronic kidney disease (CKD) progression and improving cardiovascular outcomes. It has been investigated in phase 3 trials, FIGARO-DKD and FIDELIO-DKD. The FIDELIO-DKD trial included 5,674 patients, 46.8% of whom had diabetic retinopathy, while the FIGARO-DKD trial involved 7,352 patients, with 30.8% having diabetic retinopathy. Hypothesis-generating studies, such as ReFINEDR and DeFineDR, found finerenone effective in slowing the progression of non-proliferative diabetic retinopathy (NPDR) and reducing the need for ocular interventions (Rossing et al., 2022).

14.4. Semaglutide

Semaglutide, a glucagon-like peptide-1 receptor agonist, is approved for managing type 2 diabetes mellitus (T2DM) and chronic weight management. Phase 3 trials under the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) program evaluated its safety and efficacy. While SUSTAIN 1-5 excluded patients with proliferative diabetic retinopathy or diabetic maculopathy requiring immediate treatment, SUSTAIN 6 included such patients, with 29.4% of participants having diabetic retinopathy. Diabetic retinopathy-related complications necessitating retinal photocoagulation or intravitreal injections were significantly higher in the semaglutide group than in the placebo group. Factors contributing to this progression included high HbA1c levels, concomitant insulin use, and pre-existing diabetic retinopathy. The rapid reduction in HbA1c levels with semaglutide compared to placebo was hypothesized as the underlying cause. However, a meta-analysis of 23 randomized trials involving 22,096 patients with T2DM did not find an increased risk of diabetic retinopathy with semaglutide treatment. A dedicated ophthalmic trial, FOCUS, initiated to evaluate the risk of diabetic retinopathy progression over five years, is expected to report results by 2026.

15. LIFESTYLE MANAGEMENT

Lifestyle modifications play a critical role in managing diabetic retinopathy alongside medical interventions. A balanced, nutrient-rich diet, emphasizing vitamins, minerals, and antioxidants from fruits, vegetables, and whole grains while limiting processed foods and sugary beverages, helps achieve optimal glycemic control, delaying the onset and progression of diabetic retinopathy. Regular physical activity improves blood sugar regulation, enhances circulation, and supports healthy weight maintenance. Smoking exacerbates diabetic retinopathy by constricting blood vessels, increasing retinal complications, and accelerating vision loss. Adopting these lifestyle changes significantly slows diabetic retinopathy progression and enhances overall well-being.

16. DIABETIC RETINOPATHY AND PREGNANCY

Pregnant women with diabetes should undergo ophthalmic examinations within the first trimester and continue follow-ups until 12 months postpartum, as they are at higher risk for diabetic retinopathy progression. Women with gestational diabetes generally have a lower risk and may not require ophthalmic evaluation. Between 16% and 85% of pregnant women with pre-existing diabetes experience progression of diabetic retinopathy. The

Diabetes in Early Pregnancy Study highlighted that poor control of pre-existing diabetic retinopathy exacerbates its progression during pregnancy, though long-term risks remain unchanged.

Management strategies for diabetic retinopathy during pregnancy are like those for non-pregnant individuals. Laser therapy and vitrectomy can be performed if necessary. Limited studies on anti-VEGF agents during pregnancy report mixed outcomes. One case series noted normal pregnancies and child development after intravitreal anti-VEGF administration during pregnancy. However, another study reported miscarriages following bevacizumab injections early in unrecognized pregnancies. Thus, a careful risk-benefit assessment is essential when considering anti-VEGF therapy during pregnancy.

17. ROLE OF TRADITIONAL MEDICINE AND ACUPUNCTURE

Traditional medicine has been integral to healthcare for centuries, particularly in oriental medicine, and has potential applications in diabetic retinopathy management. Traditional Chinese medicine (TCM) has identified herbs that target signaling pathways implicated in diabetic retinopathy pathogenesis. These herbs are known to mitigate inflammation, angiogenesis, oxidative stress, and apoptosis through a synergistic interaction among various signaling pathways.

Similarly, acupuncture has shown promise in improving retinal capillary lesions, enhancing microcirculation, and reducing thrombosis. A systematic review and meta-analysis of six randomized controlled trials demonstrated the benefits of acupuncture as a standalone or adjunct treatment (Ang et al., 2020). However, concerns regarding bias in these studies persist. Traditional medicine faces limitations, including a lack of large-scale clinical trials and rigorous negative controls, underscoring the need for further research [67].

Conclusion

Diabetic retinopathy (DR) represents a significant public health challenge, being a leading cause of preventable blindness worldwide. Its progression from non-proliferative stages to severe proliferative phases underscores the importance of early detection and timely intervention. The complex interplay of metabolic, inflammatory, and angiogenic pathways elucidates the disease's pathophysiology, highlighting opportunities for targeted treatment.

Advancements in therapeutic strategies, including laser photocoagulation, anti-VEGF agents, and intravitreal steroids, have substantially improved the management of DR and diabetic macular edema (DME). Surgical options, such as pars plana vitrectomy, remain critical for advanced cases. Emerging pharmacological agents, like fenofibrate, pemafibrate, finerenone, and semaglutide, offer promising adjunctive benefits, though further research is required to establish their roles comprehensively.

Lifestyle modifications, emphasizing glycemic control, blood pressure management, and smoking cessation, play a vital preventive role, particularly when integrated with routine ophthalmic evaluations. Pregnant women with diabetes necessitate specialized monitoring due to heightened risks of DR progression. Furthermore, traditional medicine and acupuncture present complementary approaches warranting more robust clinical validation.

As research evolves, a multidisciplinary approach combining lifestyle management, pharmacologic interventions, and innovative therapies will be pivotal in mitigating the burden of diabetic retinopathy and improving quality of life for individuals with diabetes.

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