Beyond The Vasculature: Decoding Neurodegeneration, Mitochondrial Dysfunction and Nanotherapeutic Strategies in Diabetic Retinopathy

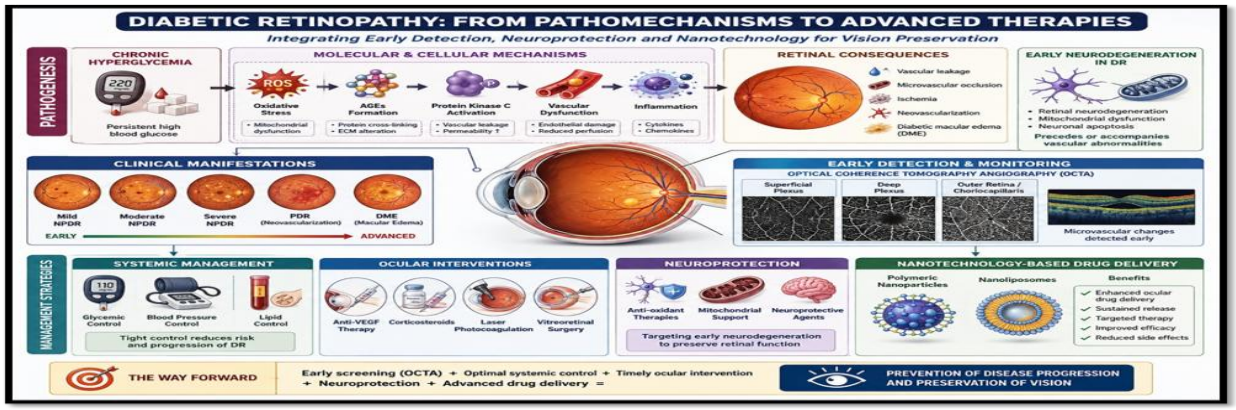
Nasheer Shaikh[1], Khune Mayuri[2], Swami Snehal,[3], Akkangire Bhagyashri[4], Bhaidode Manjunath[5] Gajanan Mugale[6]

[1]*Corresponding Author Associate Professor & Head, Dept. of Pharmaceutics, Channabasweshwar Pharmacy College (Degree), Near Basweshwar Chowk, Kava Road, Latur-413512 (MS),*

[2,3,4,5,6]*Department. of Pharmaceutics, Channabasweshwar Pharmacy College (Degree), Near Basweshwar Chowk, Kava Road, Latur-413512 (MS)*

***Abstract*—Diabetic retinopathy (DR), a major microvascular complication of diabetes mellitus, is a leading cause of preventable visual impairment and blindness, particularly among the working-age population. Chronic hyperglycemia plays a central role in the onset and progression of DR by promoting oxidative stress, advanced glycation end product (AGE) formation, protein kinase C activation, vascular dysfunction, and chronic inflammation. These pathological mechanisms contribute to retinal vascular leakage, microvascular occlusion, ischemia, neovascularization, and diabetic macular edema (DME). Increasing evidence indicates that retinal neurodegeneration and mitochondrial dysfunction are important early events in DR, preceding or accompanying clinically detectable vascular abnormalities. Inflammatory mediators and chemokines further contribute to neuronal apoptosis, vascular dysfunction, and retinal tissue injury. Current management strategies include stringent control of blood glucose, blood pressure, and lipid levels, along with ocular interventions such as intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy, corticosteroids, laser photocoagulation, and vitreoretinal surgery. Recent advances in optical coherence tomography angiography (OCTA) have improved the early detection and monitoring of retinal microvascular alterations. Furthermore, nanotechnology-based drug delivery systems, including polymeric nanoparticles and nanoliposomes, offer promising approaches for improving ocular drug delivery, enhancing therapeutic efficacy, and achieving targeted treatment. Thus, early screening, optimal systemic management, timely ocular intervention, neuroprotective strategies, and the development of advanced drug delivery systems are essential for preventing disease progression and preserving vision in patients with diabetic retinopathy.**

***Index Terms*—Diabetic retinopathy; Oxidative stress, Retinal neurodegeneration, Mitochondrial dysfunction, Diabetic macular edema; Anti-VEGF therapy; Nanoparticle drug delivery; Optical coherence tomography angiography; Neuroprotection.**



Abstract: Graphical presentation

I. INTRODUCTION

A microvascular condition called diabetic retinopathy (DR) is brought on by the long-term consequences of diabetes mellitus. Diabetic retinopathy can cause vision-threatening retinal damage that ultimately results in blindness [1]. DR is more common in diabetic people with type 1 diabetes mellitus (T1DM) than in those with type2diabetes mellitus (T2DM)[2]. Non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) are the three stages of DR that are typically distinguished in clinical practice. NPDR is further subdivided into two stages: mild, moderate and severe stages. Although patients may not exhibit any symptoms, fundus photography can identify retinal abnormalities such as microaneurysms, hemorrhages, and hard exudates during this period. PDR, the more advanced stage of DR, is characterized by neovascularization. During this stage, patients may experience severe visual impairment when the new abnormal vessels bleed into the vitreous or when tractional retinal detachment is present. The most common cause of vision loss in patients with DR is diabetic macular edema (DME). DME is characterized by swelling or thickening of the macula due to subretinal and intraretinal accumulation of fluid in the macula triggered by the breakdown of the blood-retinal barrier (BRB) [3]. DME can result in visual image distortion and a reduction invisual acuity at any stage of DR. Current DR therapy approaches, such as intravitreal pharmacotherapy, laser photocoagulation, and vitreous surgery, focus on controlling the microvascular complication. For both early and advanced phases of DR, intravitreal injection of anti-VEGF medicines is presently the cornerstone of treatment. Anti-VEGF therapy can improve vision with fewer ocular side effects, but standard laser therapy just stabilizes visual acuity [4].

II. PATHOPHYSIOLOGY

CHRONIC HYPERGLYCEMIA

Hyperglycemia activate alternate pathway of glucose metabolism, particularly the polyol pathway. Oxidative stress, protein kinase C activation, and non-enzymatic protein glycation lead to the formation of (AGEs). These alternate routes activate cytokines, growth factors, and vascular endothelial dysfunction, resulting in increased vascular permeability and microvascular occlusion. Retinal ischemia caused by microvascular blockage results may promote the development of intraretinal microvascular abnormalities (IRMA) and neovascularization [5, 6]. Oxidative stress can be caused by changed serum proteins, impaired structural protein production, or the accumulation of endogenous byproducts from glucose metabolism. Increased AGEs decrease mRNA expression of the collagen-binding protein pigment epithelium-derived factor (PEDF) [7]. Diabetics have greater quantities of AGEs in ocular tissues, and the amount of AGEs in vitreous collagen correlates with DR severity [8, 9].

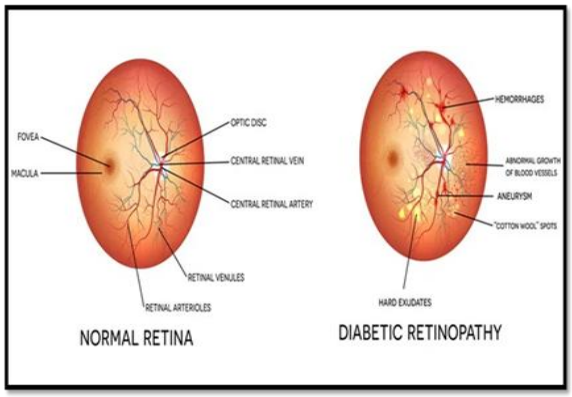


Figure 1: Comparision between Normal retina & Diabetic Retina

INFLAMMATION

Inflammation plays a crucial role in diabetic retinopathy (DR). In streptozotocin (STZ)-induced diabetic rats, retinal inflammation and leukocyte entrapment occur within a few days of diabetes induction.

Diabetic patients with PDR exhibit elevated levels of inflammatory cytokines in the vitreous fluid.[10,12] The development of DR has also been connected to c hemokines, which regulate leukocyte recruitment and activation. Diabetic individuals have higher levels of chemokines, including MCP-1, MIP-1α, and MIP-1β. In diabetic mice, the lack of MCP-1 decreases retinal vascular leakage [13].

- MCP-1 → Monocyte Chemoattractant Protein-1
- MIP-1α → Macrophage Inflammatory Protein-1 alpha
- MIP-1β → Macrophage Inflammatory Protein-1 beta
- TNF-α → Tumor Necrosis Factor-alpha

IL-6 → Interleukin-6
IL-8 → Interleukin-8
IL-1β → Interleukin-1 beta
Diabetic patients have significantly higher levels of inflammatory cytokines, including TNF-α, IL-6, IL-8, and IL-1β, which correlate with the severity of DR [14, 15].

NEURODEGENERATION

Apoptosis of retinal neurons can be detected in diabetic rats as early as one month after the onset of diabetes. Retinal neurodegeneration is an early event during the evolution of DR[16].Pro-apoptotic molecules such as cleaved caspase-3, Bax, and Fas have been found to be upregulated in retinal neurons in diabetic animal models and humans. Retinal degeneration in DR has been linked to mitochondrial dysfunction. Retinal production of pro-apoptotic mitochondrial proteins, including cytochrome c and apoptosis-inducing factor (AIF), was shown to be markedly elevated in the eyes of diabetic donors [17,18]. High glucose exposure was linked to increased mitochondrial fragmentation and cell death, according to in vitro research. Numerous studies have looked into the role of oxidative stress in diabetes-induced retinal degeneration in addition to mitochondrial damage [19].

ETIOLOGY

People with diabetes mellitus, regardless of whether diabetes has been diagnosed, are susceptible to diabetic retinopathy. The patient's age, the duration of diabetes, poor glycemic control, and blood pressure fluctuations are all strongly correlated with the risk of developing diabetic retinopathy [20]. Risk factors for diabetic retinopathy can be classified as follows:

Modified risk factor:
1. Hypertension
2. Obesity
3. Dyslipidemia
4. Poor glycemic control
5. Nephropathy

Non-modifiable risk factors:
1. Puberty
2. Pregnancy

Newer risk factors:
1. Inflammation
2. Apolipoprotein
3. Hormonal influence - leptin and adiponectin
4. Vitamin D
5. Oxidative stress
6. Genetic factors [21].

STAGES OF DAIBETIC RETINOPATHY

Individuals with NPDR typically show signs such as hemorrhages of different sizes, microaneurysms (MAs), hard exudates, soft exudates (cotton-wool spots), intraretinal microvascular abnormalities (IRMAs), and alterations in vein structure such as looping or beading [22-24].

124

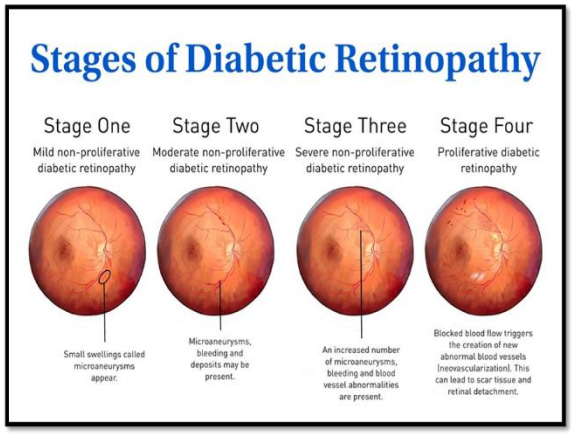


Figure 2: Stages of Diabetic Retinopathy

STAGE 1: MILD NPDR

These patients have at least one MA but no other retinal abnormalities. Because the findings are frequently mild, careful examination and regular monitoring are important. These patients should undergo a dilated eye examination every 12 months. A patient who has not yet been diagnosed with diabetes should be seen by their PCP for further testing if one or more MAs are detected in their eye [22]. Fundus photography should be used for the screening, detection, and documentation of diabetic retinopathy. Referral to a retinal specialist is generally not warranted in patients with mild non-proliferative diabetic retinopathy (NPDR), unless there is clinical suspicion of diabetic macular edema (DME) or DME has been confirmed through appropriate diagnostic evaluation[22,23].

STAGE 2: MODERATE NPDR

Patients with moderate NPDR should be evaluated every six to eight months if they have hemorrhages or

MAs in one to three retinal quadrants, cotton-wool patches, hard exudates, or venous beading. Within a year, they have a 12% to 27% chance of developing proliferative diabetic retinopathy (PDR).For these patients, fundus photography is recommended.

STAGE 3: SEVERE NPDR

These individuals have an IRMA in one or more quadrants, venous beading in two or more quadrants, or intraretinal hemorrhages (>20 in each quadrant). Neovascularization, which would suggest PDR, must be absent from these observations [22, 25].

Fluorescein angiography and macular OCT should be used to follow patients with severe NPDR in order to identify any DME or early neovascularization. Every three to four months, patients should undergo a dilated fundus examination. These patients are probably already having neuropathy elsewhere and are at a high risk of developing the condition and losing their vision permanently [23, 25].

STAGE 4: PROLIFERATIVE DIABETIC RETINOPATHY

These individuals have experienced either vitreous/preretinal hemorrhage or neovascularization of the disc or elsewhere, and their NPDR has progressed to PDR. For additional testing and care, these individuals must be referred immediately to a retinal specialist. Laser panretinal photocoagulation is typically used to treat peripheral neovascularization [22, 23, 25].

DIABETIC MACULAR EDEMA

DME is the result of a buildup of fluid, proteins, and lipids within the retinal layers, manifesting as cystic spaces in the retina that are most effectively observed using OCT. The current understanding of the pathogenesis of DME is multifactorial but is primarily associated with two main factors [26]. First, retinal ischemia occurs in patients with poorly controlled diabetes mellitus due to retinal microvascular obstruction and capillary dropout throughout the retina. Vascular permeability is increased by the ensuing hypoxia-induced elevation of vascular endothelial growth factor (VEGF), which results in neovascularization in both the retinal periphery and pre-existing macular vessels. Second, pro-inflammatory cytokines, including interleukin (IL)-1b and IL-6, are upregulated in many patients with chronic diabetes mellitus, partly due to the generation of free radicals and the buildup of advanced glycation end products (AGEs). As inflammation progresses and vascular pericytes are damaged, this process causes additional vision-threatening effects of DME. The extravascular fluid and hard lipid exudates that are characteristic of DME are a result of compromised junctional proteins in retinal microcapillaries making them more prone to leaking [27].

Management of Diabetic Retinopathy

Systemic Management

The management of diabetic retinopathy has mostly concentrated on the systemic control of blood glucose levels and their variability as well as weight loss, blood pressure, sleep apnea, and lipids. Reducing oxidative stress appears to be an important early treatment approach for the diabetes-induced degeneration of the retinal neurovascular unit. The initial strategy is to strictly control hyperglycemia and related comorbidities. Other treatment techniques may be required if macular edema worsens following Panretinal photocoagulation (PRP), with a moderate decrease in vision. Laser photocoagulation, intravitreal anti-VEGF and steroidal injections, and vitreoretinal surgery are among the ocular therapy methods for DR. Treatment of severe diseases such as PDR or DME, is the focus of modern therapies. Panretinal photocoagulation (PRP) is the initial treatment for PDR. A DR study demonstrated that PRP can reduce the incidence of severe vision loss inpatients. Laser burns applied to the peripheral retina can cause permanent retinal damage [28]. Peripheral visual-field loss, delayed dark adaptation, and progressive retinal atrophy over long follow-up are among the complications associated with post-PRP eyes. Pain, treatment time, coagulation expansion, nerve fiber layer loss, and inflammatory cytokine levels were significantly reduced when the pattern-scanning laser photocoagulation was used to address these complications [29].

Three clinical sessions of intravitreal anti-VEGF injections improve visual gains in eyes with DME in the present age [30, 31]. Aflibercept, bevacizumab, and ranibizumab were all successful in improving vision, according to a new comparative efficacy analysis of the most recommended anti-VEGF injections [32, 33]. Anti-VEGF drugs have been strongly advised as a

way to reverse retinal neovascularization in PDR eyes [34]. Anti-VEGF has been demonstrated in recent research to be a successful therapeutic choice for PDR eyes, particularly when coexisting DME is present. Anti-VEGF also has a lower risk of peripheral visual field loss, DME, and vitrectomy during a two year period than PRP laser. Anti-VEGF medication might not be the best option for patients who are unable to attend the nearly monthly follow-up, despite these favorable results. Because steroids have an anti-inflammatory impact and down regulate pro-inflammatory and pro-angiogenic mediators linked to the development of DME, they are taken into consideration while treating diffuse macular edema. For DME, topical corticosteroids are better than systemic treatment because the latter has several adverse effects. Corticosteroids can be administered via intravitreal injection, sub-Tenon injection, or intravitreal implantation of dexamethasone [35].

III. PREVENTION

Controlling diabetes at the systemic level is the most crucial way to avoid visual complication such as diabetic retinopathy. The incidence and progression of retinopathy are greatly decreased by strict glycemic control, including appropriate insulin therapy [36].

Hypertension is another important systemic risk factor that requires appropriate management in patients with diabetics. In fact, coordinated management of blood pressure and glycemic levels has been found to greatly delay the start and reduce the progression of diabetic retinopathy, despite conflicting data regarding the benefits of antihypertensive therapy alone[37,38]. The possible effect of serum lipid levels on diabetic patients eyesight deterioration has also drawn attention. In particular, it has been demonstrated that the development of retinal hard exudate is strongly correlated with dyslipidemia and high low-density lipoprotein (LDL). DME is also linked to these variables and elevated total cholesterol [39, 40]. Lipid-lowering medications like fibrates and statins are being studied for their potential to prevent diabetic retinopathy, and preliminary findings indicate that they may be beneficial in delaying the start and progression of the condition [41, 42]. Male smokers with type 1 diabetes have a higher prevalence of ocular illness, according to various epidemiological research [43, 44]. Ocular abnormalities have also been linked to prior diagnoses of diabetic nephropathy or albuminuria [45, 46]. Pregnancy, puberty, and, most obviously, the length of the illness are additional risk factors [47, 48]. Thus, regular screening is essential for early detection.

IV. RECENT ADVANCES

A noninvasive imaging method called optical coherence tomography angiography (OCTA) produces finely detailed pictures of the retinal and choroidal microvasculature. It can identify the existence of blood flow in various retinal layers and areas [49]. The influence of various treatment modalities on retinal microvasculature and blood flow, as well as effects in different layers of the retina in DR, can be detected using OCTA, an emerging imaging modality. Particularly in diabetic patients who have not yet developed the condition are all made possible by OCTA, an emerging imaging modality [50].

Prediabetic retinopathy stage alterations can be predicted and detected with the use of OCTA's imaging modality, which can reveal more significant changes that ophthalmologists fundoscopy might miss. OCTA can find sensitive and promising indicators under many modalities in clinical applications and DR research, providing fresh perspectives on the early-stage pathogenesis, treatment, and screening of DR [51].

Nanoliposomes both lipophilic (loaded in the bilayer) and hydrophilic (loaded in the core) drugs can be delivered via nanoliposomes [52]. Because drug-loaded nanoliposomes are smaller and more biocompatible, the drug has a longer residence time, drug half-life, and contact time with the target site [53].

Nanoparticle poly (lactic-co-glycolic acid) (PLGA) nanoparticles biocompatible, and biodegradable drug delivery systems, and their degradation products are generally non-toxic. PLGA has been cleared by the USFDA for certain clinical application [54]. After intraocular topical application, surface-modified poly-lactic-co-glycolic acid-NPs loaded with pioglitazone may carry medications to the posterior portion of the eye in diabetic rats, and VEGF levels in suspension were significantly decreased [55]. Poly-

lactide-co-hydroxyacetic acid poly-ethylene glycol-poly-lactide-co-hydroxyacetic acid hydrogel was created using chitosan nanoparticles. Through subconjunctival injection, this approach demonstrated sufficient neuroprotective effects on the retina of DR rats, enabling regulated insulin delivery [56]. Both in vitro and in vivo apatinib-loaded polyethylene glycol and human serum albumin nanoparticles successfully reduced VEGF-induced retinal vascular hyperpermeability [57].

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are the two primary types of lipid nanoparticles. SLNs are composed of solid lipids and surfactants, with co-surfactants used when required, and can encapsulate both hydrophilic and lipophilic drugs, depending on the formulation. In contrast, NLCs are composed of mixture of solid or liquid lipids, which helps to improve drug loading and reduce drug explosion during storage. The advantages of SLNs and NLCs include their small particle size, high stability, good biocompatibility, potential to enhance drug transport across biological barriers, controlled drug release, and potential for targeted drug delivery [58].

Nanoemulsions are nanoscale oil-in-water (O/W) or water-in-oil (W/O) dispersions stabilized by surfactants that can be used for ocular drug delivery. They may facilitate drug solubilization and improve drug delivery to ocular tissues, depending on their composition and formulation. Drugs can interact with dendrimers through hydrogen bonding, hydrophobic interactions, covalent bonding, and ionic interactions. Dendrimers are highly branched, tree-like macromolecular structures with multiple functional groups that can facilitate drug association or conjugation [59]. Nanogels are nanoscale, three-dimensional networks of hydrophilic polymers that absorb water and swell. They can serve as drug delivery systems and facilitate drug transport across ocular barriers, depending on their properties and formulation.

V. CONCLUSION

In conclusion, diabetic retinopathy, a major microvascular complication of diabetes mellitus, remain a significant cause of avoidable contributor to avoidable blindness and visual impairment, particularly among working-age individuals. Chronic hyperglycemia, oxidative stress, advanced glycation end products, inflammation, vascular dysfunction, and retinal neurodegeneration are all closely linked to its multifactorial development. If not identified and treated promptly, the development of diabetic macular edema and the progression from non-proliferative diabetic retinopathy to proliferative diabetic retinopathy can cause substantial and irreversible visual loss. Strict control of blood pressure, blood glucose, cholesterol, and other systemic risk factors, along with the appropriate ophthalmic treatment, are all necessary for effective management. The treatment of vision-threatening diabetic retinopathy has greatly improved thanks to developments in intravitreal anti-VEGF medication, corticosteroids, laser photocoagulation, and vitreoretinal surgery. To avoid serious consequences, early detection and routine screening are still crucial. Therefore, reducing the burden of diabetic retinopathy and preserving vision in diabetic patients require early screening, adequate systemic management, timely ophthalmic intervention, and the development of advanced drug delivery systems.

REFERENCES

[1]. Eisma JH, Dulle JE, Fort PE. Current knowledge on diabetic retinopathy from human donor tissues. World J Diabetes. 2015 Mar 15;6(2):312-20.

[2]. Deutsche DG. Nationale Versorgungs Leitlinie Typ-2-Diabetes Preventions und Therapie von Netzhautkomplikationen. Berlin, Germany: Bunde särztekammer(BÄK); 2010. 1–42 pp

[3]. Romero-Aroca, P.; Baget-Bernaldiz, M.; Pareja-Rios, A.; Lopez-Galvez, M.; Navarro-Gil, R.; Verges, R. Diabetic macular edema pathophysiology: Vasogenic versus inflammatory. J. Diabetes Res. 2016, 2016, 2156273

[4]. Gonzalez, V.H.; Campbell, J.; Holekamp, N.M.; Kiss, S.; Loewenstein, A.; Augustin, A.J.; Ma, J.; Ho, A.C.; Patel, V.; Whitcup, S.M.; et al. Early and long-term responses to anti-vascular endothelial growth factor therapy in diabetic macular edema: Analysis of protocol I data. Am. J. Ophthalmol. 2016, 172, 72–79.

[5]. Behl T, Kotwani A. Exploring the various aspects of the pathological role of vascular

endothelial growth factor (VEGF) in diabetic retinopathy. Pharmacol Res. 2015 Sep;99:137-48.

[6]. Kador PF, Wyman M, Oates PJ. Aldose reductase, ocular diabetic complications and the development of topical Kinostat(®). Prog Retin Eye Res. 2016 Sep;54:1-29.

[7]. Morya, A.; Ramesh, P.; Nishant, P.; Kaur, K.; Gurnani, B.; Heda, A.; Salodia, S. Diabetic retinopathy: A review on its pathophysiology and novel treatment modalities. World J. Methodol. 2024, 14, 95881.

[8]. Ono,Y.; Aoki, S.; Ohnishi, K.; Yasuda, T.; Kawano, K.; Tsukada, Y. Increased serum levels of advanced glycation end-products and diabetic complications. Diabetes Res. Clin. Pract. 1998, 41, 131–137.

[9]. Fosmark, D.S.; Bragadóttir, R.; Stene-Johansen, I.; Berg, J.P.; Berg, T.J.; Lund, T.; Sandvik, L.; Hanssen, K.F. Increased vitreous levels of hydroimidazolone in type 2 diabetes patients are associated with retinopathy: A case-control study. Acta Ophthalmol. Scand. 2007, 85, 618–622.

[10]. Miyamoto, K.; Khosrof, S.; Bursell, S.E.; Rohan, R.; Murata, T.; Clermont, A.C.; Aiello, L.P.; Ogura, Y.; Adamis, A.P. Prevention of leukostasis and vascular leakage in streptozotocin-induced diabetic retinopathy via intercellular adhesion molecule-1 inhibition. Proc. Natl. Acad. Sci. USA 1999, 96, 10836–10841.

[11]. Miyamoto, K.; Hiroshiba, N.; Tsujikawa, A.; Ogura, Y. In vivo demonstration of increased leukocyte entrapment in retinal microcirculation of diabetic rats. Investing. Ophthalmol. Vis. Sci. 1998, 39, 2190–2194.

[12]. Yuuki, T.; Kanda, T.; Kimura, Y.; Kotajima, N.; Tamura, J.; Kobayashi, I.; Kishi, S. Inflammatory cytokines in vitreous fluid and serum of patients with diabetic vitreoretinopathy. J. Diabetes Complicate. 2001, 15, 257–259.

[13]. Suzuki, Y.; Nakazawa, M.; Suzuki, K.; Yamazaki, H.; Miyagawa, Y. Expression profiles of cytokines and chemokines in vitreous fluid in diabetic retinopathy and central retinal vein occlusion. Jpn. J. Ophthalmol. 2011, 55, 256–263.

[14]. Koleva-Georgieva, D.N.; Sivkova, N.P.; Terzieva, D. Serum inflammatory cytokines IL-1beta, IL-6, TNF-alpha and VEGF have influence on the development of diabetic retinopathy. Folia Med. 2011, 53, 44–50.

[15]. Boss, J.D.; Singh, P.K.; Pandya, H.K.; Tosi, J.; Kim, C.; Tewari, A.; Juzych, M.S.; Abrams, G.W.; Kumar, A. Assessment of neurotrophins and inflammatory mediators in vitreous of patients with diabetic retinopathy. Investing. Ophthalmol. Vis. Sci. 2017, 58, 5594–5603.

[16]. Barber, A.J.; Lieth, E.; Khin, S.A.; Antonetti, D.A.; Buchanan, A.G.; Gardner, T.W. Neural apoptosis in the retina during experimental and human diabetes. Early onset and effect of insulin. J. Clin. Investing. 1998, 102, 783–791.

[17]. Kowluru, R.A.; Koppolu, P. Diabetes-induced activation of caspase-3 in retina: Effect of antioxidant therapy. Free Radic. Res. 2002, 36, 993–999.

[18]. Abu-El-Asrar, A.M.; Dralands, L.; Missotten, L.; Al-Jadaan, I.A.; Geboes, K. Expression of apoptosis markers in the retinas of human subjects with diabetes. Investing. Ophthalmol. Vis. Sci. 2004, 45, 2760–2766

[19]. Sasaki, M.; Ozawa, Y.; Kurihara, T.; Kubota, S.; Yuki, K.; Noda, K.; Kobayashi, S.; Ishida, S.; Tsubota, K.Neurodegenerative influence of oxidative stress in the retina of a murine model of diabetes. Diabetologia 2010, 53, 971–979.

[20]. Wang Y, Lin Z, Zhai G, Ding XX, Wen L, Li D, Zou B, Feng KM, Liang YB, Xie C. Prevalence of and Risk Factors for Diabetic Retinopathy and Diabetic Macular Edema in Patients with Early- and Late-Onset Diabetes Mellitus. Ophthalmic Res. 2022;65(3):293-299.

[21]. Schreur V, van Asten F, Ng H, Weeda J, Groenewoud JMM, Tack CJ, Hoyng CB, de Jong EK, Klaver CCW, Jeroen Klevering B. Risk factors for development and progression of diabetic retinopathy in Dutch patients with type 1 diabetes mellitus. Acta Ophthalmol. 2018 Aug;96(5):459-464.

[22]. American Optometric Association. Evidence-based Clinical Practice Guideline: Eye Care of the Patient With Diabetes Mellitus. Accessed May 2, 2019.

[23]. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification: ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98(5):786-806.

[24]. Fundus photographic risk factors for progression of diabetic retinopathy: ETDRS report number 12. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98(5):823-833.

[25]. Wong TY, Sun J, Kawasaki R, et al. Guidelines on diabetic eye care: The International Council of Ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. Ophthalmology. 2018;125(10):1608-1622.

[26]. Joussen AM et al. Am J Pathol. 2001;158(1):147-152.

[27]. Wong TY et al. Nat Rev Dis Primers. 2016; 2:16012. doi:10.1038/nrdp.2016.12.

[28]. Nguyen TT, Kawasaki R, Wang JJ, Kreis AJ, Shaw J, Vilser W, Wong TY. Flicker light-induced retinal vasodilation in diabetes and diabetic retinopathy. Diabetes Care. 2009;32:2075–2080.

[29]. Striph GG, Hart WM Jr, Olk RJ. Modified grid laser photocoagulation for diabetic macular edema. The effect on the central visual field. Ophthalmology. 1988;95:1673–1679.

[30]. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, Edwards AR, Ferris FL 3rd, Friedman SM, Glassman AR, Miller KM, Scott IU, Stockdale CR, Sun JK. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2010;117:1064–1077.e35.

[31]. Heier JS, Korobelnik JF, Brown DM, Schmidt-Erfurth U, Do DV, Midena E, Boyer DS, Terasaki H, Kaiser PK, Marcus DM, Nguyen QD, Jaffe GJ, Slakter JS, Simader C, Soo Y, Schmelter T, Vitti R, Berliner AJ, Zeitz O, Metzig C, Holz FG. Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies. Ophthalmology. 2016; 123:2376–2385

[32]. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, Antoszyk AN, Arnold-Bush B, Baker CW, Bressler NM, Browning DJ, Elman MJ, Ferris FL, Friedman SM, Melia M, Pieramici DJ, Sun JK, Beck RW. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015;372:1193–1203.

[33]. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, Brucker AJ, Ferris FL, Hampton GR, Jhaveri C, Melia M, Beck RW Diabetic Retinopathy Clinical Research Network. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology. 2016; 123:1351–1359.

[34]. Avery RL, Pearlman J, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ, Wendel R, Patel A. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. Ophthalmology. 2006;113:1695.e1–1695.15.

[35]. Martidis A, Duker JS, Greenberg PB, Rogers AH, Puliafito CA, Reichel E, Baumal C. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology. 2002;109:920–927.

[36]. Zhu CH, Zhang SS, Kong Y, et al. Effects of intensive control of blood glucose and blood pressure on microvascular complications in patients with type II diabetes mellitus. Int J Ophthalmol. 2013;6:141–5.

[37]. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998;317:703–13.

[38]. Group AS, Group AES, Chew EY, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010;363:233–44.

[39]. Idiculla J, Nithyanandam S, Joseph M, Mohan, et al. Serum lipids and diabetic retinopathy: A cross-sectional study. Indian J Endocrinol Metab. 2012;16:S492–94.

[40]. Miljanovic B, Glynn RJ, Nathan DM, et al. A prospective study of serum lipids and risk of diabetic macular edema in type 1 diabetes.

Diabetes. 2004;53:2883–92. doi: 10.2337/diabetes.53.11.2883.

[41]. Dodson PM. Management of diabetic retinopathy: could lipid-lowering be a worthwhile treatment modality? Eye. 2009;23:997–1003. doi: 10.1038/eye.2008.428.

[42]. Wong TY, Simo R, Mitchell P. Fenofibrate—a potential systemic treatment for diabetic retinopathy? Am J Ophthalmol. 2012;154:6–12. doi: 10.1016/j.ajo.2012.03.013.

[43]. Hammes HP, Kerner W, Hofer S, et al. Diabetic retinopathy in type 1 diabetes-a contemporary analysis of 8,784 patients. Diabetologia. 2011;54:1977–84. doi: 10.1007/s00125-011-2198-1.

[44]. Rani PK, Raman R, Chandrakantan A, et al. Risk factors for diabetic retinopathy in self-reported rural population with diabetes. J Postgrad Med. 2009;55:92–6. doi: 10.4103/0022-3859.48787.

[45]. Wirta O, Pasternack A, Mustonen J, et al. Retinopathy is independently related to microalbuminuria in type 2 diabetes mellitus. Clin Nephrol. 1999;51:329–34.

[46]. Gilbert RE, Tsalamandris C, Allen TJ, et al. Early nephropathy predicts vision-threatening retinal disease in patients with type I diabetes mellitus. J Am Soc Nephrol. 1998;9:85–9. doi: 10.1681/ASN.V9185.

[47]. Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular edema. Curr Diab Rep. 2012;12:346–54. doi: 10.1007/s11892-012-0283-6.

[48]. Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular edema. Curr Diab Rep. 2012;12:346–54. doi: 10.1007/s11892-012-0283-6.

[49]. KoustenisAJr.HarrisAGrossJJanulevicieneIShahASieskyB. Optical coherence tomography angiography: an overview of the technology and an assessment of applications for clinical research. Br J Ophthalmol. (2017) 101:16–20. doi: 10.1136/bjophthalmol-2016-309389

[50]. VujosevicSCunha-VazJFigueiraJLöwensteinAMidenaEParravanoM et al. Standardization of optical coherence tomography angiography imaging biomarkers in diabetic retinal disease. Ophthalmic Res. (2021) 64:871–87. doi: 10.1159/000518620

[51]. LiuKZhuTGaoMYinXZhengRYanYet al. Functional OCT angiography reveals early retinal neurovascular dysfunction in diabetes with capillary resolution. BioMed Opt Express. (2023) 14:1670–84. doi: 10.1364/BOE.485940

[52]. Akbarzadeh A, Rezaei-Sadabady R, Davaran S, Joo SW, Zarghami N, Hanifehpour Y, et al. Liposome: Classification, preparation, and applications. Nanoscale Res Lett (2013) 8:102. doi: 10.1186/1556-276X-8-102

[53]. Andra VVSNL, Pammi SVN, Bhatraju LVKP, Ruddaraju LK. A comprehensive review on novel liposomal methodologies, commercial formulations, clinical trials and patents. BioNano Science (2022) 12:274–91. doi: 10.1007/s12668-022-00941-x

[54]. Tahara K, Karasawa K, Onodera R, Takeuchi H. Feasibility of drug delivery to the eye's posterior segment by topical instillation of PLGA nanoparticles. Asian J Pharm Sci (2017) 12:394–9. doi: 10.1016/j.ajps.2017.03.002

[55]. Laddha UD, Kshirsagar SJ. Formulation of PPAR-gamma agonist as surface modified PLGA nanoparticles for non-invasive treatment of diabetic retinopathy: In vitro and in vivo evidences. Heliyon (2020) 6:e04589. doi: 10.1016/j.heliyon. 2020.e04589

[56]. Rong X, Ji Y, Zhu X, Yang J, Qian D, Mo X, et al. Neuroprotective effect of insulin-loaded chitosan nanoparticles/PLGA-PEG-PLGA hydrogel on diabetic retinopathy in rats. Int J Nanomed (2019) 14:45–55. doi: 10.2147/IJN.S184574

[57]. Jeong JH, Nguyen HK, Lee JE, Suh W. Therapeutic effect of apatinib-loaded nanoparticles on diabetes-induced retinal vascular leakage. Int J Nanomed (2016) 11:3101–9. doi: 10.2147/IJN.S108452

[58]. Sharma DS, Wadhwa S, Gulati M, Kumar B, Chitranshi N, Gupta VK, et al. Chitosan modified 5-fluorouracil nanostructured lipid carriers for treatment of diabetic retinopathy in rats: A new dimension to an anticancer drug. Int J Biol Macromol (2023) 224:810–30.

[59]. Dave R, Randhawa G, Kim D, Simpson M, Hoare T. Microgels and nanogels for the delivery of poorly water-soluble drugs. Mol Pharm (2022) 19:1704–21.