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Research paper

Chronic ocular small vessel disease: An overview of diabetic retinopathy and its relationship with cardiovascular health

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ABSTRACT

Diabetic retinopathy (DR) is a potentially blinding disease originating from small vessel damage in the retina in chronic hyperglycemic states. DR has a complex multi-pathway driven pathogenesis resulting in diabetic macular edema and retinal ischemia, the former being the most common cause of vision impairment in DR. Hypoxia induced cytokines stimulate vascular endothelial growth factor (VEGF) production and subsequent angiogenesis with resultant mechanical retinal damage over time. Anti-VEGF therapy is effective for the treatment of center-involving diabetic macular edema. There is evolving evidence showing the effectiveness of anti-VEGF as both adjuvant and monotherapy in the treatment of proliferative DR, however laser photocoagulation continues to remain the standard of care. DR in large cohort studies has been shown to be an independent risk factor for the development of cardiovascular disease and mortality. In addition, changes in retinal vascular caliber ratios may have implications for risk of macrovascular events with a gender discrepancy towards women.

1. Introduction

Diabetic retinopathy (DR) is a small vessel-based end organ insult resulting from uncontrolled blood sugar and is increasing at an alarming rate in the United States [1]. Despite continued research from around the world for this disease there are still many questions that surround the risk of developing advanced retinopathy and the association of retinopathy and non-ocular disease. The answers to these concerns continue to challenge researchers and clinicians. In this review we briefly explore the anatomy of ocular perfusion important to the understanding of diabetic microvascular disease, the pathophysiology of diabetic retinopathy, and its current treatment. We conclude with a discussion of relevant literature about diabetic retinopathy and its relationship to cardiovascular disease.

2. Ocular perfusion

The ocular blood supply is provided by the ophthalmic artery, the first branch of the internal carotid artery within the cranium following it departure from the cavernous sinus [2]. Abnormal origins of the ophthalmic artery may arise from the middle meningeal artery [2]. The ophthalmic artery further sub-divides into the central retinal artery and the ciliary arteries which supply the eye, ethmoidal, palpebral and orbit branches [2]. The anastomotic interlace of ciliary vessels in the circle of Zinn-Haller are present in the posterior sclera and surround the optic nerve with branches that provide blood to the laminar region [3]. Any significant and prolonged interruption in the flow of blood at the level of the ophthalmic artery will result in compromised perfusion to all parts of the eye.

The choroid, a major uveal component in the eye mostly consists of vascular structures [4]. The main vascular layers include the choriocapillaris, and the adjacent Sattler and Haller layers. The choriocapillaris, a single layer of vessels with fenestrated endothelium arises from branches of arterioles within Sattlers layer [4]. This network of capillaries allows for the nourishment of the outer third of the retina. Its large diameter (20–40 μm) and endothelial characteristics allow for the passage of fluid through oncotic gradients [4,5]. This ability along with other structural attributes allow the choroid to be multifunctional and

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affect the structure, perfusion and health of the retina and surrounding anatomy [4].

The retina is provided blood from two sources: the central retinal artery, and the choroidal vascular complex. The main blood supply to the retina is the central retinal artery [6]. The central retinal artery supplies the inner two-thirds of the retina and the choroid sub-serves the outer one third. In up to 32 % of eyes, a full thickness portion of the retina may be supplied by a cilioretinal artery (an independent branch from the ciliary circulation) [6]. The central retinal artery gives rise to retinal arterioles which eventually form the extensive retinal capillary network [7]. The very center of the retina (the fovea in the macula) is devoid of capillaries and it is so called the foveal avascular zone (FAZ), a region of mitigated light scatter [6,8,9]. The blood supply in this region is provided by the choroidal circulation [4] (Fig. 1 [10,11]). The choriocapillaris is of the highest density in the fovea (10 μm) decreasing in thickness by 30 % in the periphery [4]. There are four macular retinal vascular beds: the radial peripapillary capillary plexus (supplying the nerve fiber layer), superficial plexus, intermediate plexus (above the inner nuclear retinal layer), and deep plexus (below the inner nuclear retinal layer) [7]. The vasculature within the retina normally does not have arterio-venous anastomosis nor does it have autonomic innervation [6]. The inner blood retinal barrier is formed by tight junctions within the endothelium. The outer blood retinal barrier is formed by tight junctions within the retinal pigment epithelial cells [6].

3. Diabetic retinopathy

DR affects over a third of individuals with diabetes with the major risk factors being duration of diabetes, glycemic control, and blood pressure control [12]. DR combines two dangerous components: a slowly degrading condition + silent symptoms [13]. Patients may not seek care until the vision is noticeably affected, and by this time the retinopathy may have advanced. Worldwide, 1 % of visual impairment is attributed to DR [13]. 1 out of 29 people over the age of 40 years old in the United States have DR [1]. Uncontrolled Type 1 diabetics, unfortunately, meet substantial ocular morbidity earlier in life due to the age of diagnosis with over a third of those having DR with vision threatening stages [14]. DR increases substantially with age in Type 1 diabetics with over 90 % prevalence over the age of 40 [14].

3.1. Pathophysiology in diabetic retinopathy

Retinal capillary health is the centerpiece in early diabetic microvascular disease of the retina [15]. Chronic microvascular damage from glycosylation and glycated end products secondary to long standing uncontrolled elevated blood sugar lead to dilatation of vasculature and early pericyte loss [16–18]. The sequela of pericyte loss is structural compromise of the capillary wall [16,19]. Clinically this structural integrity loss manifests as microaneurysm formation as the first sign of DR [19]. Intraretinal hemorrhaging, microvascular anomalies and areas of localized ischemia are other common findings in DR [1,17]. The localized state of hypoxia creates free radical damage and oxidative stress and sets the stage for a surge of growth factors and cytokines that further wreak havoc on an already compromised state [20]. DR involves mechanical endothelial damage, inflammation, ischemia, and free radical damage [16]. A schematic of basic pathophysiology in DR is shown in Fig. 2.

Sparse and localized loss of retinal capillaries outside of the macula typically does not affect the vision. Retinal ischemia can result in relative scotomas (loss of the visual field), but this may not be noticeable to the patient in different conditions of daily living (Fig. 3 A, B). It is for these reasons that screening examinations are important so advancing disease may be realized earlier [15]. DR primarily manifests as diabetic macular edema (DME), and/or proliferative diabetic retinopathy (PDR) [15].

The most studied and major growth factor specific for vascular

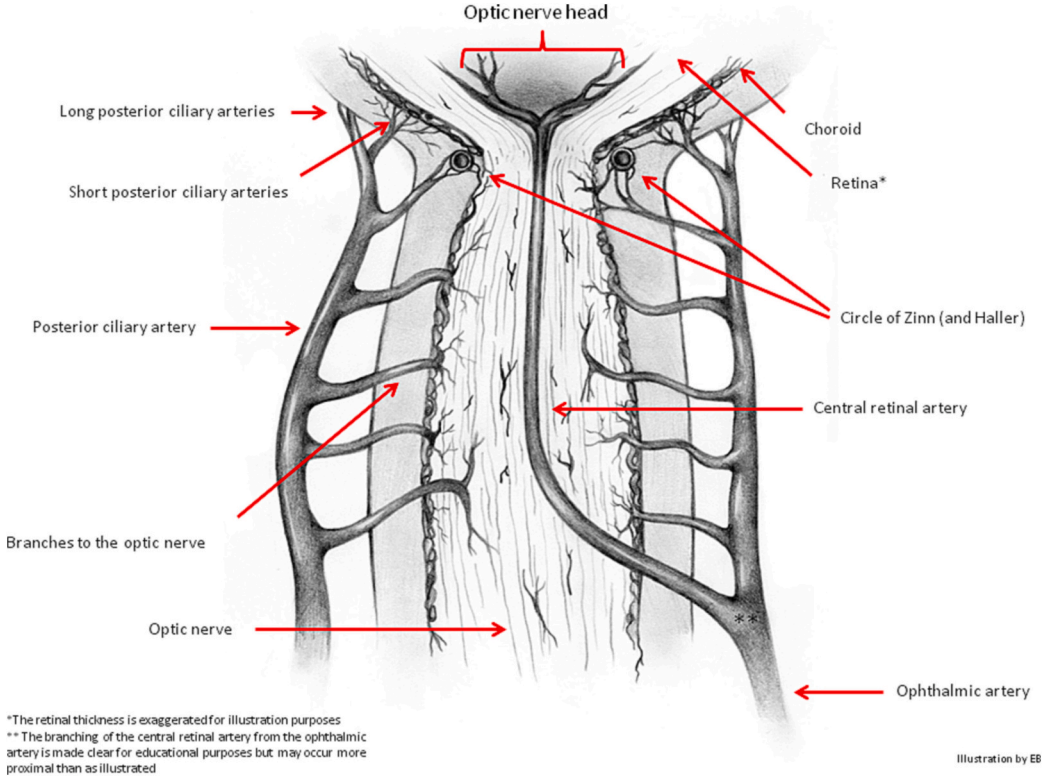

Fig. 1. Cross section illustration of the ocular blood supply showing perfusion of the optic nerve, choroid, and retina via branches from the ophthalmic artery. The posterior ciliary arteries, central retinal artery, and Circle of Zinn (and Haller) are shown. Concepts for this original illustration were derived from established knowledge of anatomy from previous literature [10,11].

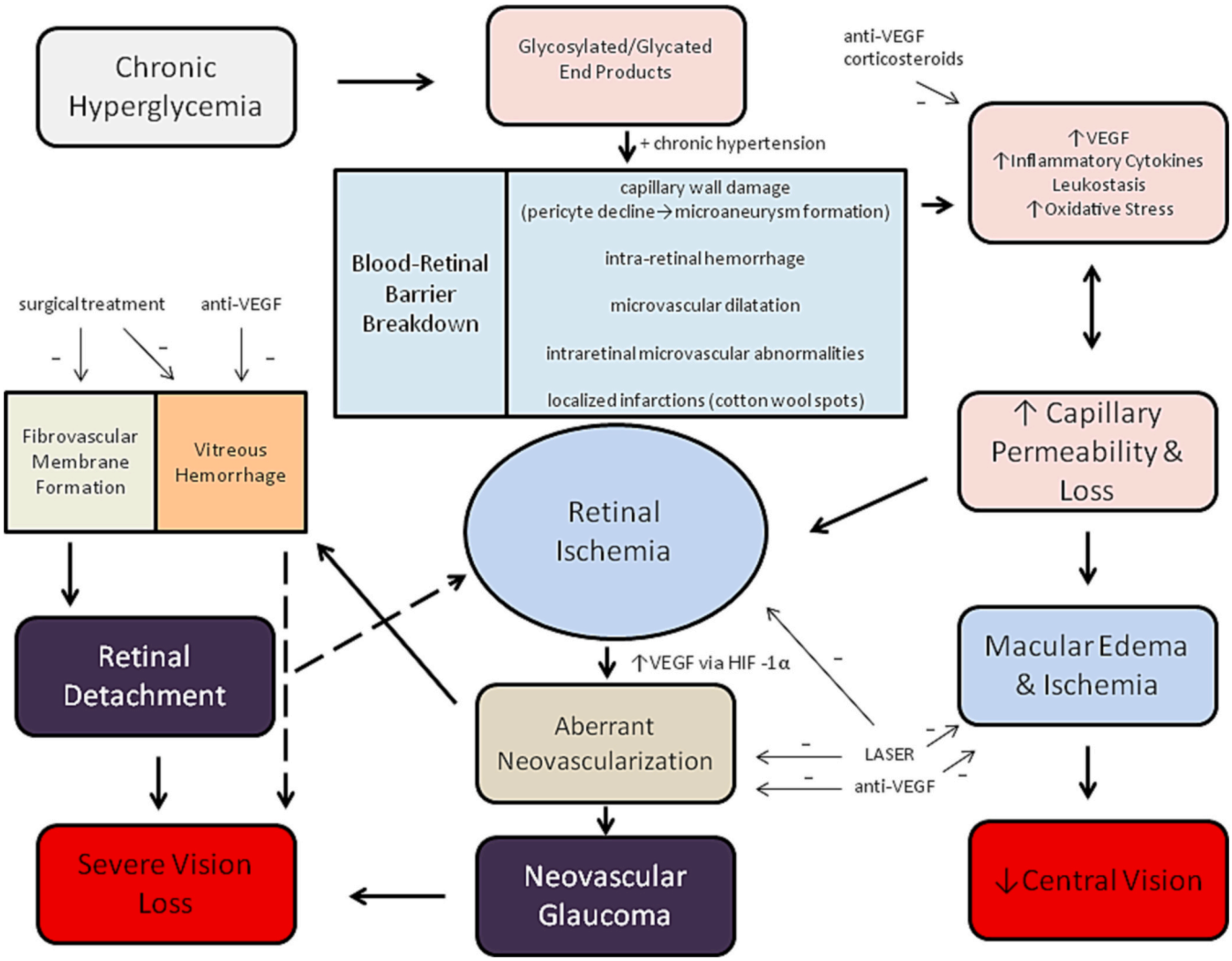

Fig. 2. Schematic diagram showing the basic pathophysiology of diabetic retinopathy. Chronic hyperglycemia leads to capillary damage and a breakdown of the blood-retinal barrier. This leads to both macular edema, and retinal ischemia. The consequence of maculopathy is central vision decline. The new hypoxic environment causes a surge of VEGF that stimulates aberrant neovascularization leading to retinal detachment and neovascular glaucoma. The end stage of this proliferative pathway if untreated is catastrophic vision loss. The dotted arrows indicate that vitreous hemorrhage *may* directly cause severe vision loss, and retinal detachment leads to additional retinal ischemia by an alternative mechanism (it is mechanically separated from a portion of its blood supply while detached).

endothelial cells is vascular endothelial growth factor (VEGF), introduced in 1989 [21]. VEGF is released in hypoxic conditions via hypoxia induced factor-1α (HIF-1α) [20,22]. VEGF then spawns the growth of aberrant vasculature in response, further converting the state of ischemia into proliferative disease [23] (Fig. 2). This new vasculature grows into the vitreous gel structure, and lacks the integrity of normal retinal vasculature (Figs. 3C, D; 4 A, B). This leads to bleeding and mechanical damage of the retina and further deleterious angiogenesis from ongoing ischemia [24]. Ultimately there is irreparable loss of normal anatomy with significant loss of vision and blindness [25].

3.2. Diabetic macular edema and ischemia

Vision decline in diabetic patients is most commonly caused by diabetic macular edema (DME) [26]. DR that is allowed to progress can result in extravascular fluid leakage from the capillaries in the macula. Pericyte health decline, and endothelial cell damage ultimately lead to breakdown of the blood-retinal barrier, and increased levels of VEGF [18,27,28]. The pathophysiology of DR and DME is complex and multifactorial and extends beyond VEGF-mediated pathways. Alternative cytokines such as interleukins (e.g., IL 6, ILβ), adhesion molecules, eicosanoid derivates, inflammatory cytokines such as tumor necrosis factor -α (TNF-α) along with leukostasis give way to inflammation, and continued pericyte decline [15,16,29]. DME can be focal (localized within regions of the macula) or diffuse (throughout the macular region) and necessitate different approaches to treatment with laser being more difficult to manage diffuse macular edema [26]. DME may occur both in non-proliferative and proliferative DR, although diffuse DME is more associated with advanced DR [26].

Continued microvascular loss in the macula may manifest as diabetic macular ischemia (DMI) (Fig. 4C, D) [30]. Macula ischemia alone may account for vision decline, and has yet to have a standard approach to treatment [31]. Traditional retinal angiography with fluorescein sodium is unlikely to capture the full breadth of the macular multi-capillary plexus layers [7]. Newer technologies such as optical coherence tomography angiography (OCTA) allow for better assessment of retinal capillary beds without the usage of dye [7,31]. However, there is no currently accepted standardized method of assessment of DMI with OCTA [31]. In addition, clinical assessment with visual acuity levels do not always correlate with the degree of DMI or FAZ morphology [31]. These newer tools will help to better assess capillary health over time in a non-invasive way and provide guidance in interpretation in the setting

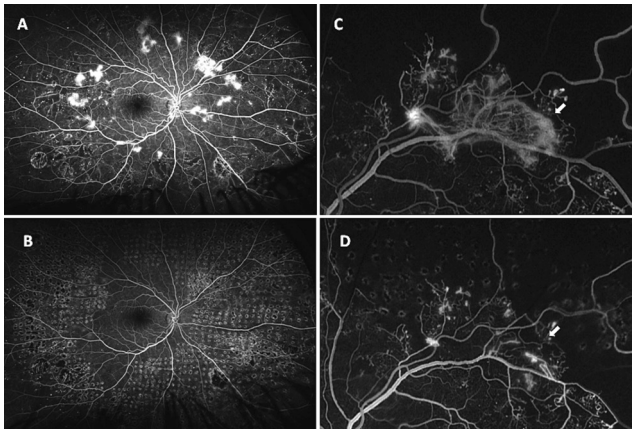

Fig. 3. Fluorescein retinal angiography of proliferative diabetic retinopathy. (A) Asymptomatic capillary loss in the mid-peripheral retina in a 21-year-old Type 1 diabetic female. (B). Quiescent disease following pan-retinal photocoagulation treatment alone. (C). Neovascularization (arrow) at the border of retinal perfusion and ischemia. (D). Regression of neovascularization (arrow) following treatment with anti-VEGF and retinal photocoagulation.

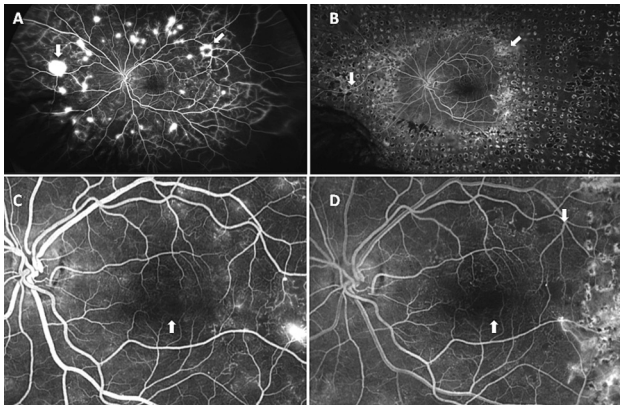

Fig. 4. Proliferative diabetic retinopathy (PDR) with macula ischemia. Leakage from mid-peripheral angiogenic vessels (A, arrows) and regression (B, arrows) following pan-retinal photocoagulation treatment alone as seen on fluorescein angiography. C—D. Loss of macular capillaries over a four-year period despite quiescence of PDR following treatment.

of DR [7,30].

3.3. Proliferative diabetic retinopathy (PDR)

The most advanced form of DR is PDR [15]. This category is end organ ocular damage from diabetes at its highest level and can range from localized growth of aberrant vasculature to mechanical destruction of the retina with fibrotic transformation and eventual neovascular glaucoma. The VEGF-A isoform through action of the VEGF receptor 2 stimulate the permeability of microvasculature and endothelial proliferation as well migration [23,32]. In response to hypoxic conditions, new vessels emanate from the border of perfused and non-perfused retina (Fig. 3C,D) and from the optic disc (Fig. 5). These vessels penetrate the internal limiting membrane and grow into the posterior vitreous cortex forming a fibrovascular membrane complex (FVM) [24,25]. These vessels, due to their compromised integrity often bleed into and under the vitreous gel obscuring vision and the retinal surface. Continued growth leads to antero-posterior and tangential traction with contraction of the vitreous cortex – fibrovascular membrane complex [24,29]. The tethering of vessels from the retina into the vitreous cortex causes epiretinal trauma and tractional retinal detachments [25]. The

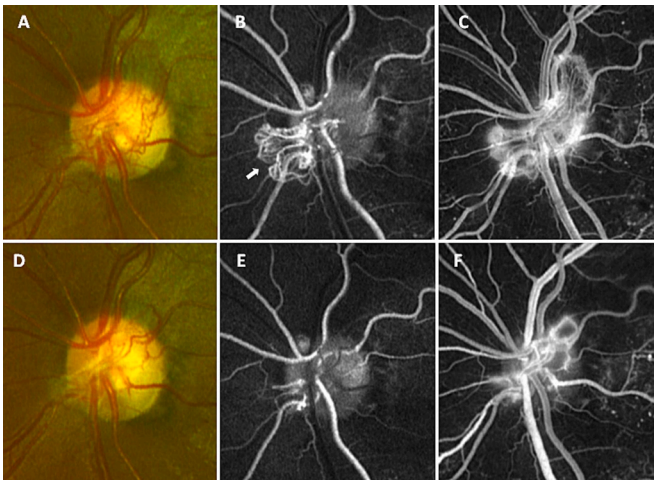

Fig. 5. Neovascularization of the optic disc. Pre-treatment appearance (A) with early filling of neovessels (B, arrow), and late leakage (C) on angiography. Regression of neovascularization (D) following combined treatment with anti-VEGF and pan-retinal laser. *E*-F showing angiographic evidence of regression.

eventual ischemia of the outer retina (now mechanically separated from the choriocapillaris perfusion) combined with inner retinal ischemia from inherent retinal capillary loss results in full thickness retinal ischemia along with mechanical damage. A pro-fibrotic response from growth factors such as transforming growth factor beta (TGFβ) and connective tissue growth factor (CTGF) cause eventual fibrotic change [33,34]. Fibrotic bands can often be seen in chronic diabetic tractional retinal detachments (Fig. 6). The fibrotic response along with a combined positive feedback loop of ischemic drive eventually lead to a continuous cycle of catastrophic damage [24,29].

3.4. Treatment of diabetic retinopathy

The mainstay of systemic treatment in DR is glycemic control, blood pressure control, and generalized risk factor reduction for vascular disease [35]. Treatment for DR beyond this is dependent on the longevity, severity, and current vision along with a host of social considerations. The management plan can range from observation with risk factor reduction to complex vitreoretinal surgery [24]. Prior to the anti-VEGF era, laser application for the treatment of DME was the most widely used option [17]. Focused laser to areas of capillary leakage is an effective way to reduce edema by way of induction of vascular remodeling and a decrease of hydrostatic pressure [17,36]. Remodeling with subsequent vasoconstriction at and around the site of vascular leakage following laser treatment still effectively can be used independently and also in combination with intraocular anti-VEGF injection [36,37]. Newer approaches to macular laser including subthreshold (without retinal coagulation) micropulse laser have been investigated with growing favorable data [38,39]. The advantage of the 810-nm diode, and 577-nm yellow laser technology compared to conventional laser is a lack of scarring as there is no protein denaturation [39]. For center-involving DME, there is sufficient evidence for effective treatment with

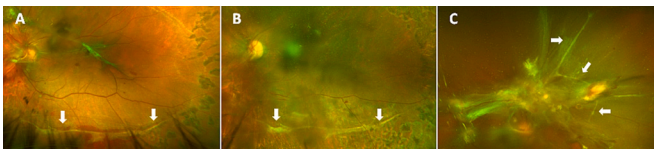

Fig. 6. Subretinal fibrosis in advanced Type 2 proliferative diabetic retinopathy. (A). Preoperative subretinal banding (arrows) that remains (B, arrows) following surgical repair. (C). More advanced subretinal fibrosis (arrows) in a different patient with chronic diabetic tractional retinal detachment.

intraocular anti-VEGF [40,41]. There are currently four medications that are FDA approved for the treatment of DME: ranibizumab, aflibercept, faricimab-svoa, and brolucizumab [40,42–45]. Bevacizumab has been used off label since 2005 as a cost-effective agent, and has been shown to reduce center-involving DME [46]. However, only 35 % of DME eyes completely respond to bevacizumab after six months of treatment [47]. Refractory DME has been targeted with other agents; aflibercept showing the highest affinity to bind VEGF. There is increased success in the treatment of DME with aflibercept compared to bevacizumab and ranibizumab in those with poorer pre-treatment vision [48]. Faricimab-svoa is both an anti-VEGF and anti-angiopoietin-2 (Ang-2) antibody which separates it from its predecessors [44,49,50]. Brolucizumab is a low molecular weight single-chain anti-VEGF antibody fragment [45]. Recent Phase III randomized controlled trials have shown positive results for both agents with significant reduction in DME [45,50]. Both agents were FDA approved in 2022 for the treatment of DME. As they are relatively new, there is still the need for more current scientific data regarding their efficacy for DME in the real world. Treatment with intraocular steroids has also been shown to be effective as the physiology of DME formation involves pro-inflammatory pathways mentioned above [27] (Fig. 2). Triamcinolone and dexamethasone are both used in the treatment of DME as primary and adjunctive agents [51,52]. Fluocinolone acetonide implants have also garnered interest in the treatment of DME as intraocular sustained release implants [53].

Pan-retinal photocoagulation (PRP) is the gold standard of treatment for PDR and has been the standard of care for over five decades [54,55]. The usage of anti-VEGF agents as sole treatment in PDR is also being considered, with optimistic initial data. Prospective multicenter trials have shown its non-inferiority to PRP laser at 5 years follow up [56]. PRP addresses the hypoxic environment created by retinal ischemia [36,54]. It treats retinal ischemia directly by ablation and allows for increased oxygen diffusion from the choroidal circulation [17,36,54,55]. Application of laser in a pan-retinal fashion may however cause reduction of night vision and/or reduction of the visual field as it reduces the amount of retina available for functional vision requirements [57,58]. These known co-morbidities of laser treatment highlight some of the potential benefits of anti-VEGF monotherapy for PDR. Patients treated with anti-VEGF injection monotherapy however, have also shown visual field decline beyond two years of treatment, the reason for which requires further investigation [56]. PRP continues to be highly effective (Figs. 3B, 2B) and has been shown to have minimal effects on DME in the case of co-existing disease particularly when anti-VEGF is co-administered [56,59]. PRP also potentially circumvents the long-term need for repeated intraocular injections as often as once per month in the clinic on an already burdened patient population. A summary of the common and current non-surgical treatment modalities for DR are shown in Table 1.

Surgical management of advanced PDR is highly effective but outcomes range depending on the health of patient, the health of the retina at the time of repair, and the severity level of TRD if present [24]. These surgical repairs typically require advanced surgical technique and may be affected by surgeon experience. At the time of surgical repair, the FVM-vitreous cortex complex is removed (Fig. 7) in areas of affected retina and laser is applied to the retina in a pan-retinal pattern, so the mechanical component as well as the underlying ischemic component are both treated [24]. Surgical treatment may be the only viable option when faced with permanent loss of vision for some patients with advanced disease. Pre-treatment with anti-VEGF (Fig. 7D) has been shown to be helpful in the surgical repair in advanced PDR even in the setting of TRD [24].

Table 1
Summary of Current (non-surgical) Treatment Modalities for Diabetic Retinopathy in the United States.

Name	Treatment modality	Category	General indications	Effect
bevacizumab (off label)	Intravitreal injection [1.25 mg/0.05 mL]	Anti-VEGF 149 kDa monoclonal antibody	DME, PDR	↓[VEGF-A] activity [40]
ranibizumab	Intravitreal injection [0.3 mg/0.05 mL]	Anti-VEGF 48 kDa monoclonal antibody fragment	DME, PDR	↓ macular edema [40,45,48,49] [a]rapid (days) regression of neovascularization [60]
aflibercept	Intravitreal injection [2 mg/0.05 mL]	Anti-VEGF, anti-PIGF (soluble decoy receptor) 115 kDa fusion protein	DME, PDR	
faricimab-svoa	Intravitreal injection [6 mg/0.05 mL]	Anti-VEGF + anti-angiopoietin-2 (Ang-2) antibody	DME	
brolucizumab-dbll	Intravitreal injection [6 mg/.05 mL]	Anti-VEGF, 26 kDa single chain antibody fragment	DME	
triamcinolone acetonide	Intravitreal injection suspension [4 mg/0.1 mL]	(Acetonide) crystalline corticosteroid	DME (focal, diffuse)	↓retinal capillary permeability [61]
dexamethasone	Intravitreal implant (0.7-mg sustained release) poly(lactic acid-*co*-glycolic acid) (PLGA) matrix [62]	(Betamethasone) corticosteroid	DME (focal, diffuse)	↓VEGF expression [61] ↓ [ICAM-1] [51,61]
fluocinolone acetonide	Intravitreal implant (0.19-mg sustained release)	(Acetonide) corticosteroid	DME (focal, diffuse)	↓phospholipase A2 [61,62]
532-nm, 577-nm, 810-nm (Nd:YAG, diode, sub-threshold micropulse) LASER	LASER application to retina	LASER	DME (focal application) PDR (pan-retinal application)	capillary leakage site closure, stimulation of vascular remodeling [17,36,39] ablation of ischemic retina [36,54] ↓hypoxia → ↓[VEGF] [13,36] slow (months) regression of neovascularization [54,63]

Abbreviations: VEGF = vascular endothelial growth factor; PIGF = placental growth factor; DME = diabetic macular edema; PDR = proliferative diabetic retinopathy; ICAM-1 = intracellular adhesion molecule-1; Nd:YAG = neodymium-doped yttrium aluminum garnet; LASER = light amplification by the stimulated emission of radiation.

[a] there is currently a paucity of clinical evidence for faricimab-svoa and brolucizumab-dbll's effect on retinal neovascularization in PDR (both agents were FDA approved in 2022 for DME).

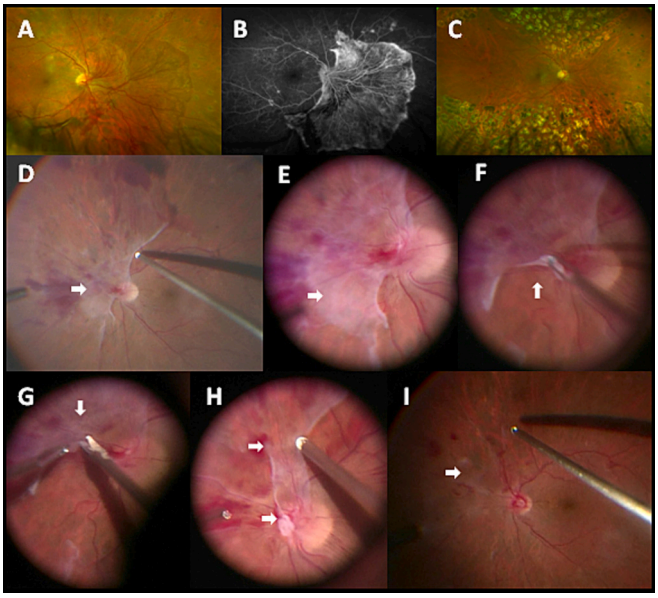

Fig. 7. Fibrovascular Membrane (FVM) complex in a Type 2 diabetic male with surgical repair. (A). Fan-shaped retinal angiogenesis emanates from the optic disc on presentation. Fluorescein angiography (B) showing the extent of neovascular growth and adjacent ischemia. (C) Quiescence of PDR following surgical repair with vitrectomy. D—I. Surgical steps in repair. FVM has opaque appearance (D, E arrow) following pre-treatment with bevacizumab four days prior to the operation. (F, G). Manipulation and resection of FVM with intraocular scissors and forceps. (H) Last remaining portion of FVM on retinal and optic nerve removed with vitreous cutter assistance. (I). Appearance immediately after removal of FVM, arrow points to area where FVM was previously.

4. Cardiovascular disease and diabetic retinopathy

In contrast to what has been historically thought of as separate entities because of vascular caliber, the bridge between microvascular and macrovascular disease is shortening. The number of studies evaluating this association has increased since the late 1990s and early 2000s. An early study in the late 1990s showed that cardiovascular disease was nearly twice as likely in those with diffuse diabetic macular edema compared to focal macular edema in DR [26]. In a much more recent study in 2021, Type 2 diabetics even with a mild stage of retinopathy had an increased 5- year risk of first-time myocardial infarction (MI) and congestive heart failure (CHF) compared to those without retinopathy [64]. In large cohort studies such as the 2018 Finish Diabetic Nephropathy Study (FinnDiane), a cohort of Type 1 diabetics were evaluated for a median of 9.5 years [65]. In univariate analysis, severe diabetic disease (defined as a history of photocoagulation) was an independent predictor of cardiovascular events, peripheral vascular disease and coronary artery disease [65]. This was true even without the presence of diabetic kidney disease [65]. Cardiovascular disease was also increased in patients with diabetic kidney disease with the presence of severe diabetic retinopathy compared to without [65]. The reasons for this are yet to be elucidated but it is possible that overlapping factors may play a role in both micro and macrovascular disease processes. HIF-1 for example, is a key component in the stimulation of VEGF in retinal microvasculature [22]. HIF has also been shown to be involved in large vessel plaque advancement [65]. Findings such as this shed light on possible reasons why a spectrum of vascular damage may be more prevalent than previously thought.

In the landmark Wisconsin study (2004), arteriolar to venular diameters and DR were evaluated for risk of cardiovascular disease and mortality with over a 60 % retention rate for 20 years follow up. Severity of DR and lower arterio-venous ratio (AVR) was statistically associated with increased odds for MI [66]. Severity of DR was also associated with a higher risk of mortality, and increasing trend of heart-related mortality with increasing severity of DR in multivariate analysis [66]. Both measured variables correlated with duration of diabetes and blood pressure and diabetic kidney disease [66]. There are however inconsistencies and significant gaps in the data obtained from larger studies. The findings mentioned in the FinnDiane were in contrast to studies such as the Wisconsin study which showed a lack of independent risk increase of cardiovascular events from diabetic retinopathy alone in Type 1 diabetics [66]. The Wisconsin Study also did not find a significant correlation between glycemic levels and coronary disease [66]. In the longitudinal analysis of patients with Type 1 diabetes from Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) published in 2021, those with advanced diabetic retinopathy had a higher association with cardiovascular disease and major events such as MI and stroke [67]. However, PDR independently was not significantly associated with increased cardiovascular disease or events once general risk factors were taken into account [67].

Vessel caliber as a unique finding has been investigated in a number of studies as it relates to cardiovascular disease and risk of mortality. The Atherosclerosis Risk in Communities Study (ARIC) started in the late 1980s prospectively evaluated arteriolar-venular ratio (AVR) by fundus photography [68]. The ARIC study published in 2002 found a significant association between decreased AVR and coronary heart disease (MI, silent MI) in women (but not men) after adjustment for other variables [68]. Revascularization procedures were not significantly associated with lower AVR in either gender but presence of retinopathy (hypertensive) was more likely to be associated with CVD in women [68]. Miller and colleagues studied data from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study and also focused on retinal vessel size. They found that there was a risk increase of 42 % in coronary artery disease for each standard deviation decrease of arteriolar size even when general risk factors were accounted for [69]. The Blue Mountain Eye Study group in Australia reported in their analysis of over 3000 individuals that arteriolar caliber and venular size were important predictors of cardiovascular disease mortality [70]. Lower AVR was associated with more severe hypertension. There was a 1.5-to-2-fold increase in cardiovascular disease associated death with larger venular size in both genders aged 49–75, but that lower arteriolar caliber and AVR was associated with mortality in women below the age of 75 [70].

5. Conclusions

The longitudinal studies in the literature have provided a wealth of information regarding the importance of small vessel disease in cardiovascular disease risk. Variations in data and data analysis may have influenced confounding conclusions. However, the trend of information that has been obtained shows that microvascular disease may reflect a risk for the development and association of both microvascular and macrovascular cardiovascular disease. Vessel caliber may be an important indicator of mortality risk even without findings of end organ damage like diabetic retinopathy. The microvascular damage from similar conditions may work differently between men and women. Further research is required to better elucidate these subtleties and may pave the way for a more specific approach to risk stratification and prevention of disease.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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