Review Article

Asymmetric diabetic retinopathy

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Increasing prevalence of diabetes mellitus warrants recognition of factors related to asymmetric diabetic retinopathy (DR). This thematic synthesis based on an iterative literature review conducted in Medline and Google Scholar pertaining to diabetes with coexistent asymmetry of retinopathy included 45 original articles, 21 case reports and series, and 18 review articles from 1965 to 2020. Asymmetric DR is defined as proliferative DR (PDR) in one eye and nonproliferative, preproliferative, background, or no DR in the other eye lasting for at least 2 years. It is observed in 5%–10% of patients with PDR. Associated factors can be divided into (i) vascular: carotid obstructive disease, ocular ischemic syndrome, and retinal vascular diseases; (ii) Inflammatory: uveitis, endophthalmitis, and Fuchs' heterochromic cyclitis; (iii) degenerative: posterior vitreous detachment, high myopia and anisometropia, uveal coloboma, retinal detachment, retinitis pigmentosa, and chorioretinal atrophy and scarring; (iv) cataract surgery and vitrectomy; and (v) miscellaneous: elevated intraocular pressure, glaucoma, amblyopia, retinal detachment, and optic atrophy. The gamut of diagnostic modalities for asymmetric DR includes thorough ocular examination, slit-lamp biomicroscopy, fundus photography, fundus fluorescein angiography, optical coherence tomography, and newer modalities such as ultra-widefield fluorescein angiography and optical coherence tomography angiography, along with a complete systemic evaluation and carotid Doppler studies. The differential diagnosis includes other causes of retinal neovascularization that may present in an asymmetric manner, such as sickle cell retinopathy, retinal vein occlusions, and featureless retina. This review discusses in detail the aforementioned considerations and draws a comprehensive picture of asymmetric DR in order to sensitize ophthalmologists to this important condition.

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Diabetic retinopathy (DR) is a microvascular disease leading to capillary closure due to various intra- and extravascular factors and is considered primarily a microangiopathy. Progression of DR in the two eyes is usually symmetrical but at times may be varied, with one eye showing slow or no progression. Such a condition is an exception to the rule and has been observed in 5%–10% of cases of PDR[1-5] Recognition of progression of DR is the key to management to prevent blindness; therefore, the identification of asymmetric DR is important to decide treatment protocols and predict the clinical course. Moreover, with rising global prevalence of diabetes mellitus (estimated 9.3% [463 million] in 2019),[6] the recognition of factors related to asymmetric diabetic retinopathy (DR) has become extremely valuable for early recognition and treatment of vital comorbid systemic and ocular conditions. This paper aims to review the available literature on asymmetric DR, present a comprehensive picture on the topic, and sensitize ophthalmologists to this important condition.

Method of Literature Search

To prepare this thematic synthesis, the ENTREQ statement was used for iterative literature review in Medline (search based on MeSH and keywords) and Google Scholar with no date, country, or language restrictions. Search words used included "asymmetric," "unilateral," "diabetes," "complications," "diabetic retinopathy," "progression," "regression," "carotid occlusive disease," "ocular ischemic syndrome," "retinitis pigmentosa," "myopia," "anisometropia," "carotid Doppler," "retinal imaging," etc. Literature pertaining to asymmetric diabetic retinopathy due to diabetes itself and due to coexistent disease were included. Three independent reviewers assessed the content and utility of the findings of 1250 observational studies and case reports through 1965–2020 and reviewed the title, abstract, and full texts to manually extract the data from results, discussion, and conclusions and inductively derive the themes and interpretations. Manuscripts where retinopathy was not conclusively attributable to diabetes, those where asymmetry did not fulfill any definition of asymmetric DR, those not mentioning possible mechanisms behind the association between disease entities and asymmetric DR, and those with asymmetric maculopathy but not retinopathy were excluded. Thereafter, all three reviewers reached a consensus on 45 original articles, 21 case reports and series, and 18 review articles included.

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Asymmetric DR – Definition

Historically, various authors have defined asymmetric DR [Table 1]. Although there is no universal criterion to define asymmetry, most authors now believe that asymmetry should be recognized once it has remained for two years as it has been seen that within this period, DR in the lesser affected eye may slowly evolve to reach symmetry between the two eyes (short-term asymmetry). Shorter follow-up periods are not sufficient to rule out short-term asymmetry and the effect of select intraocular factors and treatment influences.[3] Recently, asymmetric DR has been defined as the presence of PDR in one eye and nonproliferative (NPDR), preproliferative (PPDR), background (BDR), or no DR in the other eye lasting for at least two years.[7] It is pertinent to note that treated or treatment-naïve diabetic maculopathy is not included in this recent definition of asymmetric DR.

Associated Modifying Factors

Various factors cause asymmetry of DR by accelerating or retarding its appearance or progression. These are related to both systemic and ocular status and must be considered while evaluating a case of asymmetric DR [Table 2].[10]

Age and asymmetric DR

Most studies on asymmetric DR have been conducted on type II diabetes patients; however, the age ranges from 21 to 84 years across various studies.[1,3,9] Among PDR patients with NPDR in the other eye, a bimodal distribution of age has been observed, with peaks in the third and sixth decades.[1] Retinopathy has a greater tendency toward symmetry in younger patients, consistent with possible preponderance of older age and unilateral PDR.[2]

Vascular causes

Asymmetric DR can be a significant sign of mortal systemic disorder.[7] Among patients with PDR in one eye and NPDR in the other, vascular disease has been observed in 63%, including hypertension in 36%, cardiac problems in 43%, and other circulatory problems in 14%.[1,2] Brain infarction has been reported to be much more common (41.7%) in patients with asymmetric DR than those with symmetric DR or controls (7.7%) with similar baseline epidemiological characteristics.[5] Ophthalmologists have an important role in the recognition and counseling of patients having these disorders, with rationale and appropriate referrals to other specialists.

Carotid occlusive disease (COD)

Among the vascular causes, this is the first disorder to be implicated in the development of asymmetric DR.[8] However, PDR has been found to exist ipsilateral and contralateral to hemodynamically significant carotid artery stenosis in an equal number of cases. Hence, the protective or aggravating effect of carotid artery disease against PDR was disputed.[4] These conflicting reports about the progression of DR in carotid stenosis may be the result of a difference in time of onset and relative severity of the two entities.

Etiology: Usually, if significant DR develops before severe carotid occlusion, added ischemia may be responsible for the progression of the ipsilateral DR. However, in a few cases of DR with coexistent hypertension, moderate carotid stenosis developing before DR decreases its severity ipsilaterally[11] and leads to asymmetry of DR because of added deleterious effects of hypertension on the contralateral side.[10,12,13] It has been hypothesized that reduction in retinal intravascular pressure could retard leakage of blood, thereby preventing "retinitis proliferans." A retinal diastolic difference of 15% or more as measured by ophthalmodynamometry, with lower pressure always in the eye with less advanced or minimal retinopathy, has been found in adults with asymmetric DR.[8] Significant association has been shown to exist between low ocular perfusion pressures and incidence of retinopathy in juvenile-onset diabetic subjects after correcting for covariates.[14]

Clinical features: Apart from asymmetry in fundus findings as defined by Turgut,[7] COD is suspected when a bruit is auscultated at the jaw. Hemodynamically significant carotid artery stenosis occurs when an atherosclerotic lesion occludes at least 75% of the carotid bulb or proximal internal carotid artery as seen on duplex scanning. The accompanying Doppler study may or may not be abnormal. Reversal of flow through the carotid system detected on Doppler study implies total internal carotid artery obstruction.[4]

Treatment and Prognosis: Lifestyle modifications, namely regular exercise, smoking cessation, proper diet, and

Table 1: Historical Definitions of Asymmetric Diabetic Retinopathy

Authors	Year	Classification system for DR	Definition	Minimum duration of follow-up
Gay and Rosenbaum[8]	1966	Ballantyne's classification	Difference of at least two stages between the two eyes	1 year.
Valone[1,2]	1981	Grading of angiopathy and exudation in NPDR and of proliferation in PDR	PDR in one eye, and no DR or NPDR in the other eye	3 months
Browning *et al.*[3]	1988	Diabetic Retinopathy Study	PDR in one eye, and BDR or no DR in the fellow eye	2 years
Duker *et al.*[4]	1990	Diabetic Retinopathy Study	High-risk PDR in one eye, and no evidence of concurrent PDR or PPDR in the opposite eye	2 years
Schatz *et al.*[9]	1994	Grading of microaneurysms, hemorrhages, exudates, and macular edema on fundus photographs and fluorescein angiograms in a radius of three-disc diameters from the fovea (range of possible scores: 0-16)	Difference of more than 3 points between the two eyes.	2 months

DR=Diabetic retinopathy, BDR=background DR, PPDR=preproliferative DR, NPDR=nonproliferative DR, PDR=proliferative DR

Table 2: Modifying Factors for Asymmetric DR Prevalence and Progression

Modifying factors	Clinical conditions	Major mechanisms	Relationship with ipsilateral DR
Vascular	Carotid obstructive disease	Carotid stenosis occurring after DR onset causes increased ischemia	Progression
		Carotid stenosis developing before DR with coexistent hypertension	Protection
	Ocular ischemic syndrome	Added ischemia	Progression
	Retinal vascular diseases Unilateral BRVO Unilateral CRAO	Thinning of inner retina Reduced retinal oxygen demand	Protection
Inflammatory	Uveitis Acute retinal necrosis in Herpes Zoster infection Toxoplasmosis Other causes	Blood-ocular barrier breakdown Vasculitis-induced ocular ischemia Free-radical induced damage Increased VEGF and intraocular cellular fibronectin Efflux of albumin and lymphocytes into aqueous and vitreous Juxtapapillary retinitis and vitritis in toxoplasmosis	Progression
	Endophthalmitis	As in Uveitis Effect of cataract surgery and vitrectomy	Progression
	Fuch's heterochromic iridocyclitis	Sympathetic denervation hypersensitivity, reflex vasoconstriction, reduced perfusion	Protection
Degenerative	Posterior vitreous detachment	Removal of scaffold for neovascularization Release of subtle tractions on retina	Protection
	Axial refractive errors Unilateral, High or Anisomyopia Anisometropia>1D	Reduced retinal metabolic demand Stretched vessel walls, increased pressure attenuation Effect of uveal coloboma and PVD Thinning of veins Dilution of VEGF	Protection
	Uveal coloboma	Lack of nutrition from the choroid in colobomatous area Outer retinal atrophy Relative decrease in oxygen demand	Protection*
	Retinitis pigmentosa	Greater oxygen and nutrient flux from choroid to inner retina Secondary attenuation of retinal blood vessels Early PVD Release of a cytokine that inhibits neovascularization from the retina Effect of Optic atrophy	Protection
	Healed choroiditis	Chorioretinal atrophy and scarring, reduced metabolic demand	Protection
	Optic atrophy	Reduced metabolic demand	Protection
Surgery	Cataract surgery	Breakdown of blood-retinal barrier Increased inflammation including prostaglandin production	Progression
	Vitrectomy	Increased diffusion and clearing of sequestered growth factors PVD Increased retinal oxygen saturation	Protection
Miscellaneous	Elevated intraocular pressure and glaucoma	Decreased metabolic demand Decreased perfusion	Protection
	Amblyopia, visual deprivation, and retinal detachment Idiopathic	Decreased metabolic demand Decreased perfusion	Protection

DR=diabetic retinopathy, PVD=posterior vitreous detachment, VEGF=vascular endothelial growth factor. *Cannot be conclusively opined

control of blood pressure, are important. Anticoagulation with aspirin alone or aspirin with dipyridamole as well as statins may delay the occurrence of cerebrovascular accidents. Angiotensin-converting enzyme inhibitors reduce inflammation and prevent thrombosis. Carotid endarterectomy (CEA) in presence of severe carotid stenosis ipsilateral to the eye with PDR may preserve vision in the eye.[15] Treatment of NPDR and PDR remain the same as per Early Treatment of Diabetic Retinopathy Study (ETDRS), Diabetic Retinopathy Study (DRS), and Diabetic Retinopathy Clinical Research Network (DRCR.net) protocols.[16–18]

Ocular ischemic syndrome (OIS)

Ocular ischemic syndrome encompasses a spectrum of clinical findings that result from chronic ocular hypoperfusion, involving both anterior and posterior segments.[19] Conditions that might present with OIS are listed in Table 3. The incidence is not precisely known, and 7.5 cases per million is likely

Table 3: Associations of Ocular Ischemic Syndrome[23]

Associations	Clinical conditions
Systemic	Atherosclerosis of internal carotid/ ophthalmic artery
	Dissecting aneurysm of the carotid artery
	Giant cell arteritis
	Fibrovascular dysplasia
	Takayasu arteritis
	Aortic arch syndrome
	Behçet's disease
	Trauma or inflammation causing carotid artery stenosis
	Radiotherapy, e.g., for nasopharyngeal carcinoma
Ocular	Intravitreal anti-VEGF injections

an underestimation.[19] Approximately 70% of patients with COD may initially present with OIS,[20] and it may even be the first manifestation of bilateral carotid occlusive disease.[21] Asymmetric DR due to OIS was found to be associated with iris neovascularization in 45.5% of patients in a series.[22]

Etiology: Severe carotid stenosis resulting in OIS definitely results in a hypoperfusion proliferative retinopathy and can overlay on preexisting DR to produce a result impossible to distinguish from PDR clinically. Stenosis of 90% or more of the ipsilateral internal carotid artery (ICA) lumen presents clinically as OIS as flow in the CRA gets halved,[24] although it may also occur with lower grades of ICA stenosis.[25,26] Patients who suffer from new collateral patency of posterior communicating artery and middle cerebral artery stenosis may be more susceptible to OIS. Flow reversal in the ophthalmic artery (OA) produces the steal phenomenon from ocular circulation to the low-pressure intracranial circuit, causing a reduction in the retrobulbar blood flow.[27,28]

Clinical features: Visual loss, orbital pain, visual field changes, neovascularization of the iris, neovascular glaucoma, iridocyclitis, asymmetric cataract, iris atrophy, and sluggish reaction to light can occur. Fundus changes include narrowed retinal arteries and dilated retinal veins, perifoveal telangiectasias, mid-peripheral retinal hemorrhages, microaneurysms, neovascularization, cherry-red spot, cotton-wool spots, vitreous hemorrhage, and normal-tension glaucoma.[23]

Diabetic patients with OIS have significantly lower systolic, diastolic, and mean anterograde OA blood-flow velocities than the controls. Systolic blood flow velocities in rubeotic eyes with OIS are significantly lower than in rubeotic eyes with PDR alone.[29] The most sensitive signs include peak systolic velocity (PSV) of blood in the CRA and choroidal thickness while the arm-to-retina transit time is most specific.[27] This is important to distinguish DR from hypoperfusion retinopathy superimposed on DR. A statistically significant lowering of mean PSV of the ICA has been found in eyes with PDR, compared to NPDR, with no significant difference in the mean resistive index.[30] FFA shows delayed arm to retina transit time, prolonged arteriovenous transit, choroidal perfusion defects, and late staining of arteries and veins. With severe OIS, choroidal vascular insufficiency and subsequent outer retinal ischemia can cause a decreased "a" wave on electroretinogram.[4]

Treatment and Prognosis: It is important to recognize OIS in DR because of the poor visual prognosis once neovascularization develops.[22,31] Resolution of proliferative venous stasis retinopathy has been reported after carotid endarterectomy in cases of asymmetric DR with posterior segment neovascularization due to OIS associated with critical ipsilateral carotid stenosis.[15]

Retinal vascular disease

Among the retinal vascular diseases, only unilateral branch retinal vein occlusion (BRVO) correlates significantly with the presence of asymmetric PDR.[3] In a series of 12 patients with no abnormality in one eye, DR in the fellow eye was accompanied by BRVO in 50% of the patients.[1,2] Central retinal artery occlusion also results in thinning of the inner retina, including the ganglion cell layer, so that retinal oxygen demand is reduced, leading to asymmetric DR.[32]

Inflammatory Diseases

Increase of VEGF or pro-inflammatory cytokines in different conditions is believed to exaggerate DR progression in many conditions which, if unilateral, can lead to asymmetric DR.[33]

It has been postulated that severe inflammation causes additional blood–ocular barrier breakdown and vasculitis-induced ocular ischemia superimposed on the effect of DM. Intraocular inflammation and DR may be characterized by similar biochemical mechanisms such as free-radical induced oxidation of lipids and carbohydrates toxic to retinal endothelium and pericytes.[34] High intraocular levels of vascular endothelial growth factor (VEGF) have been implicated due to its effects on angiogenesis and vascular permeability. Intraocular inflammation (regardless of the type of uveitis) may be more severe in patients with diabetes mellitus, causing numerous complications and recurrences; the amount of inflammation may also be related to intraocular cellular fibronectin.[35,36] Sympathetic paralysis in some conditions such as Fuchs' heterochromic cyclitis may cause increased efflux of albumin and lymphocytes into the aqueous and vitreous.[37] However, some authors have contrarily found uveitis to be protective against ipsilateral DR progression by unclear mechanisms.[38,39] It is hypothesized that denervation hypersensitivity following sympathetic paralysis can lead to rebound vasoconstriction with reduced blood flow exerting protection.

Uveitis

Uveitis with asymmetric DR has been rarely reported. In a series of 24 patients of uveitis with DR, the only patient who developed asymmetry presented with unilateral panuveitis in the eye that progressed to PDR over three months while the fellow eye did not experience progression.[36] Acute retinal necrosis caused by Herpes Zoster in a 58-year-old-male was accompanied by severe PDR and vitreous hemorrhage in the ipsilateral eye within three months, while the background DR in the other eye remained unchanged.[40] By contrast, another 20-year old patient of insulin-dependent diabetes mellitus with right eye (RE) PDR and left eye (LE) uveitis showed no evidence of DR in LE even after a 36-month follow-up.[39] Toxoplasmosis has been also been reported to cause NVD overlying NPDR in the affected eye of diabetic patients and hence produces a picture of asymmetric DR.[33,40] This may have been due to associated juxtapapillary retinitis and vitritis.

Endophthalmitis

Endophthalmitis was reported to accelerate DR progression in a case series where 33% of eyes with DR showed asymmetry after endophthalmitis, while no eyes without pre-existing DR progressed.[34] A case report of an 84-year old female concluded that the rapid onset and progression of unilateral severe exudative DR was related to late-onset presumed endophthalmitis.[41] Thus, eyes of diabetic patients with or without DR that experience endophthalmitis must be monitored for onset or progression. The mechanism behind the aggravation of DR in these eyes may be similar to other conditions with intraocular inflammation. However, the effect of preceding intraocular surgery and subsequent vitrectomy for endophthalmitis in these cases may have produced additional modifying effects.[34]

Fuchs' heterochromic cyclitis

FHC protects against DR progression, but the mechanism behind it is unclear.[38] Sympathetic paralysis in FHC leads to increased permeability of the blood ocular barrier, but consequent denervation hypersensitivity may result in reduction of blood flow.[38,42] FHC has also been reported to be associated with other modifiers of DR progression such as ocular toxoplasmosis, ocular trauma, retinitis pigmentosa, chorioretinal scars, glaucoma, and the subclavian steal syndrome.[37,42-47] This suggests that multiple factors may be involved and the state of DR in a particular eye could be the summation of the influence of each of them.[48]

Degenerative diseases

Posterior vitreous detachment (PVD) in early NPDR may prevent progress of the retinopathy. As retinal neovascularization is known to develop along edges of posterior precortical vitreous pockets, complete PVD protects against the development and progression of DR.[49] In addition, PVD carries the advantage of releasing unobserved subtle tractions,[50] which may be responsible for asymmetry of DR if unilateral. PVD, whether spontaneously or surgically induced, may even cause regression of proliferation in DR.[51] In a study, all eyes with asteroid hyalosis but without PVD had ipsilateral PDR. This may be related to the inability of vitreous contraction due to coexistent asteroid bodies.[52]

Refractive error

Myopia is demonstrated to be one of the protective factors for onset and progression of DR in several studies; however, most of these are cross-sectional, retrospective, or have a small sample size, which limits the strength of their statistical analyses.

In anisometropia, diabetic symptoms on the myopic side are either absent or poorly manifest.[53] A clinical retrospective study of asymmetric DR found no PDR in eyes with high myopia.[52] In another retrospective study including eyes with myopia more than −6.5D, it was observed that patients with monocular myopia over −13D Sph had no signs of DR, while the fellow emmetropic eye showed severe NPDR or PDR.[54] Another study found no PDR in medium severity myopic eyes and no DR in high myopic eyes.[53] In a study of ten patients with anisometropia >1D, four had PDR in the more myopic eye and six in the more hypermetropic eye.[1,2] For every diopter of myopic refractive correction (spherical equivalent), the incidence of DR was found to decrease by 30% in South Korean subjects.[55] Thus, high myopia can delay the onset of DR, the effect being proportional to its degree.[56]

Etiology: The linear and continuous protective effect of axial myopia on DR has been attributed to changes in the retina that occur due to elongation of the globe.[57] This includes chorioretinal thinning, which is associated with decreased metabolic demands.[58] In addition, increasing axial length results in stretching of vessel walls, producing 16% greater pressure attenuation than controls. A linear relationship between mean pressure attenuation index and axial length results in reduced blood flow and resultant lesser pressure on the vessel wall, causing decreased leakage and signs of typical DR.[59] A combination of other factors, including increased prevalence of uveal coloboma, thinning of retinal veins, accelerated and more frequently encountered posterior vitreous detachment, and alteration of the cytokine profile including a more marked dilution of VEGF in myopic eyes may also be responsible.[60-63]

Increased axial length has a protective effect on the risk and severity of DR.[64] DR prevalence decreases by 19% for each mm increase in axial length.[65] Axial length of >24.5 mm has been associated with no or mild NPDR in 83.2% of patients, but PDR and high-risk PDR in only 10.5%.[57] With >1-mm axial length difference between the two eyes, the prevalence of PDR was 61.7% in shorter eyes and 23.5% in longer ones while being significantly lower in eyes with a subfoveal choroidal thickness of <250 μm.[66] However, subfoveal choroidal thickness is not related to the prevalence and stage of DR when the axial length is >24.5 mm.[57]

Uveal coloboma

Asymmetry in the occurrence and extent of uveal colobomas are well known. The mechanism of choroidal coloboma as an inhibitory factor in DR may involve lack of nutrition from the choroid despite the presence of retinal tissue in the colobomatous area, outer retinal atrophy, and a relative decrease in oxygen demand, which is understandably proportionate to the extent of the coloboma.[32] However, there are no other reports in the literature. Hence, it cannot be conclusively opined that the condition leads to asymmetric DR.

Retinitis pigmentosa (RP)

Whenever RP is asymmetric, DR may also be asymmetrical because of several postulated factors, including greater oxygen and nutrient flux from the choroid to the inner retina, secondary attenuation of retinal blood vessels, early PVD, or release of a cytokine that inhibits neovascularization from the retina.[67] RP prevents full dark adaptation, and this has drawn considerable recent interest in the pathogenesis of progression of DR.[68] Optic atrophy in RP also contributes to reduced oxygen demand, and DR in such cases was found to regress over two years.[52,69]

Healed choroiditis

Eyes with extensive chorioretinal scarring from any cause experience reduced prevalence and severity of diabetic retinopathy due to reduced metabolic demand. Laser photocoagulation also produces the same effect.[70] Unilateral chorioretinal scarring correlates significantly with the presence of asymmetric PDR.[3]

Optic atrophy

Loss of retinal nerve fibers may reduce metabolic requirements and thus ischemic stimulus for proliferation, leading to asymmetric DR by arresting progression.[3,71] Eyes with optic atrophy and NPDR were found to have visual field defects extending over a quadrant that did not correspond to areas of asymmetric DR, although causes of optic atrophy in the study subjects were not elaborated in this study.[52] Trauma causes atrophy and scarring of ocular structures, reducing oxygen demand. Optic atrophy from fractures of the optic canal would also have the same effect.[32]

Surgery

Cataract surgery

Cataract extraction is postulated to cause DR progression due to the breakdown of the blood–retinal barrier or enhanced inflammation seen in diabetic patients. This may as well be associated with iatrogenic prostaglandin production.[72] Progression has been seen in 16.2%–47.9% of cases after surgery but does not vary between eyes undergoing conventional extracapsular cataract extraction and phacoemulsification.[73-75] Patients without previous DR were found to have a higher risk of NDPR after undergoing cataract surgery.[76] Preoperative NPDR, PDR, and limited surgical experience have been shown to be associated with retinopathy progression in 25% of patients and poorer visual outcomes.[77]

However, there are conflicting reports regarding whether unilateral cataract surgery, uncomplicated,[72] or with vitreous loss,[3] results in ipsilateral DR progression. Some of these studies may have suffered from selection bias due to preexisting asymmetry.[9] Moreover, posterior capsulotomy does not increase the development or progression of proliferative retinopathy or macular edema.[78]

The general view now is that majority of eyes suffering DR progression after cataract surgery reflect a combination of the natural course of the disease and systemic factors rather than the influence of the intervention itself.[79]

Vitrectomy

After vitrectomy, the mechanisms that contribute to the asymmetry of DR include increased diffusion and clearance of sequestered growth factors (including VEGF) and the added effect of PVD as discussed above. In addition, increased retinal oxygen saturation induces arteriolar constriction (which decreases capillary hydrostatic pressure and the outward flux of fluid), decreases VEGF production, improves perifoveal circulation, and reduces hypoxia in ischemic areas of the retina.[50]

Miscellaneous

Intraocular pressure and glaucoma

Diabetics with unilateral or asymmetric glaucoma would be expected to have asymmetric DR. The mechanism of protection is probably decreased metabolic demand from loss of ganglion cells or decrease in vascular perfusion.[80] However, the literature carries variable reports on whether such a relationship exists.

Valone observed that in two patients with asymmetric IOP, the eye without DR had higher IOP than that with DR. In addition, 12% of patients with NPDR in one eye and PDR in the other had IOP higher in the eye with PDR. Overall, a significantly more (20%) number of eyes with NPDR had higher IOP, but elevated IOP in the eye with NPDR could not account for the asymmetric retinopathy in 80% of cases.[1,2]

Unilateral surgical treatment of glaucoma in diabetics has been reported to accelerate DR progression in that eye.[81] Therefore, prevention of glaucomatous optic neuropathy has to be weighed against the risk of progression of DR, and treatment should be individualized.

Amblyopia, visual deprivation, and retinal detachment

Amblyopia probably protects against severe DR due to reduced ipsilateral oxygen demand, as is the case with other causes of visual deprivation such as traumatic cataract. Another mechanism may be the reduced blood flow in such cases. Lesser metabolic activity in the functional resting state of "non-seeing" retina protects against DR, as opposed to increased metabolic activity during the performance of visual functions in the posterior pole "receptive" retina.[3,82,83]

Idiopathic

A retrospective study among patients of asymmetric DR found no risk factors in nearly 60% of them over a mean period of 4.8 years.[3] In another study, 80% of patients with asymmetric DR did not have any detectable predisposing factors. These findings were attributed to either chance or undiagnosed local factors such as previous venous occlusive disease.[4]

Diagnostic Tools

The following investigations enable complete evaluation of cases of asymmetric DR.

Slit lamp biomicroscopy

Slit-lamp biomicroscopy with a fundus-viewing lens is the basic routine clinical procedure for the evaluation of diabetic fundi. Details of the posterior pole, such as microaneurysms and neovascularization, are best viewed on a slit-lamp biomicroscope. Fundus photography including stereophotography allows magnification and careful examination of small lesions thereby allowing early diagnosis.

Fundus Fluorescein angiography (FFA)

FFA shows prolonged arm-to-retina transit time and slow filling of choroidal and retinal vasculature in ocular ischemic syndrome, vascular abnormalities, and leakage from any neovessels on the posterior pole, thereby simplifying the diagnosis of asymmetric DR.[15] Peripheral retinal capillary closure and neovascularization, if present, can be detected with ultrawide-field (UWF) angiography and not by standard angiography. Thus, evaluation with UWF fluorescein angiography (UWF-FA) may help eliminate misidentification of asymmetry that may seem apparent clinically, or identify asymmetry that might be missed otherwise. However, eyelid (or eyelash artifacts) and nonlinear distortion of the fundus image complicate interpretation of the UWF-FA images. Some of these limitations can be minimized by comparing UWF-FA to color UWF photographs obtained in the same sitting.[84-86]

Asymmetric DR can be described angiographically by calculating the ischemic index (ISI) by dividing the nonperfused retinal area by the total retinal area and multiplying by 100%,

as viewed on a single frame of UWF angiogram from the arteriovenous phase (between 45 s and 2 min). Symmetry is defined as the "likeness of the total value of peripheral nonperfusion as measured by ischemic index in the right eye compared to the left eye." However, no cutoff value of symmetry based on the ISI difference between the two eyes has been defined.[86]

Optical coherence tomography and OCT angiography

OCT of the posterior pole, especially with enhanced depth imaging, is useful in the quantification of retinal damage by measurement of the macular thickness and subfoveal choroidal thickness. Spectral-domain OCT measurements may be beneficial in the early detection of ocular damage due to ICA stenosis as average macular thickness and measurements of outer macular quadrants in the ICA stenosis group have been found to be lower than in controls.[29] OCT angiography may be useful for evaluating blood flow and treatment efficacy in OIS.[87] Discussion on ultra-widefield OCT/OCTA imaging in DR is beyond the scope of the present article.

Measurement of axial length and refraction

This is particularly useful in the evaluation of axial ametropia, anisometropia, or refractive amblyopia associated with asymmetric DR. The axial length can be measured by optical biometers or by immersion A-B scan ultrasound biometry, while contact ultrasound biometry may be less accurate. It is important to consider that in the presence of an eccentric staphyloma, the axial length chosen for biometry calculations may not necessarily represent the maximum geometric dimension of the eye.[88]

Differential Diagnosis

This includes other causes of retinal neovascularization that may present in an asymmetric manner, such as sickle cell retinopathy, retinal vein occlusions, and featureless retina. Featureless retina is a unique condition in patients of DR where retinal neovascularization occurs alone in the absence of cotton-wool spots, dot-blot hemorrhages, and intraretinal microvascular abnormalities leading to the appearance of atrophic retina. FFA reveals extensive capillary nonperfusion with neovascularization. It is explained by the transient nature of cotton-wool spots and/or disappearance of dot-blot hemorrhages, microaneurysms, and IRMAs in areas of extensive capillary closure.[89]

Conclusion

Although asymmetric DR can be idiopathic, it may be a harbinger of sinister underlying conditions. Symmetry of retinal vascular changes in diabetics is affected by various aggravating and protective mechanisms in different associated conditions. In the published literature, there is a paucity of studies on many aspects of asymmetric DR and a broad search strategy had to be adopted. Hence, this condition merits further investigation with large multicentric studies with a cohort design and larger sample size to add credibility to the various hypotheses proposed and conclusions drawn. There is a need to sensitize general ophthalmologists and residents about the prevalence, risk factors, and diagnosis of asymmetric DR.

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Conflicts of interest

There are no conflicts of interest.

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