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Review Article

Diabetic Retinopathy, Clinical Features and Treatment: A Review

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Abstract

Diabetic retinopathy (DR) is a major health problem worldwide, sharpened by the steep raise of diabetes mellitus incidence. Complex metabolic pathogenetic pathways triggering inflammation, oxidation and neurodegeneration lead to a retinal impairment and consequent visual symptoms. A clinical ophthalmologic examination is strictly bound to a multimodal imaging approach in the correct management of DR. Color fundus photograph, fundus autofluorescence, optical coherence tomography (OCT), fluorescein angiography (FA) and ultra-wide field FA, OCT-angiography (OCT-A) are proper tools to add essential elements for a complete diagnosis, follow-up and to recognize complications. Telemedicine and the application of artificial intelligent are the promising perspective for the future of DR screening and management. Big steps ahead were made in the treatment of DR: intravitreal injection of long-acting corticosteroids and anti-VEGF completely changed the prognosis of DR/diabetic macular edema (DME) and, along with laser photocoagulation, are now the mainstays of the therapy. Surgery is needed especially in DR complications as vitreous hemorrhage or tractional retinal detachment. New long acting anti-VEGF drugs or port delivery system could be the candidate for the future therapy of DR.

Keywords: *Diabetic Retinopathy (DR); Optical Coherence Tomography (OCT); Fluorescein Angiography (FA); OCT-Angiography (OCT-A)*

Introduction

Diabetes is a major health problem worldwide, leading to cardio-vascular, renal and ocular impairments. Diabetic retinopathy (DR), a common ocular complication, is one of the major causes of preventable blindness with heavy social, health and economic burden. Prevention, screening and standardized treatments are the mainstays to reduce the impact of the diabetic epidemy, which will constantly increase in the next decades. The management and treatment in DR are effective but needs a continuous monitoring and education of the patient.

Diabetic retinopathy

Diabetes mellitus is a metabolic disease based on chronic hyperglycemia derived by insufficient insulin action. The American Diabetes Association classify diabetes in type 1, type 2, other types and gestational diabetes. The most part of the cases falls in the first two categories.

Type 1 diabetes (DM1) is responsible for 5 - 10% of total cases of diabetes [1]. Previously named as insulin-dependent diabetes or juvenile diabetes, it derived from an autoimmune destruction of pancreatic β-cells and its onset is usually in the first decades of life.

Type 2 diabetes (DM2) accounts for 90% of patients and is determined by insulin resistance in tissues, not balanced by insulin excretion.

DR is the clinical manifestation of diabetes in the eye. Good glycemic control is vital for prevention or slowing of DR. The therapeutic goal of metabolic control should avoid the risk of hypoglycemia, in particular in older people. Indeed, aggressive glycemic control does not improve retinal status and might even be associated with increased mortality. Guidelines recommend an HbA1c target of 6.5 - 7.5% (48 - 58 mmol/mol), but targets should be individualized [2].

Epidemiology

The prevalence of type 1 diabetes in the US in patients younger than 20 years was 1.93 per 1000 in 2009 with 2.6% - 2.7% relative annual increase [3]. The estimated global prevalence of DM2 is 8,3%, men more affected between 40 and 60 years, and almost 175 million people undiagnosed [3]. Almost patients with DM1 and more than 60% of those with DM2 develop some degree of DR during the first 20 years of elevated blood glucose [4]. Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20 - 74 years [4]. Estimated prevalence for diabetic macular edema from different population-based studies results 4.2 - 7.9% in type 1 diabetes and 1.4 - 12.8% in type 2 diabetes [5]. Hypertension and dyslipidemia are independent risk factors for the worsening of DR and need to be controlled.

DR pathogenesis

The retinal damages consequent to diabetes depend mostly on the duration and glycaemia control. The ascertained pathophysiological mechanisms in DR are:

- Accumulation of advanced glycation end products (ages);
- Activation of the polyol pathway;
- Activation of the hexosamine pathway;
- Activation of the protein kinase C pathway;
- Poly (ADP-ribose) polymerase activation [6].

Activation of these pathways produces oxidative stress and inflammation with consequent microvascular dysfunction and up-regulation of pro-inflammatory mediators, chemokines and adhesion molecules as ICAM-1, VCAM-1, and sVAP-1. Blood retinal barrier (tight junction between endothelial cells) breakdown and VEGF release lead to diabetic macular edema (DME) and vascular proliferation. VEGF family regroups 5 different molecules: placental growth factor, VEGF-A, VEGF-B, VEGF-C and VEGF-D; VEGF-A, especially $VEGF_{165}$ isoform, plays the protagonist in the pathogenesis of DME. Dysfunction of capillary endothelial cells and deleterious effects on tight junction proteins (i.e. occludin, claudins, and ZO-1) is induced by inflammatory cytokines, hyperglycemia and loss of pericytes. Leukocyte activation, leukostasis and extravascular differentiation of monocyte, with releasing of cytokines and growth factor, increase vascular leakage. This mechanism, associating with structural damages in basal membrane and glial cells impairment, results in an augmented paracellular and transcellular passage of fluids and macromolecules with leakage from vessels [7]. Clinically evident DME occur when central retina is involved by fluid accumulation and central vision acuity is affected.

Retinal peripheral ischemia is another cornerstone in DR. In DR and DME, an imbalance between proangiogenic and antiangiogenic factors in favor of the former is observed. PEDF is a glycoprotein produced by the RPE which inhibits angiogenesis and its level is found reduced in DR. Platelet-derived growth factor (PDGF), secreted by endothelial cells, is responsible for the good function of pericytes: a lowering of its levels increases the secretion of tumor necrosis factor- α (TNFα), which in turn increases ICAM-1 expression [8]. Hyperglycemia and inflammatory insult induce endothelial cells apoptosis, leukostasis and microthrombosis and consequent vascular occlusion. Thus, hypoxia is a trigger for hypoxia pro-angiogenic factors, as VEGF. New vessels network sprawls in an inordinate manner and

misdirection toward vitreous surface could lead to pre-retinal hemorrhages from new frail vessels. Next step is the activation of fibrosis mechanisms, which usually accompany vascular proliferation. Fibrous membrane formation intervenes along vitreo-retinal interface. Contraction of fibrous tissues could provoke retinal detachment and serious visual impairment. Anti-VEGF therapies have revolutionized DR treatment, but a sub-group of patients doesn't respond or responds poorly to these molecules. The multifactorial aspect of the disease complicates the pharmacological research approach.

New recent evidences highlight the importance of neural dysfunction in DR pathogenesis, explaining the changes in color perception, visual field and dark adaptation [9]. Impaired vascular supply to neuro-retinal demand is an interesting field of research. Ganglion cells degeneration and changes in interneurons as Müller cells are now considered an important feature in the progression of DR, confirmed by the reduced nerve fiber layer thickness in DR patients compared to control. Müller cells are specialized glial cells responsible for the uptake and recycling of neurotransmitters and retinoic acid compounds, control of neural metabolism and regulation of retinal blood flow. Müller cells' nuclei are in the internal nuclear layer of retina and their axons and dendrites reach all nuclei of retinal cells. Several studies highlight that Müller cells are dysfunctional in DR. Loss of neurons can be due to glutamate excitotoxicity, whose metabolism is impaired, and oxidative stress from reactive oxygen species (ROS) release by hyperglycemia-damaged mitochondria. Elevated level of ROS can activate nuclear factor-κB (NF-κB) transcription factor leading to the upregulation of nitric oxide (NO) and proinflammatory cytokine production (TNFα, interleukin-8 and interleukin-6 expression). Dysfunctional Müller cells are the major source of inflammatory factors. Interleukin 1β (IL-1β) is a major inflammatory cytokine: it activates NF-κB, which in turn includes the production of interleukin 8, monocyte chemoattractant protein-1 and TNF-α. Moreover, IL-1β induces interleukin 6 production by Müller cells. IL-1β participates to vasoregression and neurodegeneration. Similarly, TNFα is involved in the breakdown of the blood-retinal barrier by downregulating tight junction proteins of endothelial cells [10].

Microglial cells, derived from monocyte line, modulate immune response and help maintaining retinal homeostasis. Microglial cells result activated in diabetes and, assuming an ameboid structure, migrate to subretinal space from plexiform layers. Activated microglia release NO, ROS, proteases, cytokines determining toxic effect on neurons and amplifying the inflammatory response through recruitment of other immune cells. Hyperglycemia can lead to electron transport chain dysfunction as the primary site of ROS production and this may lead to an increased level of ROS, mitochondrial dysfunction, reduction of mitochondrial membrane potential, mitochondrial DNA damage, reduction in mitochondrial ATP production, increasing mitochondrial membrane permeability and releasing of apoptotic factors [11]. Mitochondrial ROS, increased by hyperglycemia, generate further damage to mitochondrial DNA resulting in a vicious cycle of ROS overproduction and mitochondrial DNA insult.

Epi-genetic modifications could have a role in pathogenesis of DR. Micro RNAs (miRNAs) are involved in many biological pathways, regulating almost one-third of human genes, and are also considered important in the occurrence of metabolic disease [12]. MiRNAs fulfil their function in the post-transcriptional phase of protein synthesis. After exposure to hyperglycemia, miR-23b -3p is expressed in endothelial and outer nuclear layers cells. MiR-23-3P down regulates SIRT1, which mediates acetylated-NF-κB up-regulation in DR and consequent inflammatory stimulus.

DR classification and clinical findings

DR is graded through retinal findings from fundus examination and fluorangiographic study. Basing on modified Early Treatment of Diabetic Retinopathy Study (ETDRS) and Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) classification, DR is categorized in non-proliferative (NPRD) and proliferative diabetic retinopathy (PDR), depending on evidence of absence or presence of neovascularization [13]. NPDR is further classified in mild, moderate and severe on the basis of the degree of the alterations (Table 1).

Common clinical findings in DR are: microaneurysms, retinal hemorrhages (dot and blot or splinter shape hemorrhages), intraretinal microvascular abnormalities (IRMA), venous alterations, cotton wool spots, areas of non-perfusion. Cotton wool spots derived from nerve

DR stage	Sub-type	Clinical features
No DR		No abnormalities
NPDR	Mild	Microaneurysms only
	Moderate	More than just microaneurysms, less than severe NPRD
	Severe	Intraretinal hemorrhages in all the 4 quadrants or venous beading in +2 quadrants or intraretinal microvascular abnormalities in 1+ quadrant and no signs of PDR
PDR		One or more neovascularization or preretinal hemorrhage

Table 1

fiber layer infarction. Mild NPDR have no other sign than microaneurysms. Moderate NPDR is denoted by microaneurysms/hemorrhages in one to three quadrants; IRMA, venous alterations or cotton wool spots can be present, but mild. One of the following must be found to consider a DR case as severe: diffuse microaneurysms/hemorrhages in all four quadrants, venous beading in at least two quadrants or severe IRMA at least in one quadrant.

The hallmark of PDR is neovascularization. This latter is distinguished in neovascularization of the optic disc (NVD) or neovascularization elsewhere in the remaining retina (NVE). High risk characteristics of PDR are: concurrent vitreous hemorrhage or eyes with NVD on or within 1 disc diameter of the optic disc equaling or exceeding one-fourth to one-third of a disc area.

DME can occur in every stage of the disease, although occurrence is more probable in latest stage. DME evaluation has been made precise and easier thanks to structural optical coherence tomography (OCT). The Early Treatment Diabetic Retinopathy Study Group (ETDRS) defined clinically significant diabetic macular edema" (CSME) as:

- Retinal thickening at or within 500 μm or 1/3 disc diameter of the macular center.
- Hard exudates at or within 500 μm of macular center with adjacent retinal thickening.
- Retinal thickening greater than 1 disc diameter in size within 1 disc diameter from the center of the macula [14].

The EDTRS classification is used in particular in research studies. On the other hand, the simplified DME classification is more applied in clinical setting:

- Vasogenic DME, with retinal thickening and vascular dilations, often associated with hard exudate deposition, at biomicroscopy evaluation;
- Non-vasogenic, as retinal thickening without identified vascular dilations;
- Tractional DME, caused by vitreo-macular interface adherence;
- Mixed DME, combination of tractional and vasogenic edema [15].

Multimodal imaging in diabetic retinopathy

Although the primary method to examine DR is direct and indirect ophthalmoscopy, different imaging modalities are significant methods in the screening, grading, treatment and follow-up of this disease. In fact, multimodal imaging, defined as the use of more than one technologic device to get complementary images of disease, has now become the standard of care. Color stereographic photography has been the gold standard for DR for years. With this technique we can categorize the disease in a non-proliferative and a proliferative form, according to internationally-accepted criteria [16]. Fluorescein angiography (FA) is also an important examination, showing microaneurysms, intraretinal microvascular abnormalities, epiretinal proliferation, areas of capillary non-perfusion, and vascular leakage, an indirect sign of blood-retinal barrier alteration.

Moreover, optical coherence tomography (OCT) confirm the presence of DME and macular damage. Besides these techniques, newer tools have been achieving validation and popularity, as fundus autofluorescence (FAF) and OCT angiography (OCTA).

Widefield e ultra-widefield fundus photography

Traditional fundus retinography and fluorangiographic photograms only include 30° of the posterior pole; this method was referred as "Early Treatment Diabetic Retinopathy Study (ETDRS) 7 standard fields (7SF) protocol" which is still considered as the gold standard. The "ETDRS 7 standard fields (7SF) protocol" involved the acquisition of 7 retinal photographs, covering 30° each: 3 set horizontally through the macula and 4 arranged around the optic nerve. These photographs are subsequently combined to obtain an image of about 75°. Despite being optimal for imaging pathologic changes of the optic nerve and of the macular area, this field is incomplete for the imaging of the medium-far and of the very-far retinal periphery. Moreover, it has numerous disadvantages: the need for highly qualified technical staff and optimal mydriasis, high patient collaboration, the impossibility of acquiring pictures simultaneously and, as we reported, limited amount of information from the retinal periphery.

The visualization of retinal periphery permits to identify early retinal diabetic signs in patients who are otherwise considered healthy by traditional methods and who are at increased risk of progression to severe stages of retinopathy. Therefore, widefield (WF) and ultra-widefield (UWF) retinal imaging techniques have been imported in clinical practice.

UWF imaging allows the evaluation of the peripheral and central retina without the requirement of eye steering.

The ability to find more retinal lesions allows for earlier detection, improved accuracy and increased identification of diabetic retinopathy as well as having potential prognostic implications.

The introduction of mountable lenses on the traditional fundus camera or on a confocal scanning laser ophthalmoscope (cSLO) was used in the clinical practice and in the scientific research. The Staurenghi lens and the Heidelberg Spectralis® lens are the most commonly used, scanning up to 150° and 105° of the retina, respectively, in a single frame. The Optos Optomap® is a confocal scanning laser ophthalmoscope (cSLO) with an ellipsoid mirror with two focal points that captures the 82% of retinal surface (200°) in a single shot with no need of mydriasis or contact lens. It can get retinal photography, FAF, FA and indocyanine green angiography. Peripheral alterations and decreased resolution of the peripheral retina are the most relevant limitations. Optos Optomap® acquires a significantly larger total retinal surface area, compared to Heidelberg Spectralis®. Moreover, UWF has the potential to identify peripheral vessel leakage (PVL), which represents the leakage of dye by arteries and veins in the context of active DR. Panretinal photocoagulation (PRP) aims to destroy ischemic areas of retinal tissue outside the temporal arcades and prevent the development of PDR. This technique has side effects, including visual field reduction, onset/worsening of DME, choroidal detachment, and reduction in color and contrast sensitivity. For this reason, performing a selective photocoagulation of the non-perfused areas identified on Optos Optomap® could represent a promising alternative. In the group of patients treated with UWF-targeted PRP, a reduction in the side effects of laser photocoagulation without sacrificing the therapeutic benefits has been observed [17].

There are several limitations to UWF technology. These include images with pseudocolor representation, lower resolution, map distortion with disproportionate magnification of the peripheral retina, eyelash and reflection artifacts, and significantly higher costs. The Diabetic Retinopathy Research Network international study group has recently encouraged the AA protocol. This protocol aims to investigate the correlation between peripheral lesions visible with the UWF angiography and progression of DR. These results, which will be available in 2020, will allow defining the role of UWF imaging in the DR management [18].

Fundus autofluorescence

FAF is based on the phenomenon of emission of light from retinal pigments acting as natural fluorophores: lipofuscin and melanin. These substances release energy when hit by a light ray of a specific wavelength.

Lipofuscin is produced by retinal pigment epithelial (RPE) cells and an accumulation of its molecules is considered a sign of normal aging or metabolic impairment of the RPE itself. Melanin, on the contrary, is a protective pigment found in the apical pole of RPE and in the choroid, protecting the RPE from excessive light scattering, radiation, oxidative stress, and light damage. Loss of RPE melanin granules has been observed with retinal aging.

In clinical practice, the use of FAF is important in retinal pathologies where the RPE is primarily involved, like age-related macular degeneration or inherited macular dystrophies. Although the role of FAF in DR and DME isn't well defined, this imaging modality could be useful to better understand DME pathogenesis and estimate a correct prognosis.

Some FAF patterns have been reported in DME, correlating with various OCT features and a linear correlation between the amount of hyper-autofluorescence and the severity of DME has been described [19].

There are two possible explanations to link the intraretinal fluid and the increased macular autofluorescence. It might be due to the dispersion of macular pigments normally masking foveal fluorescence by the intraretinal cysts, or to the activation of retinal microglial cells in eyes with DR.

In this second hypothesis, the activation of microglial cells is associated to the oxidation of proteins and lipids, and the accumulation of the by-products of this cascade may be the source of the increased fluorescence.

Optical coherence tomography

Since its commercial introduction in 1991, OCT obtained great relevance in the evaluation of the macular morphological features in patients with DR. OCT images are used to measure central macular thickness (CMT) and the macular volume, which are the main anatomical outcomes in many therapeutic clinical trials regarding DME. Identification of these features of DME is important not only in diagnosis but for determining the most appropriate treatment modality and monitoring treatment response.

The qualitative evaluation of the OCT also allows identifying important signs determining the visual prognosis, such as the ellipsoid zone and the external limiting membrane, whose integrity is an indirect sign of the photoreceptors' functional health [33].

There are other biomarkers that can be identified on OCT:

- Hyper-reflective intraretinal spots (HRS) that are intraretinal foci with increased reflectivity and smaller size in comparison to hard exudates. It has been hypothesized that they are precursors of hard exudates, or, alternatively, a morphological sign of the hyper-activation of Müller cells.
- Vitreoretinal adhesion or epiretinal membrane [23].
- Subfoveal neurosensory detachment [24] and disorganization of the inner retinal layers (DRIL), which is thought to be a feature of macular ischemia and therefore a negative prognostic factor.

Recently an easy-to-use morphologic classification based on OCT was proposed for DME [25]. The grading system employs seven morphologic parameters as foveal thickness, size of intraretinal cysts, ellipsoid zone and/or external limiting membrane status, DRIL, hyper- reflective foci, subfoveal fluid and vitreoretinal relationship, to classify DME in four stages. Early, advanced, severe and atrophic maculopathy are the progressive stages of DME, leading progressively to a sight-threating damage to the macula [25].

OCT provides precious information on retinal nerve fiber layers (RNFL), ganglion cell complex (GCC) and choroid. Recent studies have supported the role of neurodegeneration in diabetic patients: it has been demonstrated a reduction of retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thickness on OCT images even before DR onset [25].

Despite these strengths, OCT has some limitations including the inability to differentiate the alterations in the retinal blood perfusion associated with DR. In fact, it cannot identify macular ischemia, epiretinal neovascularization, and blood-retinal barrier breakdown, which are the major causes of visual compromise in patients who have suboptimal visual acuity despite a relatively normal macular OCT. For this reason, FA and OCT angiography are required to evaluate the retinal vasculature changes in DR.

OCT-angiography

OCTA is a novel modality that safely, quickly and noninvasively demonstrates the retinal and choroidal microvasculature. OCT-A technology relies on the "decorrelation principle", assuming that in a static eye the only structures in movement are erythrocytes through retinal vessels and an angiogram map is generated by software considering the variation between moving cells in the vasculature and motionless surrounding tissues [26].

OCTA is able to provide different segmentation levels: the superficial capillary plexus, the deep capillary plexus, the avascular outer retina, the choriocapillaris, and the choroid. OCTA can identify several pathological changes in DR eyes, including enlargement of FAZ area, capillary abnormalities, such as capillary non-perfusion, microaneurysm, intraretinal microvascular abnormalities (IRMAs) and neovascularization (NV).

In eyes with DR, the foveal avascular zone (FAZ) is enlarged due to microinfarctions of surrounding vessels. It is important to know that enlargement and irregularity of FAZ area can be noticed even in diabetic patients with no signs of DR and, for this reason, OCT-A could be useful as screening test to identify early microcirculatory changes.

The OCTA can be used to detect pathologic changes that occur in DR in a rapid and safer way compared to fluorescein angiography, avoiding the side effects of dye injection during FA. The quantification of the fovea with OCTA is also not influenced by leakage phenomena, which sometimes can distort the assessment of FA images.

The main problem of the OCTA is the lack of functional information about the integrity of the macula; in addition, its images is mainly restricted to the posterior pole. New image reconstruction methods (montage) has developed to get wider retinal areas. Nowadays, OCTA can be useful as a screening evaluation for early signs of DR even without symptoms. Further studies are needed to validate this examination in the clinical practice.

Fluorescein angiography

Fluorescein angiography (FA) was introduced in ophthalmologic practice since 1961 [27]. FA requires the intravenous injection of fluorescein dye, which rapidly reaches eye circulation. White light passes through a blue excitation filter, and the blue light is absorbed by fluorescein molecules, which in turn emit light in the yellow-green spectrum. A barrier filter allows capturing only light emitted from the excited fluorescein, and the images are recorded.

Furthermore, FA has some limitations: it requires an invasive dye injection with a limited transit window and it has limited resolution. Still, angiography contribution remains still valid to the assessment of vascular integrity: in contrast to OCT-A, fluorescein angiography is a dynamic examination which show vessel filling and leakage [28]. Fluorescein angiography (FA) is the gold standard procedure in DR to assess the status of blood-retinal barrier (BRB) and the presence of non-perfused and ischemic areas, vascular leakage, microvascular abnormalities (microaneurysms) and neovascularization. Fluorescein angiographic features of mild-to-moderate non proliferative retinopathy include pinpoint areas of early hyperfluorescence corresponding to microaneurysms, dot-and-blot hemorrhages which appear hypofluorescent. Microaneurysms leak in the later frames with blurring of margins and diffusion of fluorescein dye, whereas hemorrhages remain hypofluorescent throughout the study. Hard yellow exudate generally does not appear on a fluorescein angiogram unless it is extremely thick, in which case it is hypofluorescent. In more severe non proliferative retinopathy, in addition to the features notes

above, there are cotton-wool spots, usually hypofluorescent, sometimes with late hyperfluorescence along the margins. Areas of capillary dropout appear as smooth, hypofluorescent "ground-glass" patches, with staining at the margins in the later frames of the angiogram. IRMAs fill in the arterial phase of the angiogram and does not leak significantly in the later frames.

Evaluation of peripheral retina with FA is critical for screening, diagnosis, monitoring, treatment and prognosis of DR.

Telemedicine and artificial intelligence

The latest novelties that have been introduced in non-invasive imaging of DR are pivotal in programming modern, cost-effective screening programs for DR, which are able to face the recent epidemiological raise in its worldwide prevalence. In fact, the cost-effectiveness of a screening program is crucial for its success, and the choice of the preferred DR screening method should take into consideration the different availability of resources between the different countries.

The recently published guidelines for DR screening from the International Council of Ophthalmology (ICO) recommend annual DR screening to be done by means either of ophthalmoscopy (direct or indirect) or fundus photography [29]. Since the demand for annual retinal examination is feared to exceed the supply of resources provided by ophthalmologists, newer strategies are needed for meeting realistically the global demands.

Telemedicine and artificial intelligence-based image analysis might help in overcoming these limitations. The telemedicine approach in DR screening relies on the execution of fundus photographic examinations to large cohorts of diabetic patients, that are subsequently interpreted by trained personnel in off-site reading centers. The main advantages of teleophthalmology are the possibility of screening a wider share of population, especially those living in remote areas, with the concomitant alleviation of the burden for local ophthalmologists. The diagnostic accuracy of this approach has been reported to be over 80% in detecting low- and high-risk PDR, and over 70% in recognizing DME and mild and moderate NPDR [30]. Potential limitations are the need of skilled readers required to interpret retinal fundus photographs and the inevitable discrepancies (both inter-reader and intra-reader) that come from subjective interpretation of images.

Oppositely, the use of artificial intelligence-based reading programs relies on pattern recognition of common DR features, with the aim of distinguishing patients who should be referred to a complete clinical examination from those who should be kept in the screening program without the aid of the human judgment. Multiple algorithms for automated image analysis are currently available, with a reported grading performance comparable to trained specialists. The integration of deep learning algorithms has been linked to even higher diagnostic results. It must be noted, however, that these systems are still susceptible to artifacts misinterpretation, and further studies are needed to assess the feasibility of their introduction in clinical practice.

Treatment

Metabolic control

Glycemic control is a key factor in preventing complications of diabetes. Thus, a good metabolic control in diabetic patients reduces the incidence of DME and the need for treatment. The Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study demonstrated that tight blood glucose control reduced the cumulative incidence of macular edema and the requirement for laser treatment in patients with type 1 diabetes and type 2 diabetes respectively [31]. High blood pressure is also another important risk factor for DME, and its decrease reduces the burden of treatment. Improving the control of serum glucose levels and blood pressure is an effective strategy to prevent and slow down the natural history of diabetic ocular complications.

Laser

Before the introduction of Anti-VEGF drugs, retinal laser photocoagulation was the only efficient treatment for DME. The pivotal study demonstrating the efficacy of argon laser for DME was the Early Treatment Diabetic Retinopathy Study (ETDRS) [14]. EDTRS was a mul-

ticenter randomized clinical trial carried out between 1980 and 1985, whose first report was published in 1985. 3711 patients diagnosed with non-proliferative diabetic retinopathy, early proliferative retinopathy, and/or DME in each eye were enrolled in the trial. This study demonstrated a better visual outcome with focal/grid laser for clinically significant macular edema (CSME) (Table 1) compared to untreated group. Thanks to the results of the EDTRS, laser became the standard care for DME over the next three decades.

Despite improving visual outcome, laser treatment with EDTRS focal/grid photocoagulation for DME had some side effects and complications, such as a possible initial transient decrease in central vision, accidental foveal burn, paracentral scotomas, subretinal fibrosis, secondary choroidal neovascularization and expansion of laser scar area over time. Moreover, macular laser has no impact on retinopathy severity scale compared to anti-VEGF agents [32]. Macular laser photocoagulation had been for decades the pillar of DME treatment, and still remains an important treatment option. However, intravitreal injections of anti-VEGF drugs or corticosteroids are favored, because intravitreal treatment usually achieves a greater improvement in visual acuity in the majority of patients.

AntiVEGF

Diabetic macular edema is caused by a pathologically increased permeability of retinal vessels and alteration of blood-retinal barrier. Intraocular VEGF levels are increased in DME, and this molecule is recognized as a pivotal actor in the pathogenesis of DME. Activation of VEGF pathway signal disrupts the tight junctions between endothelial cells, leading to vascular hyperpermeability and fluid extravasation. For this reason, blocking VEGF signaling with intravitreal injections of anti-VEGF drugs is beneficial in restoring normal retinal anatomy and improving vision loss from DME.

Pegaptanib

Pegaptanib is a pegylated oligonucleotide that binds VEGF165 isoform with high specificity and inhibits its activity. Initially used for neovascular age related macular degeneration, it was then investigated also for DME [33].

The Macugen Diabetic Retinopathy Study evaluated the efficacy of intravitreal pegaptanib compared to sham in eyes with DME. 172 patients were enrolled and randomized in four groups (receiving respectively 0.3 mg, 1.0 mg, 3.0 mg of intravitreal pegaptanib and sham injection). Pegaptanib was administered at baseline, week 6 and week 12, with additional injections or focal laser if needed for another 18 weeks. The trial demonstrated that all treatment arms had a better VA at 36 weeks compared to the control arm, but the 0.3 mg dose appeared to have a better efficacy profile. At week 36 the 0.3 mg group had a median VA of 20/50 compared to 20/63 of control group and also experienced a greater reduction of mean central retinal thickness and less need of photocoagulation.

Another trial compared the efficacy of intravitreal injections of pegaptanib 0.3 mg with sham injections, with a follow up of 2 years [34]. The study confirmed the gain in VA of treated subjects at year 1 and 2 compared to sham. At week 102, the mean gain in VA was 6.1 letters versus 1.3 letters of control group.

Actually, due to its cost and the availability of other anti-VEGF drugs that may have a greater efficacy, pegaptanib is rarely used for DME.

Bevacizumab

Bevacizumab is a recombinant humanized antibody binding all isoforms of VEGF-A. It was approved in 2004 for colon cancer and then for other neoplastic entities [35]. Due to its relatively cheap cost and high cost efficiency, it is used off-label for treating several ocular diseases.

Diabetic Retinopathy Clinical Research (DRCR) network is an organization supported by the National Eye Institute (part of USA National Institutes of Health), coordinating several trials for diabetic retinopathy. DRCR network led a pilot study to assess the efficacy and safety of bevacizumab for DME [36]. 121 eyes with DME were randomized in 5 groups, treated respectively with: focal photocoagulation

at baseline, intravitreal bevacizumab (1.25 mg) at baseline and 6 weeks, intravitreal bevacizumab (2.5 mg) at baseline and 6 weeks, intravitreal bevacizumab (1.25 mg) at baseline and sham injection at 6 weeks, intravitreal bevacizumab (1.25 mg) at baseline and 6 weeks and also focal photocoagulation at 3 weeks. At 12 weeks, the groups treated with two consecutive injections of bevacizumab without laser showed an improved VA compared to the group treated with laser only. The BOLT study evaluated the efficacy of bevacizumab compared to macular laser [37]. 80 patients with clinically significant macular edema were randomized in two groups, receiving either intravitreal injections of bevacizumab or laser treatment. At 12 months, patients treated with bevacizumab gained a median of 8 ETDRS letters, while the group receiving macular laser therapy lost a median of 0.5 ETDRS letters. At 2 years, the VA gain was sustained (9 ETDRS letters for bevacizumab group compared to 2.5 letters for laser group).

Despite the evidence supporting the use of bevacizumab for DME, two important issues concerning intravitreal bevacizumab are the lack of an official indication for DME and the need of compounding pharmacies for its preparation.

Ranibizumab

Ranibizumab is a monoclonal antibody fragment which inhibits Vascular Endothelial Grow Factor A, and it was the first Anti-VEGF drug approved for neovascular age related macular degeneration in 2006.

It was also the first anti-VEGF approved for DME in 2012, following the results of the RISE and RIDE study [38]. RISE and RIDE studies were two similar phase 3 randomized and controlled studies, whose aim was to evaluate the efficacy and safety of intravitreal ranibizumab in DME. The enrolled patients (377 in RISE study and 382 in RIDE study) where randomized 1:1:1 in three groups: injections with 0.3 mg ranibizumab, injections with 0.5 mg ranibizumab or sham injections, each one receiving monthly ranibizumab or sham injection for 24 months according to the randomization.

In both studies, the percentage of patient treated with ranibizumab gaining 15 ETDRS letters or more at the 24^{th} month was significantly higher than the sham arm. In the RISE trial, 39.2% (0.5 mg ranibizumab) and 44.8% (0.3 mg ranibizumab) of treated subjects achieved this visual outcome, compared to 18.1% of control group. In the RIDE study, the results were similar: 45.7% (0.5 mg ranibizumab) and 33.6% (0.3 mg ranibizumab) of patients receiving therapy compared to the 12.3% of sham group.

Aflibercept

Aflibercept is a recombinant fusion protein acting as a soluble decoy receptor; it binds with high affinity not only VEGF-A, but also VEGF-B and PIGF. Compared to ranibizumab or bevacizumab, aflibercept binding affinity to VEGF-A is considerably higher (almost 100-fold).

Aflibercept was approved for DME in 2014. The phase 3 clinical trial VISTA and VIVID were two similarly designed study evaluating the efficacy and safety of aflibercept compared to macular laser photocoagulation [39]. The VISTA trial was carried out in United States, while the VIVID trial was conducted in European, Japanese and Australian sites. In the two studies, 872 patients with central-involved macular edema were enrolled. The participants were randomized in three groups: one receiving intravitreal injection of aflibercept (2 mg) every 4 weeks, another one treated with aflibercept (2 mg) every 8 weeks after 5 monthly doses, and the laser control group. Both groups treated with aflibercept achieved a better visual outcome and anatomical improvement than the laser group at weeks 52, and these results were maintained at weeks 100 and 148. Both monthly and bimonthly regimens had comparable results in treating DME, thus treating patient with a loading dose and then intravitreal injection of aflibercept every 8 weeks allows to reduce the burden of treatment without losing efficacy.

Protocol T

Three intravitreal anti-VEGF agents are widely used for DME: ranibizumab, aflibercept and bevacizumab. All three molecules have shown efficacy and safety in the treatment of DME, but only the first two are approved for ocular use by the Food and Drug Administration

(FDA) and the European Medicines Agency (EMA). Bevacizumab is commonly used off-label in many ocular diseases and it costs sensibly less than the other two anti-VEGF drugs [40].

In order to assess the efficacy and safety profile of the three drugs, Protocol T promoted from Diabetic Retinopathy Clinical Research Network (DRCR) compared aflibercept, bevacizumab, and ranibizumab in the treatment of DME [41]. In this clinal trial, 660 patients were randomized in three groups, receiving respectively intravitreal aflibercept (2.0 mg), bevacizumab (1.25 mg) or ranibizumab (0.3 mg) as often as every 4 weeks.

The results of the study at 1 year confirmed the efficacy of intravitreal aflibercept, bevacizumab and ranibizumab in improving visual acuity in eyes with DME, with a comparable number of injections. The mean improvement in the visual function was better in the group treated with aflibercept, but actually this difference depended on the initial visual acuity: when the baseline BCVA was from 20/32 to 20/40 the efficacy of the three drugs at year 1 were similar, while if BCVA was 20/50 or less aflibercept seemed to give a greater benefit. No significant difference in the incidence of adverse events were found between the three study groups. The two years results of protocol T showed that all three anti-VEGF drugs gave a visual acuity improvement at 2 years, but with about half injections were needed in the second year compared to the first year [42]. For eyes with good baseline visual acuity, BCVA outcomes were comparable among the three arms of the study. Among eyes with initial visual acuity of 20/50 or less, aflibercept had superior outcomes in comparison to bevacizumab, but superiority of aflibercept over ranibizumab was no longer significative.

Steroids

VEGF is a major target in DME, but it is not the only mediator involved in the increased vascular permeability underlying the formation of macular edema. In addition to VEGF, diabetic retinopathy induces the production of several inflammatory cytokines and chemotactic factors for leukocytes. As the role of inflammation in well established in the pathogenesis of DME, the powerful anti-inflammatory action of corticosteroids can be effective in treating this condition: steroids inhibit the release of inflammatory mediators and improves the function of the blood-retinal barrier [43]. Treatment of DME with systemic corticosteroid is not advisable since it causes several adverse effects. Intraocular injection of steroids can overcome the issue, as the eye is a relatively isolated organ and the injected drug remains mostly in the eye. First approach with intravitreal triamcinolone acetonide showed short-term benefits in improving visual acuity and reducing the macular edema in patient with diffuse DME [44]. Since then, intravitreal injected drug delivery systems were developed, allowing a sustained delivery of low doses of corticosteroids. Given the long duration of these implants, the corticosteroids treatment requires less frequent injections than Anti-VEGF therapy. Moreover, some patients respond poorly to anti-VEGF drugs, or do not benefit at all from the therapy. Anti-VEGF agents are effective for treating patient with DME, but steroids offer an additional valid treatment option.

Dexamethasone

The MEAD study evaluated the safety and efficacy of dexamethasone intravitreal implant in the treatment of patients DME [45]. Dexamethasone intravitreal implant is a biodegradable implant which releases the a powerful corticosteroid into the vitreous up to 6 months. In the MEAD study, two identical-designed phase III trials enrolled 1048 patients with DME, randomized equally in three arms (dexamethasone implant 0.7 mg, dexamethasone implant 0.35 mg, sham procedure). At three years follow-up, patients treated with the implant achieved a better visual acuity and a reduced CRT from baseline than the sham group.

The implant demonstrated an excellent systemic safety but induced some ocular adverse events. In one-third of the patients receiving the implant there was a significative increase in IOP requiring treatment (a lower incidence compared to intravitreal fluocinolone acetonide treatment) [46]. In addition, more than half of the treated eye underwent cataract surgery, compared to less than 10% of sham group. Overall, even if the development or progression of cataract is likely in eyes treated with dexamethasone implant, prompt cataract surgery allows a clinically significant improvement in visual function compared to untreated eyes.

Iluvien

The intravitreal insert of fluocinolone acetonide is a nonbiodegradable cylindrical tube injected in the vitreous through a 25 gauge needle, providing a sustained release of the steroid. The FAME study assessed the efficacy and safety of fluocinolone acetonide inserts in patient with DME [47]. Two identically designed phase III trials enrolled patients with persistent DME, randomized to receive a low-dose insert releasing 0.2 µg/day (375 subjects), an high-dose insert releasing 0.2 µg/day (393 subjects) or a sham injection (185 subjects).

28.7 and 28.6 of patients treated respectively with low-dose and high-dose insert of fluocinolone acetonide achieved the primary outcome of the trial (improvement of 15 letters ETDRS or more at month 24), compared to 16.2 percent of the control group. The treated group had also better anatomical results, with a rapid reduction of central retina thickness already at 6 weeks, sustained until the end of the study (2 years).

As for dexamethasone intravitreal implant, also the fluocinolone acetonide insert increased the rate of cataract surgery or IOP elevation requiring medical or surgical treatment. Both low-dose and high-dose fluocinolone acetonide intravitreal inserts improved visual function in eyes with DME in a similar way, but the low-dose insert had less adverse events. The biggest advantage of the fluocinolone acetonide insert is its long-lasting effect: one injection can provide a substantial visual benefit in subjects with DME for at least 2 years, with sensibly less injections compared to anti-VEGF drugs or other corticosteroids releasing inserts such as dexamethasone intravitreal implant.

Due to the risk of IOP rising, it is important to rule out responders to steroids. In USA, Iluvien is approved for eyes with DME already treated with corticosteroids without a clinically significant IOP increase. Moreover, as this drug induces or worsens cataract, in some European countries (such as Italy, UK and Spain) Iluvien is reimbursed only for pseudophakic eyes.

Protocol I

DRCR network protocol I compared intravitreal injection of 0.5 mg ranibizumab with prompt or deferred (≥24 weeks) focal/grid laser, intravitreal injection of 4 mg triamcinolone combined with prompt focal/grid laser and focal/grid laser alone for the treatment of DME [48]. 691 subjects (854 study eyes) with DME participated to this trial. At year 1, the group treated with ranibizumab and laser achieved a greater improvement in visual acuity than the group treated with triamcinolone and laser or laser alone. Increased intraocular pressure and cataract surgery were more frequent in the in the group treated with triamcinolone. In pseudophakic eyes, the treatment with intravitreal triamcinolone and prompt laser gave better visual acuity results than laser alone; in this subset of patients the visual outcomes was comparable to ranibizumab and laser group, but with a higher rate of IOP elevation. At 2 years, the results were comparable to 1-year outcomes. Interestingly, the 5 years results showed that the therapy with ranibizumab may have also a favorable effect regarding the severity of retinopathy [49].

Proliferative diabetic retinopathy

Proliferative diabetic retinopathy is an advanced stage of DR, and a leading cause of visual impairment in diabetic patients. It is characterized by the presence of new vessels in the retina and around the disk. This neovascularizations are abnormal vessels prone to leakage, bleeding, and could develop fibrosis and induce tractional retinal detachment. New vessels can develop also over the iris and the iridocorneal angle, eventually obstructing aqueous humor outflow and leading to neovascular glaucoma.

Diabetic retinopathy study

Even if retinal photocoagulation had been used for some years to treat advanced form of DR, the first randomized and controlled clinical trial showing evidence of its efficacy was the Diabetic Retinopathy Study (DRS) [50]. More than 1700 patients with proliferative DR in at least one eye or severe non-proliferative DR in both eyes were enrolled between 1972 and 1975. For each patient, one eye randomly

received laser photocoagulation, while the other one was assigned to follow-up. The results of the study showed that laser photocoagulation greatly decreased the risk of severe visual loss compared to untreated eyes.

Protocol S

Panretinal photocoagulation (PRP) became the standard treatment for proliferative diabetic retinopathy since the encouraging results of Diabetic Retinopathy Study. Even if effective, PRP has some disadvantages: it distorts the retinal architecture and connectivity and induces an inflammatory process. Moreover laser-induced retinal damage and loss of photoreceptors reduce visual field sensitivity.

Protocol S compared the treatment with PRP and intravitreal injection of ranibizumab in eyes with proliferative diabetic retinopathy. 305 patients participated to this trial in 55 US sites, with a total of 394 eyes. In 203 PRP were performed (completed in one to three visits), while 191 eyes were treated with intravitreal ranibizumab 0.5mg. The schedule of ranibizumab intravitreous injection (as frequent as every 4 weeks) was based on a specific retreatment algorithm. In case of DME, both groups could receive ranibizumab.

Regarding visual acuity at 2 years, the treatment with ranibizumab resulted noninferior to PRP. At 2 years, mean visual acuity was slightly better in the ranibizumab group (+2.8 EDTRS letters, compared to +0.2 in the PRP group), while the loss of peripheral visual field sensitivity was worse in the PRP group (-422 dB compared to -23 dB of the ranibizumab group). Moreover, eye treated with PRP needed more vitrectomy and developed more frequently DME.

In order to have a longer-term follow-up, protocol S was extended to 5 years [51]. Only 66% of participant of protocol S completed the 5 years follow-up. The mean number of intravitreous injections of ranibizumab was 19.2 in the ranibizumab group and 5.4 in the PRP group. The extended follow-up showed that visual field sensibility reduction occurs also in eyes treated with ranibizumab, even if with a lesser extent. It is not known if this reduction in linked to the anti-VEGF treatment or to the natural history of the DR.

The results of protocol S suggested that PRP and anti-VEGF are both suitable treatment for proliferative DR: severe vision loss or serious complications were rare in both arms of the study, but the group treated with ranibizumab developed less frequently diabetic macular edema and had a smaller visual field loss. In order to choose between the two treatment, it is important to consider different factor (patient compliance, cost of the treatment, number of visits).

Clarity study

The Clarity study tested the efficacy of another anti-VEGF (aflibercept) for the treatment of proliferative DR [52]. This randomized and controlled trial evaluated the non-inferiority of aflibercept compared to PRP at 52 weeks. Clarity trial was carried out in UK between 2014 and 2015 and more than 200 subjects with PDR were enrolled. Patients were randomized 1:1 in an intervention arm (receiving 3 monthly injections of aflibercept, than treated following a pro re nata regimen) and a comparator arm (PRP treated group). In contrast to protocol S, the presence of DME was an exclusion criterion. At the end of the study, the group treated with Aflibercept showed better BCVA results, with a mean number of injections of 4.4 (95% CI 4.1 - 4.7). The CLARITY trial focused also on the economic implication of the treatment, showing that aflibercept treatment costs more than PRP at 1-year follow-up.

PRP Vs Anti-VEGF in proliferative DR

Anti-VEGF treatment for proliferative DR shows several advantages compared to PRP but is not devoid of risks. Severe complications (such as endophthalmitis or retinal detachment), although rare, are possible. Moreover, 5-years results of protocol S suggested that a reduction of the sensitivity of visual field occurs also in eyes treated with ranibizumab. In order to treat a proliferative DR with anti-VEGF drugs, frequent follow-up are needed, and also a quite high number of intravitreal injections repeated indefinitely in time. The cost of anti-VEGF therapy is also much greater than PRP: protocol S found that the cost of PRP was about 90% lower compared to ranibizumab at 2 years follow-up, and also significantly lower if extrapolated lifetime (about 10% than anti-VEGF therapy) [53]. Anti-VEGF treatment

could be cost-effective in patients with associated clinically significant DME. Anti-VEGF treatment could be suitable for a subset of patients (presence of DME, high compliance), but not for others (poor compliance, difficult follow-up). Actually, in most cases a combination of both laser and anti-VEGF therapy in possible and even advantageous in treating active proliferative DR.

New perspective

As DR in one of the most important causes of vision loss worldwide, research is very active in order to find new and better therapies for this pathology. In this section are described some possible innovations in the treatment of DR that over the next years could be used in clinical practice.

New anti-VEGF drugs

As the role of VEGF in the pathogenesis of DR is well known, new molecules targeting this signal protein are under investigation.

Conbercept

Conbercept is a recombinant fusion protein of VEGF receptor 1 and VEGF receptor 2 binding domains fused with fragment crystallizable (Fc) region of human IgG1 [54]. Conbercept acts as a decoy receptor and blocks all VEGF-A isoforms, as well as VEGF-B, VEGF-C, and PIGF. The structure of conbercept is similar to that of aflibercept, but in addition it includes also the VEGFR-2 fourth extracellular domain into the antigen-binding fragment (Fab) region. The presence of this domain increases receptor dimerization and thus the binding affinity to VEGF.

Conbercept is designed and produced in People's Republic of China, but it is not approved in USA or European countries. Even if small trials conducted in China demonstrated its efficacy, larger clinical trials are necessary for its routine use in clinics [55].

Brolucizumab

Brolucizumab is an humanized single-chain antibody fragment that inhibits all isoforms of VEGF-A [56]. Brolucizumab molecular weight is 26 kDa (compared to 115 kDa of aflibercept and 48 kDa of ranibizumab), thus currently is the smallest anti-VEGF antibody available. Its low molecular weight allows and high drug concentration, with a prolonged duration of action and less frequent injection. Brolucizumab have been already tested for AMD, showing its non-inferiority to Aflibercept [57]. A RCT evaluating the efficacy and safety of Brolucizumab in patients with DME is in progress [58].

Abicipar-Pegol

Abicipar Pegol is a VEGF inhibitor belonging to a new class of binding molecules called DARPin [59]. DARPin molecules contain ankyrin repeat domain and could offer some advantages compared to antibody-derived molecules, such as small size and high affinity, selectivity and stability. Abicipar Pegol molecule weights 34 kDa and consists in a small recombinant protein (14 kDa) coupled to polyethylene glycol. Phase I/II trial showed the efficacy of the drug in DME and AMD [60].

Port delivery system

Anti-VEGF treatment requires frequent intravitreal injection, thus representing a burden for the patient and for the healthcare system. The ranibizumab port delivery system (RPDS) is an innovative way of delivering ranibizumab, allowing a continuous and long-lasting release of the anti-VEGF drug into the vitreous [61]. RPDS is an implant surgically inserted in the sclera and pars plana. It contains a reservoir of drug, refillable trough a self-sealing septum without removing the device from the eye. The ranibizumab diffuses from the reservoir to vitreous cavity following the concentration gradient. The RPDS has been already investigated in neovascular AMD in a phase II trial [62]. The LADDER study concluded that the continuous intravitreal delivery of ranibizumab through the PDS implant inhibited efficaciously VEGF activity without recurring to monthly intravitreal injections in most of the treated patients. Almost 80% of patients in the

RPDS 100-mg/ml arm required an implant refill after 6 months or more. Once proved its efficacy in the treatment of neovascular AMD, RPDS could also successfully used in DME and proliferative DR.

Topical treatment

Intravitreal therapy requires the insertion of a needle through the sclera and ora serrata to reach the vitreous cavity, and it is associated with rare but potentially devastating adverse events (endophthalmitis, retinal detachment and hemorrhage). Thus, the need for a less invasive way of delivering the drugs.

Nanomedicine provides a potential way to a topical anti-VEGF treatment. Carbon dots (C-dots) are nanomaterials with unique physical properties [63]. Aptamers are oligonucleotide that bind to a specific ligand. Anti-VEGF aptamer C-dots are hybrid systems which can act as carrier for the anti-VEGF aptamer through the cornea, stimulating the release of the aptamer in the presence of VEGF. Thus is it possible to obtain anti-VEGF activity at retinal level without recurring to intravitreal injections [64].

Suprachoroidal triamcinolone acetonide

The suprachoroidal space represents an alternative way to deliver drugs to the retina. Corticosteroids injection in the suprachoroidal space may allow high drug concentration in the retina, and in the meanwhile reduce its concentration in the anterior parts of the eye. Suprachoroidal triamcinolone acetonide is a new formulation of triamcinolone acetonide administered in the suprachoroidal space through a microneedle, with a procedure similar to that of an intravitreal injection. A phase 1/2 clinical trial evaluated the safety and efficacy of suprachoroidal triamcinolone acetonide in 20 patients with DME, alone or in combination with intravitreal aflibercept [65]. This trial demonstrated that suprachoroidal triamcinolone acetonide therapy is well tolerated and with few adverse events, and showed a preliminary efficacy in DME.

Vitreoretinal surgery

Although the pathogenesis of DME is not completely understood, vitreous is one of the protagonists and is a causative factor for increased vascular permeability. Primary indications for pars plana vitrectomy (PPV) are connected to advanced form of DR, as PDR: acute massive vitreous hemorrhage or > 3 months lasting, tractional retinal detachment or combined tractional/rhegmatogenous retinal detachment, pre-macular hemorrhage. Recent reports suggest that PPV improves the diffusion of fluid from the retina and transport of oxygen in non-perfused areas [66]. Major adverse events related to the surgery are cataract formation and progression, IOP increase, retinal detachment, endophthalmitis, vitreous and choroidal hemorrhage. Some reports showed that ILM removal provides additional benefits in preventing the recurrence ERM. The ILM may act as a scaffold promoting the formation of the ERM, and its peeling leads to better anatomical and functional results.

Conclusion

DR is an ever-more common sight-threating disease and the ophthalmologist has a major role in the management of a complex disease as diabetes. Early diagnosis, correct follow-up and appropriate use of therapy weapons are essential for a good visual prognosis of the patient. Multimodal Imaging approach, in this sense, is an essential aid for the specialist. PRP, along with intravitreal injections of steroids/anti-VEGF, demonstrated to be an effective treatment in many large clinical trials and drastically reduced the necessity to perform surgery. Moreover, trials on new drugs and telemedicine/artificial intelligence are the promises for the future. However, new pre-clinical researches are needed to thoroughly investigate the complexity of DR and prevention/early screening are the key points to truly tackle the burden of DR.

Author's Contribution

Marco Battista, Maria Brambati and Vincenzo Starace contributed equally to the work presented here and should therefore be regarded as equivalent authors.

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