Diabetes and the Eye

Massimo Porta and José Cunha-Vaz

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Abstract
Diabetic retinopathy (DR) remains a leading cause of visual impairment in the industrialized world and a growing concern in developing countries, as diabetes is rapidly expanding worldwide. It is classified as nonproliferative (mild, moderate, or severe) and proliferative, with diabetic macular edema potentially developing at either stage. The prevalence and incidence of DR increase with diabetes

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duration and worsening of glycemic and blood pressure control. Current approaches to prevent DR include optimized control of blood glucose and blood pressure and screening for early identification of high-risk, though still asymptomatic, retinal lesions. Results from clinical trials suggest a role for renin-angiotensin system blockers and fenofibrate in reducing progression and/or inducing regression of mild to moderate nonproliferative DR. Laser photocoagulation remains the mainstay of treatment for proliferative DR and for non-center-involved diabetic macular edema, whereas intravitreal administration of anti-VEGF agents was shown to improve vision in center-involved macular edema and may become an option also for proliferative DR.

Keywords
Diabetes mellitus · Diabetic retinopathy · Glycemic control · Serum lipids · Retinal photocoagulation · Vascular endothelial growth factor

Introduction

Manifestations of diabetes can be found in all ocular structures as summarized in Table 1. Some of these are relatively benign, yet characteristic of diabetes, such as corneal wrinkles and iris vacuolation. Other manifestations have more serious effects on ocular function, such as diabetic retinopathy.

Eye Involvements in Diabetes

Orbit
Acute orbital cellulitis may occur in diabetes as a result of their general susceptibility to infections.

Orbital mucormycosis is a fulminant mycotic infection involving the nose, paranasal sinuses, orbit, and central nervous system. The reported mortality rate is over 80%; therefore, prompt recognition of the infection is urgent if patients are to survive. Pathologically, the most characteristic lesion of this infection is a thrombosing arteritis that results from direct invasion of the vessel wall by the fungus. This may be contrasted with bacterial involvement of the vascular system, which predominantly affects the veins (Gass 1961). Such thrombosing arteritis produces widespread ischemic necrosis affecting the nose, sinuses, eye, orbit, and brain (Table 1).

Nerves: Extraocular Muscles
Neuropathy with resultant paralysis of the third, forth, or sixth cranial nerves as a complication of diabetes was first described in 1866 by (Ogle 1866). Waite and Beetham (1935) found the sixth cranial nerve most frequently involved, while other reports have indicated that the third nerve is also commonly affected (Leopold and Mosier 1978).
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<th>Location</th>
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<tr>
<td>Orbit</td>
<td>Cellulitis, mucormycosis</td>
<td>(Gass 1961)</td>
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<td>Nerves, extraocular</td>
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<td>Cornea</td>
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<td>Corneal pigmentation</td>
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<td></td>
<td>Decreased corneal sensitivity</td>
<td>(Scullica and Proto 1965)</td>
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<td>Iris, trabecular meshwork</td>
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<td>Pigment dispersion</td>
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<td>Chronic simple glaucoma</td>
<td>(Becker 1971)</td>
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<td>Iris neovascularization and glaucoma</td>
<td>(Simmons et al. 1977; Madsen 1971; Little et al. 1976)</td>
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<td>Ciliary body</td>
<td>Weakness of accommodation</td>
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<td>Basement membrane thickening</td>
<td>(Yamashita and Becker 1961)</td>
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<td>Pupil</td>
<td>Sluggish responses</td>
<td>(Waite and Beetham 1935)</td>
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<td>Argyll Robertson pupil</td>
<td>(Waite and Beetham 1935; Gundersen 1974)</td>
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<td>Oculomotor neuropathy with pupillary</td>
<td>(Goldstein and Cogan 1960)</td>
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<td>Lens</td>
<td>Senile cataract</td>
<td>(Waite and Beetham 1935; Caird et al. 1964)</td>
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<td>Juvenile cataract</td>
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<td>Transient opacifications</td>
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<td>Fluctuations in refraction</td>
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<td>Vitreous</td>
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<td>Increased incidence of asteroid hyalosis</td>
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<td>Retina</td>
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<td>Increased incidence of vein occlusions</td>
<td>(Ditzel and White 1956)</td>
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<td>Lipemia retinalis</td>
<td>(Laws and Harpur 1958)</td>
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Diabetic ophthalmoplegia is otherwise benign, resolving spontaneously in most cases within a few months.

**Ocular Appendages**
Blepharitis and xanthelasmata were reported to occur significantly more frequently among a large series of diabetics compared with nondiabetic controls (Waite and Beetham 1935).

**Cornea**
In 1935, Waite and Beetham (1935) first described wrinkling in Descemet’s membrane in diabetic individuals.

Henkind and Wise (1961) noted a similar incidence of wrinkles among 133 diabetics. Female diabetics and diabetics with some degree of retinopathy showed a greater frequency of wrinkles.

Decreased corneal sensitivity among diabetics has been reported by Scullica and Proto (1965), Schwartz (1974), and Daubs (1975). Such decreased sensitivity is supposedly a result of diabetic polyneuropathy that affects the trigeminal nerve.

**Iris: Trabecular Meshwork**
Vacuolation of the pigment epithelium of the iris, the material within diabetic iris vacuoles, has been shown both histochemically (Yamashita and Becker) and by electron microscopy (Yanoff et al. 1970) to be glycogen.

Becker (1971) has summarized the several associations between diabetes and chronic simple glaucoma. Compared with nondiabetics, diabetics have a higher incidence not only of glaucoma but glaucoma-related findings.

These observations suggest that diabetes should be carefully followed for glaucoma, and, conversely, chronic simple glaucoma patients should be screened for diabetes. A diabetic with chronic simple glaucoma may require rigid control of his intraocular pressure.

Neovascular glaucoma often, but not invariably, supervenes in patients who have developed iris neovascularization, with a poor prognosis for both comfort and vision. Since neovascular glaucoma tends to occur in eyes already severely damaged by advanced retinopathy, treatment for the conditions has heretofore been mostly palliative.

Little et al. (1976) have reported that panretinal photocoagulation causes regression of iris and angle neovascularization, presumably by diminishing retinal hypoxia (and theoretical vasoformative factor) inciting the neovascularization.

**Ciliary Body**
After corneal wrinkles, previously discussed, Waite and Beetham (1935) noted weakness of accommodation to be the second most frequent finding among their observed series of diabetes.
Pupil
Pupillary abnormalities found by Waite and Beetham (1935) among diabetes included poor reaction to topical mydriatics, sluggish response to various stimuli, and typical Argyll Robertson pupils.

It has been suggested that diabetic autonomic neuropathy predominantly affects sympathetic over parasympathetic pupillary innervation, which may explain some of the pupillary abnormalities observed among diabetics (Hreidarsson 1979).

Lens
Rollo, in 1798, first implied an association between diabetes and cataract formation (Waite and Beetham 1935), a concept that was amplified in the bold literature under the general term diabetic cataract. This term is probably not justified, as the vast majority of lens opacities seen in diabetes are identical to various senile lens changes that occur in nondiabetics (Waite and Beetham 1935; Morse 1976; Leopold and Mosier 1978).

Recent reports have indicated that diabetic patients may develop cataracts more frequently and at earlier ages than nondiabetic ones (Caird et al. 1964; Morse 1976; Leopold and Mosier 1978; Kreines and Rowe 1979).

Optic Nerve
Typical ischemic optic neuropathy can occur in diabetes, usually middle-aged or older adults. The condition is of abrupt onset and is usually monocular, with nerve fiber bundle or altitudinal visual field defects and significant visual loss that generally do not improve.

Bilateral optic atrophy may occur in juvenile diabetics as part of a recessively inherited syndrome, first described in 1938 by Wolfram (1938). The complete syndrome includes juvenile diabetes mellitus, optic atrophy, neurosensory hearing loss, and various manifestations of hypothalamic dysfunction such as diabetes insipidus, disordered temperature regulation, vasomotor instability, and hypogonadism (Gupta et al. 1979).

Diabetic Retinopathy

Epidemiology and Risk Factors
Despite improvements in diabetes care and visual outcomes, diabetic retinopathy (DR) remains the fifth leading cause of blindness and visual impairment (Bourne et al. 2014), and the second commonest cause in working age (Liew et al. 2014), in developed countries and can reach its more advanced stages in the almost total absence of symptoms. According to historic series, DR prevalence is about 70% in patients with type 1 diabetes and 40% among those with type 2, with no difference by gender. The prevalence increases with disease duration, and more than 90% of patients with type 1 diabetes develop DR, proliferative in almost half the cases, within 20 years of the diagnosis (Klein et al. 1984b).
A recent pooled analysis on worldwide data concluded that, over a total of 35 studies conducted in 1980–2008 on 22,896 individuals with diabetes, the overall prevalence of any DR was 34.6%, with 6.96% for proliferative DR, 6.81% for diabetic macular edema, and 10.2% for sight-threatening DR from either or both. Prevalence increased with diabetes duration, HbA1c, and blood pressure levels and was higher type 1 compared with type 2 diabetes (Yau et al. 2012).

More recent series based upon population screening results report prevalence of any DR and sight-threatening DR of 56.0% and 11.2% in type 1 diabetes, respectively, and 30.3% and 2.9%, in type 2 diabetes, respectively, in Wales 2005–2009 (Thomas et al. 2015), and in 2000–2013 a prevalence of 20.12% for any DR in Germany, with HbA1c and micro- and macroalbuminuria representing the strongest risk predictors for severe DR (Hammes et al. 2015). There are no clear ethnic differences in the relationship between HbA1c and DR (Bower et al. 2013).

Natural History and Classification of Diabetic Retinopathy

Alterations of retinal capillaries are at the basis of clinically detectable DR and include multiple occlusions, increased permeability of the vessel wall, and, in the proliferative form, growth of newly formed vessels. Occlusions cause areas of ischemia and focal (microaneurysms) or generalized dilatation of the capillaries. Dilated, fragile, and hyperpermeable vessels result in microhemorrhages, larger hemorrhages, and leakage of plasma and lipoproteins in the neuroretina, causing edema and the so-called hard exudates. Occlusion of vessels may result in focal retinal ischemia, manifested as white-grayish areas with blurred margins or cotton wool spots. The presence of these lesions defines nonproliferative retinopathy, which can be mild, moderate, or severe and further develop into two forms at high risk of visual loss: diabetic macular edema (DME) and proliferative retinopathy (PDR) (Porta and Bandello 2002).

When the lesions of DR involve the macula lutea, the portion of retina responsible for vision of colors and details, severe functional impairment may result. DME affects primarily, but not exclusively, patients with type 2 diabetes, and as these represent more than 90% of the diabetic population, it is now the main cause of visual impairment in diabetes. Progressive ischemia of the peripheral retina leads to PDR, with growth of new vessels which may invade the vitreous and give rise to vitreous hemorrhages and development of fibro-glial tissue. If the latter contracts, retinal detachment may occur. Severe ischemia may proceed to the anterior chamber with development of iris neovascularization (rubeosis iridis), causing terminal evolution in neovascular glaucoma.

Although DR is considered predominantly a pathology of microvessels, increasing evidence points at degeneration of the neuroretina (mainly apoptosis of ganglion cells and glial activation) as an early event which may predate and perhaps contribute to microcirculatory abnormalities (Antonetti et al. 2006; Garcia-Ramirez et al. 2009). Damage of the neuroretina may result in loss of color discrimination and contrast sensitivity, detectable by electrophysiological studies in patients with no clinically evident DR (Shirao and Kawasaki 1998), and delayed multifocal
electroretinographic implicit time may predict the development of early microangiopathy (Fletcher et al. 2007). Metabolic and signaling pathways involved in retinal neurodegeneration may be shared with, and/or activate mechanisms involved in, the pathogenesis of microangiopathy (Asnaghi et al. 2003).

**Pathogenesis**

Among the possible mechanisms of glucose-induced vascular damage, four hypotheses have been widely entertained: (1) increased flux through the polyol pathway, (2) increased formation of advanced glycation end products (AGE), (3) protein kinase C (PKC) activation, and (4) increased flux through the hexosamine pathway.

Aldose reductase (AR) is the key enzyme of polyol pathway. It normally reduces toxic aldehydes to inactive alcohols and excess intracellular glucose to sorbitol while consuming NADPH with consequent hyperglycemic pseudohypoxia (Williamson et al. 1993; Asnaghi et al. 2003) and increased susceptibility to intracellular oxidative stress (Brownlee 2001).

Intracellular high glucose reacts with proteins, amino acids, and nucleic acids via Schiff base condensation with amino groups, followed by irreversible rearrangement into Amadori products. Further Maillard reactions slowly produce AGE, which can also derive from earlier glycation products through glycoxidation or reactive dicarbonyl fragments generated from free glucose. AGE, in turn, can modify intracellular proteins (Giardino et al. 1994), extracellular matrix (Charonis et al. 1990), and circulating proteins, leading to activation of AGE receptors and production of inflammatory cytokines and growth factors.

Intracellular high glucose increases the de novo synthesis of the lipid second messenger diacylglycerol, which in turn activates PKC synthesis, causing a number of effects, such as decreased synthesis of endothelial nitric oxide synthase and increased synthesis of endothelin-1, transforming growth factor β, plasminogen activator inhibitor-1, and NF-κB (Koya and King 1998).

Excess fructose-6-phosphate derived from high availability of intracellular glucose can be transformed into glucosamine-6-phosphate and then to UDP N-acetylglucosamine, which acts on serine and threonine residues of transcription factors, resulting in pathological changes in gene expression (Du et al. 2000).

Brownlee and associates have hypothesized that the possible common denominator (“unifying mechanism”) of these apparently independent biochemical pathways is high glucose-induced excess production of reactive oxygen species (ROS) by the mitochondrial electron transport chain inside the endothelium, as a result of increased flux through the Krebs’ cycle (Nishikawa et al. 2000; Brownlee 2001). ROS, by causing strand breaks in nuclear DNA, activate poly(ADP-ribose) polymerase (PARP) which in turn inhibit glyceraldehyde 3-phosphate dehydrogenase (GAPDH) activity (UK Prospective Diabetes Study (UKPDS) Group 1998b), therefore pushing metabolites from glycolysis in the upstream pathways mentioned above.
Thiamine (vitamin B1) and benfotiamine, a thiamine derivative which can be administered orally, block all the above pathways implicated in the pathogenesis of DR and have been shown effective in preventing experimental DR in animals (Beltramo et al. 2008). However, clinical trials demonstrating its effectiveness are still lacking.

Clinical Assessment of Diabetic Retinopathy

Early detection of diabetic retinopathy and characterization of disease progression in the initial stages of the retinopathy are priorities. It is fundamental to be able to follow the initial stages of the retinopathy, when the retinal alterations may still be reversible and may, therefore, be controlled by medical therapy and adequate metabolic control.

The predominant causes of vision loss in diabetic retinopathy are advanced macular edema and proliferative diabetic retinopathy, both identified as sight-threatening complications of the retinopathy. Visual acuity examination is, therefore, not an appropriate method to follow the initial stages of diabetic retinopathy and must be kept in mind that vision loss due to diabetic retinopathy is a sure indication that the retinopathy has already reached an advanced stage.

Fundus Photography

Color fundus photography is the tool more generally used to document retinal disease and its evolution in diabetic patients. It is used for tracking disease progression and is accepted as the best screening method for diabetic retinopathy.

Fundus photographs allow to identify microaneurysms, the most characteristic initial lesions of diabetic retinopathy. They also show the development of hemorrhages and hard and soft exudates and, finally, show well the major changes occurring in the retinal venules and arterioles as the disease progresses (Klein et al. 1985).

Fundus photographs or fundus digital images must be produced in a consistent manner following well-defined protocols, in order to allow comparisons between different examinations performed on different occasions.

Because much of the diabetic clinically significant retinal pathology occurs around the disc and macula, a standard for photographic composition has evolved, with a central 30°–40° field identified as field 2 of the ETDRS protocol that includes the entire macula, the entire optic disc, and the major vascular arcades recorded in one view (Fig. 1).

Grading Diabetic Retinopathy from Color Fundus Photographs

Fundus photography has been the method of choice to follow diabetic retinopathy, because (1) it is noninvasive, technically easy, and well accepted by patients; and (2) its usefulness has been demonstrated in a large-scale randomized clinical trial, the Diabetic Retinopathy Study (DRS), which showed the benefits of photocoagulation in the treatment of proliferative diabetic retinopathy.
Fundus photography was chosen to monitor retinopathy in the Diabetes Control and Complications Trial in the USA and UK Prospective Diabetes Study Trial. Elaborate fundus photography grading was developed from the original Airlie House Diabetic Retinopathy Classification to document progression and delineate the natural history of retinal disease, from the earliest visible alterations to more advanced stages, e.g., maculopathy and high-risk proliferative diabetic retinopathy. These gradings, however, offer little information on the initial stages of the disease. Microaneurysms need to be counted to assess progression of retinopathy, and new microaneurysms should always be added to those previously identified in the same retina (Torrent–Solans et al. 2004).

**Monitoring the Initial Stages of Diabetic Retinopathy Progression: Microaneurysm Turnover**

It is of fundamental importance to monitor the progression of the disease in a specific patient and identify if he/she is a “progressor,” i.e., a patient that shows signs of rapid progression. Some eyes/patients need special attention and timely intervention to avoid development of sight-threatening diabetic retinopathy complications, macular edema, or proliferative diabetic retinopathy.

The initial alterations that occur in nonproliferative diabetic retinopathy and need to be monitored are microaneurysm dynamics (their formation and disappearance) and vascular leakage with subsequent edema and hard exudate formation.

Visual function loss occurs characteristically late in diabetic retinopathy, because the eye has a large functional reserve of vision and diabetic retinopathy affects initially the inner layers of the retina away from the photoreceptors. Therefore, structural changes are detected in diabetic retinopathy earlier than functional changes. We have, therefore, to focus on evidence of structural changes if we want to follow progression in the earliest stages of diabetic retinopathy.
To identify progression it is essential to collect sequential series of images, and these images must be compared. The need for co-registration of these sequences of images is, therefore, of great relevance. By applying novel image co-registration comparative analysis software, it is now possible to perform reliable sequential comparisons of fundus digital photography images (Nunes et al. 2009).

Softwares are available to automatically detect changes occurring in eye fundus digital images, by comparing successive visits to the reference image, in each eye, based on co-registration and co-localization of the changes (Figs. 2 and 3).

On fundus photography, microaneurysms and small hemorrhages are the initial changes detected in the diabetic retina. They may be counted, and retinal microaneurysm counting has been previously suggested as an appropriate marker of retinopathy progression (Klein et al. 1995; Csaky et al. 2008).

Retinal microaneurysms are relevant lesions of diabetic retinopathy, and even one or two microaneurysms in an eye should not be regarded as unimportant (Klein et al. 1989; Kohner et al. 1999). More recently, Sjølie et al. (2011) confirmed that microaneurysm counts were predictive of an increased risk of retinopathy progression.

Our studies have shown that it is not the absolute total number of microaneurysms at a certain point in time that may provide the best indication of retinopathy progression, but the rate of microaneurysm turnover in successive visits during a 1- or 2-year period.

Wide Field Fundus Angiography
Currently, ultra-wide field (UWF) fluorescein angiography (FA) devices allow capture of a single high-resolution 200° retinal field covering more than 80% of the retinal surface where all vessels are in the same angiographic phase.

The nonperfusion identified on UWF FA in diabetic eyes with DR was located primarily in the midperipheral retina and pressed posteriorly with increasing severity.

Peripheral nonperfusion likely underlies the development of predominantly peripheral lesions (PPLs) and accounts for the marked increases in retinopathy progression associated with the presence of PPLs (Silva et al. 2016).

Fluorescein Angiography
Since 1961, when Novotny and Alvis introduced the technique of fluorescein angiography, its routine use has contributed much to our present understanding of diabetic retinal disease.

Sodium fluorescein, which is approximately 80% protein-bound to albumin, is the dye used in fluorescein angiography. Fluorescein is a small molecule that remains unbound in 10–20% of the amount injected and therefore diffuses freely through the choriocapillaris, Bruch’s membrane, optic nerve, and sclera. However, its diffusion through the tight junctions of the retinal endothelial cells and of the retinal pigment epithelium which are the inner and outer blood-retinal barriers is minimal (Shakib and Cunha-Vaz 1966). If there is a disruption of the blood-retinal barrier, dye leakage occurs. Similarly, the tight junctions (zonula occludens) between the retinal pigment
epithelial cells constitute the outer blood-retinal barrier, which under normal, physiological conditions does not allow visible leakage of fluorescein from the choroid into the retina.

Another fundamental contribution of fluorescein angiography to our understanding of diabetic retinopathy is the identification of areas of capillary closure or capillary dropout (Fig. 4).

**Fig. 2** This figure illustrates the automatic microaneurysm tracking over time, color-coding each detected microaneurysm as new, old, or disappeared (based on proprietary co-registration algorithm)

**Fig. 3** The software automatically calculates microaneurysm formation and disappearance rates. The patient above had a microaneurysm formation rate of 5 microaneurysms/year over a 24-month follow-up
The normal regular distribution of the capillary network appears interrupted by areas which are not perfused by the dye, identifying well areas outlined by perfused capillaries (Kohner and Henkind 1970).

Fluorescein angiography, because of the need for intravenous injection of fluorescein, is used much less frequently than fundus photography. Although sodium fluorescein is generally safe and is used in the daily routine of every ophthalmological care center, severe anaphylactic reactions may occur sporadically (1 in 200,000) (Yannuzzi et al. 1986).

In 1975, vitreous fluorometry, a clinical quantitative method for the study of the blood-retinal barrier, was introduced by our group (Cunha-Vaz et al. 1975), showing that an alteration of the blood-retinal barrier could be detected and measured in diabetic eyes apparently with normal fundi. The disturbance of the blood-retinal barrier, as evidenced by vitreous fluorometry, appeared in some patients before microaneurysms or capillary closure could be demonstrated by fluorescein angiography. These results were confirmed by Waltman et al. (1978a, b).

One major limitation of the available commercial instrumentation for vitreous fluorometry (Fluorotron Master Coherent, USA) was associated with the fact that the permeability of the blood-retinal barrier is measured as an average over the macular area. Accurate mapping of localized changes in the permeability of the blood-retinal barrier would be beneficial for early diagnosis, to explain the natural history of retinal disease and to predict its effect on visual acuity.

**Optical Coherence Tomography (OCT)**

Recently, one methodology capable of measuring objective changes in retinal thickness and giving morphological and topographic images of the retina became available, optical coherence tomography (OCT), changing dramatically the landscape of diabetic macular edema diagnostic and follow-up.
OCT is a noninvasive and noncontact diagnostic method, well tolerated by patients, that provides important information about the retina. OCT imaging is analogous to B-scan ultrasound imaging, except that it uses infrared light reflections instead of ultrasound. It produces reliable, reproducible, and objective cross-sectional images of the retinal structures and the vitreoretinal interface and allows quantitative measurements of retinal thickness.

OCT brought new insights about morphological changes of the retina in diabetic retinopathy and diabetic macular edema. It showed that macular edema may assume different morphologic patterns (Yamamoto et al. 2001; Kim et al. 2006). In addition, a quantitative characterization of macular edema became feasible, as determined by measurements of retinal thickness and volume. OCT has been demonstrated to be more sensitive than slit-lamp biomicroscopy in detecting small changes in retinal thickness (Hee et al. 1995; Yang et al. 2001; Massin et al. 2006; Lang 2007) and is clearly less subjective. In cases of diabetic macular edema, OCT scans may demonstrate diffuse thickening of the neurosensory retina and loss of the foveal depression; cystic retinal changes, which manifest as areas of low intraretinal reflectivity; and serous retinal detachment, alone or combined.

Cross-sectional images resemble closely the histological appearance of the retina (Ron Margolis and Peter K. Kaiser 2008) (Figs. 5 and 6). The top of the image corresponds to the vitreous cavity, which is optically silent, in a normal patient, or may show the posterior hyaloid face, if there is a posterior vitreous detachment (Cunha-Vaz and Coscas 2010). Central foveal depression is visible in normal eyes. The anterior boundary of the retina corresponds to the internal limiting membrane, at the vitreoretinal interface, hyperreflective and well defined, because of the contrast between the nonreflective vitreous and the backscattering of the retina.

**Fig. 5** SD-OCT normal cross-sectional macular image. (a) False color. (b) Grayscale
The internal structure of the retina has heterogeneous reflections and distinct bands, and an anatomic correlation with the layers of the human retina has been proposed (Drexler 2007) (Fig. 6). Retinal nerve fiber layer is aligned horizontally, demonstrating higher tissue signal strength and appears thicker and closer to the optic nerve as expected. Axially aligned cellular layers – ganglion cell layer, inner nuclear layer, and outer nuclear layer – have lower tissue signal compared with horizontally aligned layers, internal limiting membrane, retinal nerve fiber layer, and plexiform layers, which have higher tissue signal. Typically, nuclear layers appear hyporeflective, while plexiform layers (inner plexiform layer and outer plexiform layer and axonal layers are relatively hyperreflective).

In the outer retina, different hyperreflective structures (bands) are visualized. TD Stratus OCT images the outer retinal layers as two hyperreflective bands, the photoreceptor’s outer segments (inner) and the retinal pigment epithelium/choriocapillaris complex (outer). On the other hand, SD-OCT scans of the outer retina allow visualization of more bands than the TD-OCT. With this high-resolution technology, three or four distinct strongly reflective bands are apparent, although their histological correlation remains a matter of discussion. According to Pircher et al. (2006), the first (inner) band may correspond to the external limiting membrane and the second to the interface of the inner and outer segments of the photoreceptor layer, the third band may represent the outer segment – retinal pigment epithelium junction – and the fourth (outer) is assumed to represent the retinal pigment epithelium (Fig. 6). The analysis of structural changes in the outer retinal layers, particularly affecting photoreceptors and their interface, is now possible, using SD-OCT (Coscas and Soubrane 2009).

Since the commercialization of OCT systems, several types of software to quantify macular thickness became available. Mean macular retinal thickness is displayed as a two-dimensional false color-coded map, where bright colors (e.g., red and white) represent thick areas and dark colors (e.g., blue and black) represent thin areas, and as a numerical map, for nine ETDRS-type areas (Fig. 7).
Nowadays, OCT is increasingly used in the early detection of subclinical macular edema. Cross-sectional images of the retinal structures and thickness maps provide an objective and reproducible baseline characterization of the retinal disease. OCT imaging seems to be more sensitive than slit-lamp biomicroscopy to detect small changes in retinal thickness (Hee et al. 1995; Yang et al. 2001; Lang 2007) and to visualize infraclinical foveolar detachments (Massin et al. 2006; Bandello et al. 2015). OCT scans also allow an accurate evaluation of disease progression, over time, and particularly after treatment.

OCT images of diabetic macular edema depict the presence of low intraretinal reflectivity, due to fluid accumulation in the extracellular space of the retina. The process begins as a diffuse retinal thickening with spongelike appearance of the retinal layers, showing increase in the extracellular spaces advancing to the typical image of cystoid spaces (Otani et al. 1999; Alkuraya et al. 2005; Bandello et al. 2015) (Fig. 8).

Another advantage of the OCT is the possibility to analyze the vitreomacular interface. It is possible to determine the status of the posterior hyaloid when it is only slightly detached from the macular surface (Gaucher et al. 2005). The concept of vitreoretinal traction is now considered of major relevance in the OCT classification of diabetic macular edema (Panozzo et al. 2003; Kang et al. 2004).

A composite grading for macular edema based on Fig. 9 and Table 2 has recently been proposed. The mean RT values for the different areas of the OCT grid are
considered abnormal if they correspond to the RT values defined by the DRCR.net as subclinical macular edema for the central subfield and if they are ≥ 2 SD beyond the normative database for the device used, in the inner and outer rings of the OCT macula grid. The grading includes four characteristics: (1) location of edema (whether the central subfield is involved and which, if any, inner and outer rings are involved); (2) the amount of edema, represented by the highest absolute mean RT value registered in any of the subfields, i.e., central subfield or any quadrant of the inner and outer OCT rings; (3) the presence or absence of signs of vitreous traction (VT); and (4) the identification of the OCT instrument with which the data
was acquired. For example, an eye with increased RT in the central subfield and in two quadrants of inner ring, showing the highest mean RT value of 450 μm in one of the inner ring quadrants and no signs of vitreous traction (NVT) using Cirrus SD-OCT, Zeiss, is identified as 10/450 μm/NVT/Cirrus SD-OCT. Another eye with an increased RT only in the outer ring, involving three quadrants, showing the highest RT value of 480 μm in anyone of the quadrants involved and no signs of vitreous traction with the examination performed in the Spectralis SD-OCT, Heidelberg, would be graded as 2/480 μm/NVT/Spectralis SD-OCT.

**OCT Angiography**

Optical coherence tomography angiography visualizes vasculature using motion contrast. Optical coherence tomography operates under the basic assumption, which is an oversimplification, that the only moving thing in the retina is blood flow. Pixels from individual areas in repeated OCT images are compared over time, and those pixels which show changes or fluctuations are displayed as bright, whereas pixels from areas with little or no change are displayed as black. There are many different algorithms or methods for detection of motion contrast. Some involve using OCT signal amplitude, phase, or a combination of the two. There are also different statistical techniques for assessing changes. However, all these methods eventually visualize vasculature by detecting motion.

OCT angiography has the advantage that it is able to identify the retinal vasculature without the need for dye injection. Imaging can be performed in situations when conventional angiography is not indicated, repeated on every patient visit, and dynamic changes can be assessed.

### Table 2 Location score

<table>
<thead>
<tr>
<th>Score</th>
<th>Location with increased RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No increases in the central subfield, inner ring or outer ring</td>
</tr>
<tr>
<td>1</td>
<td>Increases in outer ring: two quadrants $\geq$ normal mean + 2 SD or one quadrant $\geq$ normal mean + 2 SD + 15 μm</td>
</tr>
<tr>
<td>2</td>
<td>Increases in outer ring: three or four quadrants $\geq$ normal mean + 2 SD</td>
</tr>
<tr>
<td>3</td>
<td>Increases in inner ring: two quadrants $\geq$ normal mean + 2 SD or one quadrant $\geq$ normal mean + 2 SD + 15 μm</td>
</tr>
<tr>
<td>4</td>
<td>Increases in inner ring: three or four quadrants $\geq$ normal mean + 2 SD</td>
</tr>
<tr>
<td>5</td>
<td>Criteria for score 3 plus score 2 or criteria for score 4 plus score 1</td>
</tr>
<tr>
<td>6</td>
<td>Criteria for score 4 plus score 2</td>
</tr>
<tr>
<td>7</td>
<td>Increase in central subfield: subclinical macular edema (DRCR.net)</td>
</tr>
<tr>
<td>8</td>
<td>Criteria for score 7 plus score 1</td>
</tr>
<tr>
<td>9</td>
<td>Criteria for score 7 plus score 2</td>
</tr>
<tr>
<td>10</td>
<td>Criteria for score 7 plus score 3</td>
</tr>
<tr>
<td>11</td>
<td>Criteria for score 7 plus score 4</td>
</tr>
<tr>
<td>12</td>
<td>Criteria for score 7 plus score 5</td>
</tr>
<tr>
<td>13</td>
<td>Criteria for score 7 plus score 6</td>
</tr>
</tbody>
</table>
The images produced from the retinal vascular network are remarkably similar to those seen in fluorescein angiography, offering more detail. Furthermore, OCT angiography reveals, for the first time, in a clinical environment the deep retinal vascular plexus which is not visualized in fluorescein angiography.

In diabetic retinopathy, OCT angiography is offering new perspectives for quantifying reliably capillary closure, particularly of the changes occurring in the superficial retinal capillary net (Agemy et al. 2015). Neovascularization is also well demonstrated and identified. Microaneurysms, however, do not correspond well with the ones identified in fluorescein angiography because of the variations in blood flow between different microaneurysms, and a consensus is needed to identify clearly what should be considered a microaneurysm in OCT angiography.

**Electrophysiological Testing**

Electrophysiological changes in diabetes may have a microvascular origin (Scholl and Zrenner 2000) or be independently due to retinal cell dysfunction (Tzekov and Arden 1999). Despite many psychophysical and electrophysiological methods that have been used to document diabetic retinopathy, a consensus on the ideal tool to detect retinal dysfunction in the initial stages of diabetic retinopathy is still missing.

In this respect, it must be kept in mind that assessment of standard visual acuity is not expected to be very rewarding since visual acuity remains stationary until ~50% of the neuroretinal pathways are affected (Frisén and Frisén 1976) and the foveal avascular zone is frequently enlarged in diabetic patients without any sign of change in visual acuity (Arend et al. 1995). This suggests that psychophysical techniques should aim to assess separately distinct functional channels (Bresnick et al. 1985; Green et al. 1985). Evidence for predominant early involvement of the parvocellular pathway suggests that the physiology of the perifoveal area should be under scrutiny in future studies, since changes in the microvasculature in this region may be predictive of visual outcome.

Diabetic retinopathy is initially focal in its nature, which renders standard electrophysiological methods that measure the global response of retinal photoreceptors, such as the flash electroretinogram (ERG), rather unpromising approaches. For these reasons conflicting reports have emerged in the literature, some describing significant differences (Juen and Kieselbach 1990; Holopigian et al. 1992) and others not (Jenkins and Cartwright 1990). The reduction of the b-wave of the conventional ERG is often reported only for advanced cases, and more sensitive results can only be obtained with the calculation of intensity-response functions, which are of limited clinical applicability.

In a recent study, Jansson et al. (2015) evaluated the role of photopic full-field electrophotometropathy and retinal thickness measurements by SD-OCT in the assessment of type 1 diabetic retinopathy. They concluded that it has limited clinical value and that thinning of the central retina leading to significant functional impairment may reflect in the retinal tissue. This process may occur independently of the retinal vascular disease.
There is an ongoing search for measures capable of detecting earlier dysfunction. Recent candidates concerning parametric evaluation have included amplitude and delay of oscillatory potentials, pattern ERG, the scotopic threshold response, and more recently the multifocal ERG.

**Oscillatory Potentials (OPs)**
Oscillatory potentials are high-frequency retinal electrophysiological responses (100–160 Hz) which are superimposed on the ascending limb of the b-wave (Yonemura et al. 1963; Wachtmeister and Dowling 1978) and seem to be changed in early stages of diabetic retinal disease. They are a signature of the involvement of inner retinal layers since they are thought to originate in the inner plexiform layer, namely, from inhibitory circuits connecting amacrine and ganglion cells.

Oscillatory potentials are usually taken as good indicators of the extent of retinal ischemia and may be reduced at all stages of diabetic retinopathy, with a good correlation with severity, especially during proliferative stages.

Bresnick and colleagues (Bresnick et al. 1984, 1985; Bresnick and Palta 1987) confirmed and extended these results, by showing that oscillatory potential amplitude predicts progression (independently from predictors taken from fundus photography and fluorescein angiography) of eyes with nonproliferative diabetic retinopathy or mild proliferative diabetic retinopathy to severe proliferative diabetic retinopathy. Eyes with abnormal oscillatory potential amplitudes had a steady rate of progression to severe proliferation (28% after 1 year and 52% after 2 years). Eyes with normal oscillatory potentials had a much lower rate of progression (0 and 7%, respectively).

**Multifocal Electroretinography**
Multifocal electroretinography (mfERG) (Sutter and Tran 1992) provides functional topographic detail that overcomes the disadvantages of conventional electrophysiology. Objective measurement of retinal dysfunction simultaneously at multiple locations, by means of this technique, is now being increasingly used in diabetes research.

Electrophysiological local amplitude changes and delays have been found in the retinas of diabetic patients with or without retinopathy, both in regional and local averages (Palmowski et al. 1997; Fortune et al. 1999; Scholl and Zrenner 2000; Bearse et al. 2004). Multiple prospective analyses of local mfERGs identified functional abnormalities in eyes with diabetic retinopathy, both in retinal regions corresponding to retinopathy and in areas without signs of it (Fortune et al. 1999; Bearse et al. 2004). In the same line, it has been found that mfERG implicit time delays are associated with retinal locations in which new nonproliferative diabetic retinopathy will develop 1 year later (Han et al. 2004). All these promising results suggest that mfERG may become a pivotal technique for the study of neural impairment in the diabetic retina. Apparently, in some eyes, functional abnormalities of the retina and vision can occur before clinical signs of retinopathy vascular damage are visible on ophthalmoscopy (Fig. 10).
Current Options for Medical Treatment

Current possibilities to prevent and/or treat retinopathy include optimized control of blood glucose and blood pressure and screening for early identification of high-risk, though still asymptomatic, retinopathy.

The Diabetes Control and Complications Trial (DCCT) demonstrated that optimized insulin treatment reduces the incidence of retinopathy by 76%, progression of mild to moderate nonproliferative DR by 54%, and the need for photocoagulation by 56% (The Diabetes Control and Complications Trial Research Group 1993) in patients with type 1 diabetes. In those with type 2 diabetes, the UK Prospective Diabetes Study (UKPDS) showed that, over 12 years, optimized metabolic control reduces progression of DR by 21% and need for cataract surgery in 24% of cases (UK Prospective Diabetes Study (UKPDS) Group 1998a). Follow-up of the patients involved in these studies showed that the benefits of glycemic control carry over in time a sort of metabolic “memory” (The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group 2009) or “legacy” (Holman et al. 2008), so that any period of life spent in good glycemic control is “accounted for” in the later prevention of retinopathy and other complications.

The UKPDS (UK Prospective Diabetes Study (UKPDS) Group 1998b) also showed that reducing blood pressure (from 154/87 to 144/82 mmHg throughout 8 years) reduces the progression of DR by 34% and the overall risk of worsening of visual acuity by 47%, possibly by reducing DME. Until recently, the only intervention study to support a role for intensive hypertension control in the prevention of DR was the UKPDS. However, the ADVANCE (Patel et al. 2007) and ACCORD (Chew et al. 2010) trials could not confirm an influence of blood pressure lowering on progression of DR. Arguably, patients in the UKPDS had larger reductions from higher blood pressure values than those in ADVANCE (−5.6 mmHg systolic

Fig. 10 Deformable image registration between color fundus photograph (background image), leakage analysis (retinal leakage analyzer) (central squared area), and multifocal electroretinography (mfERG) (curve responses in white)
and –2.2 diastolic blood pressure from 145/81 mmHg, follow-up 4.3 years) (Patel et al. 2007) or in ACCORD, starting from 135/75 down to 128/68 with a median follow-up of 3.7 years (Chew et al. 2010), suggesting either that blood pressure lowering is more effective in poorly controlled hypertension or that longer follow-up is necessary to observe an effect on DR progression. No legacy effect was observed for blood pressure control in the UKPDS patients (Holman et al. 2008).

Current guidelines recommend to maintain HbA1c below 7.0% and blood pressure below 140/90 or 130/80 for patients at higher cardiovascular risk (Krikorian 2016). However, achieving these targets is far from easy outside of clinical trials in the general diabetic population, and data collected in most countries show that less than half, often less than one third, of patients do stay within those targets. Patients on insulin therapy have worse control than those treated with oral hypoglycemic agents, and, in turn, the latter fare worse than those on diet alone (Gill et al. 2003), presumably reflecting the levels of residual endogenous insulin secretion. Possible reasons for this high level of therapeutic failure include medical inertia, reduced patient adherence to prescriptions, and the inadequacy of current pharmacological options and lifestyle measures (Mannucci et al. 2014).

In any case, the overall outcomes of diabetes care seem to be improving gradually worldwide, thanks to increasing awareness and availability of materials for self-monitoring and therapy. Data from the National Health and Nutrition Examination Survey (NHANES) 1999–2004 show a slow but steady increase in the percentage of US patients with HbA1c less than 7.0% (Ford et al. 2008). Probably in connection with this positive trend, the epidemiological data collected in Scandinavia and Wisconsin show a lower cumulative incidence of proliferative retinopathy in patients who contracted type 1 diabetes in more recent years (Hovind et al. 2003; Klein et al. 2008). In the DCCT/EDIC cohort, in 30 years of follow-up, the cumulative incidence of PDR was 21% in the patients originally randomized to optimized therapy during the DCCT, compared to 50% in those who remained all their life on conventional treatment (The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group 2009).

There are however different approaches to interpreting these data. Progression of DR might be delayed rather than reduced in absolute terms, and the prolongation of life expectancy in patients may result in PDR appearing later rather than never at all. Data extrapolated from the DCCT dataset suggest that optimized insulin treatment would prolong life free of PDR by 14.7 years, of macular edema by 8.2 years, and of blindness by 7.7 years (The Diabetes Control and Complications Trial Research Group 1996), all weighted against a 2–3 times higher risk of severe hypoglycemia and increase in body weight. In addition, other predisposing factors not yet identified may play a role, as suggested by daily clinical experience and also quantified in the DCCT series. In fact, a post hoc analysis of all patients who participated in the trial showed that 10% of those who remained in the lowest HbA1c quintile (<6.87%) still developed DR and 43% of those who remained in the worst quintile (HbA1c > 9.49%) did not develop retinal lesions during the study (Zhang et al. 2001). The search for genetic markers that make patients susceptible to, or protected...
by, microangiopathy remains an open field that has so far produced few generalizable results. Of interest is the recent identification of a point mutation associated with the gene coding for thiamine transporter hTHTR2, the minor allele of which appears to be strongly protective from PDR combined with end-stage diabetic renal disease in a large combined cohort of patients with type 1 diabetes from Finland and Wisconsin (Porta et al. 2015).

New Perspectives for Medical Treatment

Lack of therapies targeting specific pathogenic mechanisms remains a serious limitation to the prevention of diabetes-related blindness. Experimental evidence suggests involvement of the renin-angiotensin system (RAS) in that a physiologically active RAS is present in the eye, where angiotensin 2 appears to promote retinal expression of VEGF, through AT1 receptors, and endothelial cell proliferation.

The EUCLID study (Chaturvedi et al. 1998) reported that lisinopril, an angiotensin-converting enzyme inhibitor (ACEi), may reduce the progression of DR and the incidence of PDR in patients with type 1 diabetes. However, retinopathy was not a primary outcome of the study, which was also undersized from the statistical power point of view. The more recent ADVANCE/ADREM (Beulens et al. 2009) appeared to show some protective effect, though not statistically significant, on progression of retinopathy of another ACEi, perindopril, associated with indapamide, a diuretic, in 1241 patients with type 2 diabetes. DIRECT (Diabetic Retinopathy Candesartan Trials) was a group of three multicenter, randomized, placebo-controlled studies designed to determine if pharmacological RAS blockade by candesartan 32 mg either prevents onset of DR in patients with type 1 diabetes (DIRECT-Prevent 1) or progression or promotes regression of DR in patients with type 1 (DIRECT-Protect 1) and 2 (DIRECT-Protect 2) diabetes (Chaturvedi et al. 2008; Sjølie et al. 2008). A total of 5231 patients with normoalbuminuria were randomized. The average follow-up was 4.7 years. Prevent-1 showed that candesartan reduces the risk of onset of retinopathy in type 1 diabetes by 35%, with an NNT of 18 patients treated to prevent one event. The severity of retinopathy at the end of the study was significantly more favorable in patients treated with candesartan in Prevent-1, Protect-1 (Chaturvedi et al. 2008), and Protect-2 (Sjølie et al. 2008). The latter study showed a 13% reduction, not statistically significant, in the risk of progression of DR and a highly significant 34% increase in the probability of DR regression in type 2 diabetes, with an NNT of 21 patients treated to achieve an event. The results of DIRECT-Protect 2 represent the first description in the literature of regression of DR induced by a drug. The favorable effect of RAS blockade was confirmed by the RASS study (Mauer et al. 2009), conducted on 285 normotensive patients treated with enalapril 20 mg/day, losartan 100 mg/day, or placebo. Enalapril and losartan reduced the likelihood of DR progression by 65% and 70%, respectively, in patients with type 1 diabetes. Although the results of the previous studies are strongly indicative of a beneficial effect of RAS blockade in the early stages of DR, none of them was sufficient to
grant registration for this specific indication. Hence, their use cannot be formally recommended in patients with DR who do not also have hypertension and/or microalbuminuria.

With reference to other possible mechanisms, the FIELD study showed a reduction by approximately 30% in the need for laser treatment for DME and PDR in patients treated with fenofibrate 200 mg/day. The drug prevented progression of existing retinopathy, regardless of its metabolic effects, but was not effective in terms of primary prevention (Keech et al. 2007). Moreover, the retinopathy endpoint was a tertiary objective, measured in 1012 of 9795 patients enrolled in the study. Another clinical trial, ACCORD (Chew et al. 2010), confirmed reduced progression of DR in patients with type 2 diabetes treated with fenofibrate and statins, compared to patients treated with statins alone. The possible mechanisms for this unexpected action of fenofibrate remain to be elucidated.

Increased tendency to platelet aggregation in diabetes has long been suspected to play a role in determining capillary occlusions which characterize the intermediate stages of nonproliferative DR. Antiplatelet drugs such as aspirin, dipyridamole, and ticlopidine underwent clinical trials in the 1970s and 1980s, demonstrating modest efficacy in slowing the formation of new microaneurysms in early nonproliferative DR (The DAMAD Study Group 1989; The TIMAD Study Group 1990) and no effects on evolution once DR reaches the pre-proliferative and proliferative stages (Early Treatment Diabetic Retinopathy Study Research Group 1991b). Aspirin, however, does not increase the risk of bleeding from new vessels, so that proliferative retinopathy is not a contraindication to its use for other indications (Early Treatment Diabetic Retinopathy Study Research Group 1991b).

Ophthalmological Treatment

Laser and Surgical Interventions for Severe Nonproliferative and Proliferative Diabetic Retinopathy

Panretinal Laser Photocoagulation
Panretinal laser photocoagulation, in which laser burns are placed over the entire retina, sparing the central macula, is an established technique for treating proliferative diabetic retinopathy.

The strongest evidence comes from two related randomized clinical trials in the 1970s and 1980s, the Diabetic Retinopathy Study (DRS) (Group 1978; The Diabetic Retinopathy Study Research Group 1981) and the ETDRS (Early Treatment Diabetic Retinopathy Study Research Group 1991a). The DRS randomized 1758 patients with proliferative diabetic retinopathy in least one eye or bilateral severe nonproliferative diabetic retinopathy to receive panretinal laser photocoagulation or no treatment. At 2 years, severe visual loss (visual acuity <5/200 on two successive visits) was observed in 6.4% of treated versus 15.9% of untreated eyes, with the greatest benefit in eyes with high-risk characteristics (new vessels at the optic disc or
vitreous hemorrhage with new vessels elsewhere, in which the risk of severe visual loss was reduced by 50%) (Group 1978).

**Surgical Vitrectomy for Vitreous Hemorrhage and Proliferative Diabetic Retinopathy**

Vitrectomy is used for treatment of eyes with advanced diabetic retinopathy, including proliferative diabetic retinopathy with nonclearing vitreous hemorrhage or fibrosis, areas of traction involving or threatening the macula, and, more recently, persistent diabetic macular edema with vitreous traction (Ho et al. 1992). The Diabetic Retinopathy Vitrectomy Study (DRVS) randomized 616 eyes with recent vitreous hemorrhage and visual acuity of 5/200 or less for at least 1 month to undergo early vitrectomy within 6 months of observation (The Diabetic Retinopathy Vitrectomy Study Research Group 1985, 1988a, b, 1990). After 2 years of followup, 25% of the early vitrectomy group versus 15% of the observation group had 20/40 or greater vision, with the benefits maintained at 4 years and longer in individuals with type 1 diabetes.

**Intravitreal Antiangiogenic Agents**

Currently, the small accepted treatment for PDR is panretinal photocoagulation (PRP) (Waisbourd et al. 2011). PRP is remarkably effective and has saved vision in many patients over the past several decades (The Diabetic Retinopathy Study Research Group 1981; Vander et al. 1991). Nevertheless, in up to 5% of the cases, neovessels continue to grow and vitrectomy is required, despite an appropriate initial treatment (Tremolada et al. 2012). In these cases, vitreous hemorrhage is common and frequently precludes laser completion (Fernando Arevalo 2013). Furthermore, PRP adverse effects are now widely recognized, such as worsening of DME and decline in peripheral and night vision function (Fong et al. 2007).

Considering the current evidence that VEGF takes part in the pathogenesis of PDR and the limitations of PRP, antiangiogenic agents have been recently admitted as new therapeutic options.

In a recent report, the DRCR.net showed evidence that antiangiogenic agents are effective in the management of proliferative diabetic retinopathy.

In conclusion, this exploratory randomized controlled trial suggests that intravitreal ranibizumab is safe and should be considered as a therapy for high-risk proliferative diabetic retinopathy eyes. The results obtained using IVR alone or in combined therapy are comparable or better than PRP alone. It remains to be demonstrated if this beneficial effect can be sustained for periods longer than 12 months.

**Laser and Surgical Interventions for Diabetic Macular Edema**

**Focal Laser Treatment**

Like panretinal laser photocoagulation, there is good evidence that focal laser treatment preserves vision in eyes with diabetic macular edema. The ETDRS randomized 1490 eyes with diabetic macular edema to receive focal laser treatment
or observation. At 3 years, treatment significantly reduced moderate visual loss as compared with observation (Early Treatment Diabetic Retinopathy Study Research Group 1985) with the greatest benefits in eyes with clinically significant diabetic macular edema (Group 1987). Adverse effects include inadvertent foveal burn, central visual field defect, color vision abnormalities, retinal fibrosis, and spread of laser scars (Group 1995; Aiello 2003).

Focal laser applied directly to localized microvascular alterations such as microaneurysms and intraretinal vascular abnormalities has been shown to be effective, particularly if there is a good correlation between the leaking vessels and the macular edema.

**Sub-threshold Laser**
The ETDRS demonstrated that laser photocoagulation applied to patients with clinically significant macular edema reduced the incidence of visual loss by approximately 50% at 3 years of follow-up (Early Treatment Diabetic Retinopathy Study Research Group 1985). The conventional green laser treatment is applied in focal or grid pattern and produces visible burn in the retina. There have been reports demonstrating the enlargement of laser scars after treatment (Morgan and Schatz 1989).

Recently, sub-threshold micropulse diode laser was shown to be effective in the treatment of clinically significant macular edema and seems to have a theoretical advantage, since the laser burns will affect deeper layers with relative sparing of the inner neurosensory retina, reducing the scars and the complaints of paracentral scotomas posttreatment (Akduman and Olk 1999).

**Surgical Vitrectomy for Diabetic Macular Edema**
Widespread or diffuse diabetic macular edema that is nonresponsive to focal laser treatment may benefit from vitrectomy (Yang 2000; La Heij et al. 2001; Dillinger and Mester 2004; Kralinger et al. 2006). However, the few randomized clinical trials to date have had small sample sizes and short follow-up, with inconsistent results. The presence of vitreous traction in macular edema, now readily documented with optical coherence tomography (OCT), in association with visual impairment, is currently a common indication for vitrectomy.

**Intravitreal Corticosteroids**
Corticosteroids have potent anti-inflammatory and antiangiogenesis effects. Intravitreal triamcinolone, i.e., injection of triamcinolone acetonide into the vitreous cavity (Sobrin and D’Amico 2005), has been used for treatment of diabetic macular edema (Jonas and Söfker 2001; Martidis et al. 2002) with a number of small clinical trials demonstrating improvements in diabetic macular edema and visual acuity (Massin et al. 2004; Jonas et al. 2006a, b). In the largest randomized clinical trial having the longest follow-up yet reported, eyes with persistent diabetic macular edema were randomized to receive 4 mg of intravitreal triamcinolone or sham injection (saline injection into the subconjunctival space) (Gillies 2006). After 2 years, 19 of 34 intravitreal triamcinolone-treated eyes (56%) had a visual acuity
improvement of 5 letters or more compared with 9 of 35 placebo-treated eyes (26%) \((P = 0.007)\). Overall, intravitreal triamcinolone-treated eyes had twice the chance of improved visual acuity and half the risk of further loss. However, many eyes required repeated injections (mean, 2.2), and there was significant intraocular pressure elevation (5 mm Hg in 68% of treated eyes vs. 10% of controls). Cataract surgery was required in 55% of intravitreal triamcinolone-treated eyes. Thus, while this study demonstrated significant efficacy of intravitreal triamcinolone in persistent diabetic macular edema, larger randomized clinical trials are needed to provide further data on long-term benefits and safety. Additionally, the ideal dose of triamcinolone remains unclear (Spandau et al. 2005).

More recently, intravitreal or retinal implants have been developed, allowing extended drug delivery. An injectable, biodegradable intravitreal dexamethasone extended-release implant (Posurdex; Allergan, Irvine, California) was evaluated in a randomized clinical trial, with reported improvements in visual acuity and macular thickness (Kuppermann et al. 2003). A larger randomized clinical trial of Posurdex for diabetic macular edema is currently under way.

The Iluvien (fluocinolone acetonide implant, Alimera) is a small, nonbioerodable device that is injected in an office setting through a self-sealing wound with a 25-gauge inserter. The phase III FAME trial compared this device, formulated in two doses (0.2 \(\mu\)g/day and 0.5 \(\mu\)g/day), to standard of care, which could include laser or anti-VEGF injection, in 956 patients (Campochiaro 2011; Cunha-Vaz et al. 2014). Almost 30% of eyes receiving either the low-dose or high-dose formulation of the drug achieved three lines or more improvement of visual acuity, compared with 16% of controls, in the 3-year results of the study (Campochiaro 2011). Subgroup analysis showed that patients with diabetic macular edema duration of more than 3 years experienced better results than those with diabetic macular edema of less than 3-year duration (Antoszyk and Investigators 2011).

**Intravitreal Antiangiogenic Agents**

Several randomized clinical trials are currently evaluating agents that suppress vascular endothelial growth factor (VEGF) for treatment of diabetic macular edema.

**Ranibizumab** (Lucentis, Genentech and Novartis) is an anti-VEGF agent used for treatment of neovascular age-related macular degeneration (Brown et al. 2006; Rosenfeld 2006) and may also be useful for diabetic retinopathy and diabetic macular edema (Chun et al. 2006). Randomized clinical trials (the RESOLVE and RESTORE studies) (Massin et al. 2010; Mitchell et al. 2011) have demonstrated beneficial effect of intravitreal administration of ranibizumab in diabetic macular edema. It is able in the short term to improve visual acuity when some degree of vision loss associated with clinically significant macular edema is present. The DRCR.net work confirmed and extended these findings. Intravitreal injection of ranibizumab is now approved for clinical use in diabetic macular edema (Elman et al. 2010).

**Bevacizumab** (Avastin, Genentech) is an anti-VEGF agent similar to ranibizumab that is approved for the treatment of disseminated colorectal cancer and not licensed
for intraocular use. In a number of small studies and in noninferiority trials, bevacizumab appeared to show similar efficacy for treatment of neovascular age-related macular degeneration and may also be effective for diabetic macular edema (Avery 2006; Avery et al. 2006; Rosenfeld 2006; Spaide and Fisher 2006). Bevacizumab has attracted interest because of its low cost, but local and systemic safety is a concern (Gillies 2006; Carneiro et al. 2011).

Afiblerecept (VEGF Trap-Eye, Bayer) is a recombinant fusion protein, consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to Fc portion of IgG1 and formulated as an iso-osmotic solution for intravitreal administration (Ohr and Kaiser 2012).

The diabetic macular edema and VEGF Trap-Eye: Investigation of Clinical Impact (DA VINCI) study was a multicenter, randomized, double-masked phase II trial that compared various dosing regimens of afiblerecept to macular grid photocoagulation. Compared to baseline, more patients treated with afiblerecept than laser gained 0+, 10+, and 15+ letters of vision (93%, 64%, and 34% vs. 68%, 32%, and 21%). Reductions in central retinal thickness were greater in patients receiving afiblerecept than laser (−127.3 μm to −194.5 μm vs. −67.9 μm; p < 0.0066 for each afiblerecept group compared to laser) (Stewart 2012).

The relative efficacy and safety of intravitreous afiblerecept, ranibizumab, and bevacizumab in the treatment of diabetic macular edema has been examined in a comparative clinical trial performed by the DRCR.net (Network 2015). At 89 clinical sites, 660 adults with diabetic macular edema were randomly assigned to afiblerecept at a dose of 2.0 mg, ranibizumab at a dose of 0.3 mg, and bevacizumab at a dose of 1.25 mg. The study drugs were administrated as often as every 4 weeks. The primary outcome was the mean change in visual acuity at 1 year.

Although the improvement was greater with afiblerecept than with the other two drugs (P < 0.001 for afiblerecept vs. bevacizumab and P = 0.03 for afiblerecept vs. ranibizumab), it was not clinically meaningful, because the difference was driven by the eyes with worse visual acuity at baseline (P < 0.001 for interaction).

When the initial visual acuity letter score was 78 to 69 (equivalent to approximately 20/32 to 20/40) (51% of participants), the mean improvement was 8.0 with afiblerecept, 7.5 with bevacizumab, and 8.3 with ranibizumab (P > 0.50 for each pairwise comparison). When the initial letter score was less than 69 (approximately 20/50 or worse), the mean improvement was 18.9 with afiblerecept, 11.8 with bevacizumab, and 14.2 with ranibizumab (P < 0.001 for afiblerecept vs. bevacizumab, P = 0.003 for afiblerecept vs. ranibizumab, and P = 0.21 for ranibizumab vs. bevacizumab). There were no significant differences among the study groups in the rates of serious adverse events (P = 0.40).

Intravitreous afiblerecept, bevacizumab, or ranibizumab improved vision in eyes with center-involved diabetic macular edema, but the relative effect depended on baseline visual acuity. When the initial visual acuity loss was mild, there were no apparent differences, on average, among study groups. At worse levels of initial visual acuity, afiblerecept was more effective at improving vision.
**Review of Approaches for the Treatment of Diabetic Macular Edema**

**Recommendations for the Treatment of Diabetic Macular Edema**

The goal of treatment with laser photocoagulation was mostly visual acuity stabilization. With the approval of antiangiogenic drugs for the treatment of visual impairment due to diabetic macular edema, the goal of therapy is now primarily improvement or restoration of visual acuity, with stabilization of vision and prevention of further vision loss as a key secondary goal.

Treatment recommendations for diabetic macular edema are based on involvement of the center of the macula (Fig. 11). No new recommendations for the treatment of diabetic macular edema without center involvement, or for diabetic macular edema with center involvement but without vision loss, are required as current ETDRS guidelines remain appropriate (Group 1987); antiangiogenic drug monotherapy is now recommended for the treatment of diabetic macular edema with central involvement, with vision loss considered due to diabetic macular edema. In that respect, it is important to exclude other potential causes of vision loss such as epiretinal membrane, vitreomacular traction, or macular ischemia and other conditions such as cataract or glaucoma.

Systemic factors are key to the management of diabetes, and patients should attempt to achieve optimal control of hemoglobin A1c, lipid levels, and especially blood pressure (Cheung et al. 2010). Intensive control of blood glucose and hypertension reduces development of clinically significant macular edema (UK Prospective Diabetes Study (UKPDS) Group 1998a, b). Achieving control of systemic factors reduces retinal thickness and improves visual acuity to some extent in patients with very mild diabetic macular edema in the absence of other interventions (Singh et al. 2006).

Surgery should be considered in patients with diabetic macular edema due to a significant epiretinal membrane or demonstrated vitreomacular traction.

**Characterization of Responders to Treatment**

The major pathways of progression in diabetic retinopathy are leakage (alterations of the blood-retinal barrier), microaneurysms, inflammation, and ischemia. The

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**Fig. 11** Treatment algorithm for diabetic macular edema
therapies that we employ for treatment of diabetic macular edema must act on one or more of these pathways. The rationale for use of vascular endothelial growth factor (VEGF) inhibitors in diabetic macular edema is the association of VEGF with vascular leakage; VEGF increases leakage, and anti-VEGF action controls leakage. Anti-VEGF therapy may also have an effect on ischemia, depending on the level of ischemia. Steroids act on both leakage and, especially, inflammation. Although we do not fully understand the mechanism of action of laser, we observe that it stabilizes disease activity in diabetic macular edema.

Response to anti-VEGF treatment in diabetic macular edema is generally better than response to any other means of treatment. A randomized controlled trial by the Diabetic Retinopathy Clinical Research Network showed that intravitreal ranibizumab (Lucentis, Genentech) plus prompt or deferred laser resulted in greater visual acuity gain than treatment with either intravitreal triamcinolone acetonide plus laser or laser alone (Elman et al. 2010). However, in clinical trials we are always looking at the mean results of a number of patients. In any trial of a proposed diabetic macular edema therapy, there will be good responders who achieve decreased thickness and increased visual acuity in a relatively short period after the initial injections, but there will also be poor responders and nonresponders. It would be helpful to know more about the nonresponders in order to choose alternative treatments to which they might respond better.

**Role of Early Screening for Diabetic Retinopathy in Patients with Diabetes Mellitus**

**Screening for High-Risk Diabetic Retinopathy**

The major risk factors for developing diabetic retinopathy are duration of diabetes (Elshafei et al. 2010; Leske et al. 2010) and severity of hyperglycemia (DCCT 1995; Elshafei et al. 2010).

Timely intervention by laser photocoagulation can reduce severe visual loss by 90% according to ETDRS (Group 1991) and Diabetic Retinopathy Study (DRS) (The Diabetic Retinopathy Study Research Group 1981). Intravitreal anti-VEGF injections are offering new treatment alternatives and offer for the first time vision recovery. In any case, early detection of diabetic retinopathy vision-threatening complications and timely treatment of these patients remains a major challenge for healthcare providers.

Screening is a process by which unrecognized diseases or defects are identified by means of rapidly applied tests in apparently healthy individuals.

The four cardinal principles for screening recommended by the WHO (World Health Organization 2001) are as follows:

1. The condition should be an important health problem with a recognizable pre-symptomatic state.
2. An appropriate screening procedure which is acceptable both to the public and healthcare professionals should be available.
3. Treatment for patients with recognizable disease should be safe, effective, and universally agreeable.
4. The economic cost of early diagnosis and treatment should be considered in relation to total expenditure on healthcare, including the consequences for leaving the disease untreated.

Diabetic retinopathy conforms well to these principles. In diabetic retinopathy, early detection and treatment is of vital importance as it may prevent vision loss and blindness.

Diabetic retinopathy is a chronic disease with a long latent phase. Among the diabetics, 10–15% constitutes type 1 diabetics and the remainders are type 2 diabetics. In about 10 years, diabetic retinopathy develops in 71–90% of patients with type 1 diabetes, and this incidence rises to 95% in 20–30 years. Out of these, 30–50% of patients have proliferative diabetic retinopathy (Klein et al. 1984a). In type 2 diabetes, 67% of patients develop diabetic retinopathy after 10 years (Klein et al. 1992), with 10% of patients showing features of proliferative diabetic retinopathy. Up to a fifth of newly diagnosed diabetics have some form of retinopathy. Therefore, screening will prove to be beneficial at any stage of this long latent phase of the disease and will also be helpful in avoiding blindness among 90% of patients (Ferris 1994).

Screening for diabetic retinopathy is cost-effective when compared with disability loss for people going blind in the absence of a screening program. The compliance for the screening program should be more than 80% for more gains (Dasbach et al. 1991). The funds invested to increase compliance are small but a vital component of the costs of a screening program.

The efficacy of screening for high-risk DR has been demonstrated in places such as Iceland or Sweden, where it has led to reduction of diabetes-related blindness (Stefánsson et al. 2000). A countrywide screening program has been established in the UK (Scanlon 2008), and the full impact of this intervention will become available in the coming years.

It is suggested that patients with type 1 diabetes should be screened annually for retinopathy, 5 years after the onset of diabetes. Patients with type 2 diabetes should have an initial examination for retinopathy shortly after the diagnosis, and the examination should be repeated every other year. Pregnant women with diabetes should have a comprehensive eye examination in first trimester and close follow-up throughout pregnancy.

**Criteria for Review and Referral**

1. Biannual review without referral:
   (a) Normal fundus

2. Annual (or more frequent) review without referral:
   (a) Background diabetic retinopathy with small hemorrhages and/or small hard exudates more than one disc diameter distant from the fovea

3. Early referral to ophthalmologist for treatment:
(a) Background diabetic retinopathy with small hemorrhages and/or small hard exudates less than one disc diameter distant from the fovea
(b) Maculopathy

4. Urgent referral to ophthalmologist for treatment:
   (a) Proliferative diabetic retinopathy
   (b) Vitreous hemorrhage
   (c) Retinal detachment

**Screening Tests for Diabetic Retinopathy**

Many different modalities of screening are in use depending on the availability of local facilities. These include number of available ophthalmologists, other trained healthcare professionals, and equipment and resources available for screening. However, whichever method is used, it should have sufficient sensitivity (>90%) and specificity (>90%) for a single-modality screening process. The minimum sensitivity for any method to be effective if it is repeated at the recommended interval is 60%. This level of sensitivity can be achieved with ophthalmoscopy through dilated pupils (sensitivity = 65.7% and specificity = 93.8%) (Owens et al. 1998) by suitably trained observers (principally ophthalmologists, optometrists, general practitioners, or physicians) or with non-mydriatic photography (sensitivity = 87.3% and specificity = 84.8%) (Moss et al. 1985; Owens et al. 1998; Benbassat and Polak 2009). The sensitivity of detecting diabetic retinopathy by retinal photography has been reported to be higher than that of direct ophthalmoscopy (64% vs. 41%; 95% confidence interval of difference, 1.2%–44.3%) (Siu et al. 1998). Specificities of retinal photography and direct ophthalmoscopy have been reported to be 90% (95% confidence interval, 84%–96%) and 93% (95% confidence interval, 88%–97%), respectively (Siu et al. 1998). Single-field fundus photography with interpretation by trained readers could serve as a screening tool to identify patients of diabetic retinopathy. Combining two modalities of screening (e.g., direct ophthalmoscopy in conjunction with retinal photography) provides excellent sensitivity (87.3%) (Benbassat and Polak 2009), but increases the cost per case screened and is often only possible in a hospital-based setting. Screening involves measurement of visual acuity for both distance and near vision using ETDRS chart.

Tele-medical screening may be undertaken to screen patients with diabetic retinopathy. A major advantage of digital technologies is the ability to transmit images to a centralized reading center for grading. This involves a remote imaging system, a centralized grading center, and a data storage system. A significant increase in rate of diabetic retinopathy surveillance and in the rate of laser treatment for diabetic retinopathy may be achieved by implementing retinal image technology in the primary care setting.

The use of the non-mydriatic camera (sensitivity = 97.7% and specificity = 84.0%) (Boucher et al. 2003) empowers an additional cadre of health professionals who can participate in screening programs. Screening of diabetics by ophthalmic technicians increases the outreach to the periphery with sufficient sensitivity and specificity and is cost-effective (Wilson et al. 2010).
Automated Computer-Aided Analysis of Fundus Digital Photographs in Diabetic Retinopathy Screening

The development of systematic programs of screening for retinopathy has been identified as an urgent healthcare need. Indeed, studies have indicated that the severity of vision loss due to diabetes is caused largely by lack of screening (Oliveira et al. 2011).

We have developed and evaluated a novel two-step approach that automatically screens color fundus photographs in patients with the use of sequential examinations from the same patient to analyze the evolution of the disease in that patient. The automated grading system consists of software earmarking microaneurysms and “red-dot-like” vascular lesions. It includes a co-registration algorithm that allows comparison within the same retinal location between different visits for the same eye. The system generates in a first-step single analysis one of two possible outputs, “disease” or “no disease.” “Disease” category comprehends thus those images where vascular lesions are found in the central macula corresponding to level 20 and above of the ETDRS scale, therefore including mild retinopathy, maculopathy, advanced nonproliferative retinopathy, and proliferative retinopathy. In the one-step analysis, the algorithm detects the presence of red-dot-like lesions in fields 1 and 2 (field 1 is centered on the optic disc, and field 2 is centered on the fovea). We combine this initial analysis (first step) with a second analysis that compares two different and consecutive examinations from the same patient from two successive screenings with approximately 1-year interval. The images from the field centered on the macula are co-registered to complete a difference analysis which will indicate disease activity in the central 3000 μm circle of the macula. The results show a clear improvement over available fully automated screening algorithms with a sensitivity of 95.8% and a specificity of 63.2%. The system has shown that it can perform a useful role by eliminating 50% or more of the screening population who have no retinopathy. Furthermore, it did not miss urgent cases for referral, allowing, therefore, an important reduction in the burden of manual grading with less cost. This two-step analysis shows a clear improvement in specificity over other available automated systems, and its integration in a yearly screening program now in progress is expected to bring progressive decrease in the burden of human grading by safely decreasing the number of false-positive results to be submitted to human grading, with economic advantage making diabetic retinopathy screening more feasible (Ribeiro et al. 2014).

Role of Telemedicine in Eye Care in Diabetes

The standard of care for diabetic patients is at least biannual fundus examination by a qualified eye care provider (Williams et al. 2004; American Academy of Ophthalmology Retina Panel 2010). With early detection and treatment of diabetic eye disease, vision loss can be mitigated (The National Eye Institute 1993). Unfortunately, only 30% to 60% of individuals with eye disease receive a yearly eye exam (Lee et al. 2003; Varma et al. 2008). Telemedicine has the potential to increase the number of patients being screened for eye disease; it has been shown to provide cost-
effectiveness and total savings in terms of public health spending (Javitt and Aiello 1996).

Telemedicine provides a reliable, cost-effective means of screening diabetic patients for retinopathy. Since the number of diabetics is growing fast, but the supply of eye care practitioners is not, healthcare resources are strained and becoming more so.

Conclusions

Overall, the results of the trials reported above suggest that interventions targeted at potential pathogenic mechanisms may be effective in early mild, rather than moderate or more advanced, stages of retinopathy in which damage to the capillary wall and the neuroretina may already be too advanced. Here the question arises of whether a “point of no return” exists in the natural history of DR. Antiplatelet agents appeared to slow down retinopathy at a very early stage characterized by the presence of microaneurysms alone (Plu et al. 1990), but not later when capillary occlusion becomes the prevailing feature (TIMAD Study Group 1990). Similarly, in DIRECT-Protect 2 (Sjølie et al. 2008), administration of candesartan was associated with regression of minimal to mild retinopathy (occasional microaneurysms, microhemorrhages, hard exudates, and/or cotton wool spots), whereas nonproliferative stages, though classified as moderate, proved nonresponsive, suggesting that also blockade of the RAS could be effective earlier than originally envisaged, again when damage of the capillary wall is minimal. This suggests that overactivation of the intraocular RAS may exert its pathogenic effects through mechanisms different from VEGF activation or that VEGF might have pathogenic effects independent of its ability to increase vessel wall permeability and angiogenesis, possibly involving its neuroprotective characteristics. However, data from FIELD (Hermans 2011) and ACCORD (Wright and Dodson 2011) appear to show that progression of retinopathy can be stopped by fenofibrate at more advanced stages, moderate and severe nonproliferative, suggesting that different pathogenic mechanisms, responsive to different pharmacological agents, may intervene in various stages of this complication.

Progress in medical treatment of DR remains incomplete, just like our understanding of the mechanisms underlying this complication. More is achieved in the advanced stages, using VEGF inhibitors, than early in the evolution of DR, but we are still far from the day when retinopathy will be treated aiming directly at a cause (as we do, e.g., with iron for iron-deficient anemia) or a mechanism (as with proton pump inhibitors for peptic ulcers). Causes for failure so far to identify a primum movens for retinopathy and, more generally, diabetic microangiopathy involve a series of good reasons: lack of funding and researchers dedicated to the specific problem, a presumably multifactorial pathogenesis, and the undoubted complexity of the phenomena involved. It is hoped that, as diabetes and its complications rise worldwide, the mere health and economic size of its consequences will stimulate further research into this field of human disease.


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