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Novel diagnostic and therapeutic approaches to the diabetic retinopathy

C. GIUSTI

Department of Ophthalmology, "Campus Bio-Medico" University of Rome (Italy)

Abstract. – **Diabetic retinopathy is a common cause of vision loss in industrialized countries and it is now evident that adequate screening protocols can identify the disease at an earlier, more treatable stage. Novel imaging techniques and therapeutic strategies, developed during the past few years and critically reviewed in this paper, may not only increase the standard quality of actual eye care but may also improve access to ophthalmological examinations and compliance with the eye care guidelines for all diabetic patients.**

Key Words:

Diabetes, Diabetic retinopathy, Retina.

Introduction

Diabetes mellitus is a major cause of blindness in the working population of the Western world[1-5]. Ophthalmic complications of diabetes include corneal abnormalities, glaucoma, iris neovascularization, cataract and optic disc abnormalities, but by far the most frequent and potentially blinding complications are proliferative retinopathy (PDR) with tractional retinal detachment and macular edema (DME). The medical, social and financial impact of retinopathy (DR) is substantial: in the United States, diabetes mellitus affects over sixteen million people and DR is present in nearly all persons with duration of diabetes of 20 years or more[5]. Moreover, if this complication remains untreated, about 60% of subjects with PDR are expected to become blind within 5 years in one or both eyes[2-5].

There is no doubt that timely tight glycemic control with glycosylated hemoglobin (HbA1c) close to the normal range (4.0-6.0%) should lead to a significant decrease in incidence and progression of retinopathy[4-5]. However, only a minority of diabetics achieve near-normal glycemia soon and on a long-term basis and no data provide an adequate explanation for the serious and rapid involvement of the retinal microcirculation that may be observed in the disease despite a good metabolic control. Moreover, there is now ample of evidence that the development of DR is a multifactorial process where genetic, metabolic and growth factors play an important role but, at this time, its aetiopathogenesis is still not completely understood[4-5].

Therefore, prevention of visual loss relies on early detection of retinopathy and, if indicated, timely treatment with laser photocoagulation, still the first-line treatment of choice for high risk retinal microangiopathy. However, in a subgroup of patients, proliferation may persist even after well done full scatter laser applications, resulting in a 30-50% risk of severe visual loss within the next 5 years[6].

Therefore, DR is still an enormous social and clinical problem[7].

Methods

Classification

Clinically, DR is classified into two main forms: PDR and nonproliferative DR (NPDR). Nonproliferative disease may be divided into mild, "background" NPDR (BDR) and severe, "preproliferative" (PPDR)[8].

Besides this clinical classification, commonly used in routine eye examinations, and the modified Early Treatment Diabetic Retinopathy Study (ETDRS)-Airlie House Classification, generally preferred and recommended for research applications and sci-

entific publications[9-10], other photographic[11-12] and angiographic methods[13] have been proposed in order to provide simple schemes for expressing the presence and severity of the retinal diabetic lesions during large screening protocols (e.g., epidemiological studies).

Patient evaluation - diagnosis

Screening protocols have been proven to potentially identify most diabetics with vision-threatening retinopathy[3-4,14], and emphasis is appropriately directed not only at the early identification, accurate classification and timely treatment of retinopathy but also at ensuring the best compliance of patients to the lifelong routine ophthalmologic follow-up[5,15]. According to the Clinical Practice Recommendations of the American Diabetes Association (ADA)[16], a careful retinal examination, performed by a experienced ophthalmologist through dilated pupils, should be scheduled within three-five years after the onset of the disease in patients ≥ 10 years of age with type 1 diabetes and shortly after diagnosis in type 2 diabetics. Subsequent examinations for both type 1 and type 2 diabetic patients should be repeated at least annually, or more frequently if retinopathy is progressing. On the contrary, yearly exams are not necessarily required for juvenile-onset diabetics within the first decade of life, but only after five years of diabetes in younger children and after two years in adolescents[17-18]. Women with type 1 or type 2 diabetes who become pregnant should have a comprehensive eye examination in the first trimester and close follow-up throughout pregnancy and for one year postpartum. Women who develop gestational diabetes are not at increased risk for DR[16].

Given the report that microaneurysm count is an early measure of DR progression[19], the best method for evaluating the presence and severity of DR is represented by grading of stereoscopic colour fundus photographs of seven defined retinal fields[3,16,20]. However, posterior segment biomicroscopy, performed at the slit lamp using high positive power precorneal lenses, is often superior for detecting retinal thickening associated with DME and identifying fine caliber neovascularizations of the optic disk or elsewhere in the retina[16]. Fluorescein angiography (FA)[13], on the other hand, could be very useful in NPDR, for guiding laser treatment of clinically significant DME, and in high risk PPDR, for detecting retinal ischemic zones of capillary non-perfusion. On the contrary, FA is not required in the cases of ophthalmoscopically evident retinal neovascularizations as well as in uncomplicated eyes or during the earliest signs of retinopathy when laser applications are not indicated[21].

Moreover, several non-invasive methods, able to identify abnormalities at an even earlier stage of retinopathy, have been developed in the recent past. In fact, computerized perimetry[22], blu-on-yellow perimetry[23], entoptic perimetry[24], colour contrast sensitivity[25] and colour vision testing[26-27] showed early alterations even in patients with optimal visual acuity (20/20 or more) and angiographically normal retinas. Impaired hue discrimination is a common observation among participants enrolled in the ETDRS[26]: in particular, a tritan-like defect is usually prominent and increases in magnitude with increasing severity of DME. Therefore, color vision measurements have been proposed for early detection of changes in visual function in uncomplicated diabetic patients[27]. Moreover, blu-on-yellow computerized perimetry has also been recently suggested as a useful and sensitive tool for detection of preclinical visual field defects in diabetic children with microalbuminuria but without clinically detectable retinopathy[23]. Entoptic perimetry, on the other hand, has been shown to be much more sensitive than the Amsler grid test and/or the subjective impression of visual decline for the early detection of diabetic maculoapthy[24].

Electrophysiological techniques (e.g., visual evoked potentials (VEP) before and after photostress[28], multifocal oscillatory potentials (OP)[29], multifocal and pattern electroretinogram (PERG)[30-32] demonstrated that functional alterations of the optic nerve and the retina are present very early in the disease, even in diabetics without retinopathy. In particular, the earlier abnormal electrophysiological responses have been recorded from the innermost retinal layers and the postretinal visual pathways, as suggested by impaired PERGs and delayed neural conduction respectively, and, thereafter, from the macula, demonstrated by abnormal focal electroretinogram (ERG) and VEPs after photostress[31-32]. Photoreceptors appear unaffected

in this first step while a functional loss of both ganglion and preganglion cells has been already documented in the middle retinal layer, even in the absence of angiographically evident abnormalities[33]. Last additional electrophysiological changes have been recorded from the outer retinal layers, as suggested by impaired flash ERGs and OPs[32,34]. Therefore, it has been reported that measurements from VEP and ERG recordings, particularly the OP amplitudes, may be useful for predicting progression from NPDR to the more sight-threatening stages of DR[34], as a result of the fact that a significant correlation was found between greater overall severity of the retinopathy, higher fluorescein leakage, higher capillary nonperfusion and lower electroretinographic OP amplitudes[35]. Moreover, the reported PERGs and VEPs abnormalities observed in diabetics without retinopathy[31-32] suggest that electrophysiological techniques could also be a useful diagnostic method for discriminating between eyes with DR and those without this condition[34], even if their use is actually not yet included in the ADA guidelines for routine eye examinations[16].

New ophthalmic instruments and techniques have also been recently proposed: e.g. iris fluorescein angiography[36] seems to provide indirect informations on the retinal circulation when DR cannot be examined directly. Moreover, while the retinal images quality may be improved by using high resolution colour digital photography[37-38] or the Heidelberg Retinal Angiography[39], the Optical Coherence Tomography (OCT)[30,40-42], the Heidelberg Retinal Tomograph (HRT)[43-44] and the Retinal Thickness Analyser (RTA)[45] seem to be new interesting tools for detecting intraretinal structural changes, a gain potentially useful both in patient management and in some research applications. In fact, routine slit lamp biomicroscopy can provide only qualitative informations in the clinical diagnosis of DME and the actual macular thickening, particularly in the early stages of DME, is hard to estimate using this technique only. In fact, slit lamp biomicroscopy cannot identify mild or localised macular thickening and as a result of the fact that its grading is based on a distinction of the local differences rather than comparisons with absolute normal values, it is also limited in detecting diffuse edema as a total elevation of the macula. FA, on the other hand, is traditionally used to assess retinal vascular permeability in patients with DR and the degree of fluorescein leakage at the macula is generally considered to be associated with retinal thickening. However, fluorescein leakage, which physiologically indicates the breakdown of the blood-retinal barrier (BRB), is not always accompanied by appreciable fluid accumulation in the retina: e.g. in a subclinical stage, slight dye leakage on FA could appear without retinal thickening because the balance between the vascular permeability and the ability of the retinal pigment epithelium (RPE) to reabsorb fluid has been maintained. As retinopathy progresses, this balance is disturbed, resulting in fluid accumulation and DME. Thus, FA is useful for evaluating the severity of the dysfunction in the BRB, but it does not reliably quantify the degree of fluid accumulation in the retina. OCT, HRT and RTA scannings seem to be superior to conventional methods, such as slit lamp biomicroscopy and FA, for detecting macular thickening because of multiple cross sectional imaging and the direct measurement of retinal thickness.

OCT is a relatively new non-contact, non-invasive technique for in vivo examination of the human retina, based on the Michaelson interferometer. It is analogous to B-scan ultrasound except that it measures optical rather than acoustic reflectivity. The commercial OCT uses a superluminescent diode with a central bandwidth of 850 nm and a depth resolution of approx. 10 µm. Relatively high reflectivity (RHR) layers correspond to areas of horizontal retinal elements, such as the nerve fiber layer at the retinal surface or deeper plexiform layers and a single layer of RPE and choroid. Relatively low reflectivity (RLR) layers correspond to the nuclear layers and a single layer of photoreceptor inner and outer segments. Warm colors (red to white) represent areas of RHR, while cold colors (blue to black) represent areas of RLR. A good correlation has been found between retinal morphology and macular OCT imaging, even though resolution of retinal images is dependent not only on the resolving power of the instrument, but also on the contrast in relative reflectivity of adjacent structures. In fact, the OCT system cannot discriminate between the images of adjacent tis-

sues that possess matching relative reflectivity, i.e. the RPE and choroid, or the photoreceptor outer segments and their nuclei. A OCT very important feature is that provides significant information on the vitreoretinal structures, being able to determine not only the presence of a vitreomacular tractional syndrome, due to epiretinal membranes, but also the intraretinal fluid location and the response to treatment without the need to perform invasive studies such as FA. Moreover, it may highlight why some patients respond to treatment while others do not and may demonstrate the retinal changes that explain the recovery in some patients without angiographically evident improvement and the lack of recovery in others. Actually, a main limitation of this technique is represented by the reproducibility of macular measurements during follow-up examinations, as a result of the fact that accurate relocalisation of the same retinal area of interest, depending on the ability of patients to fixate on a fixation light, is difficult and, therfore, uncertain. In conclusion, despite some technical limitations, the OCT retinal mapping system seems to be a new promising tool for the study of both intraretinal fluid accumulation and alterations of the vitreoretinal interface, allowing not only measurements of retinal thickness in diabetics with DME[40,42], but also a distinction between tractional retinoschisis and retinal detachment in eyes with PDR and macular elevation[41].

At the same time, also HRT and RTA retinal scanning, novel non-invasive imaging instruments, have been found to be useful to quantitatively detect and monitor macular thickening in DR[43-45]. HRT is a scanning laser ophthalmoscope with confocal optics. It takes 32 images of the fundus in 1.6 seconds in a plane perpendicular to the optical axis. The computer software aligns the images so as to eliminate the effect of eye movement and compiles a three dimensional image of the surface scanned. This instrument has been originally used for analysis of the optic nerve head topography but it has been recently adapted also for macular investigations. Improvement of reproducibility of macular volume measurements between scans of the same eye has been obtained[43] and a new System for Classification and Ordering of Retinal Edema has been developed[44]. The main application of this technique is reported to be in very early clinically significant diabetic maculopathy, especially in detecting small increase in macular volume that may not be detected on routine clinical examination[43]. In particular, this would not only allow a earlier intervention before visual acuity is affected but would also permit an accurate monitoring of treatment effects. However, further work remains to be done and several technical modifications, to be included in future HRT software versions, have already been suggested[43]. Moreover, prospective, longitudinal studies are needed in order to assess the usefulness of this technique in the daily clinical practice.

RTA, a novel instrument developed for non-invasive, multiple optical cross sectional retinal visualisation, is based on the principle of laser biomicroscopy and provides objective and quantitative measurements of retinal thickness. The distance between the images of the anterior and posterior retinal intersections is calculated by an analysis algorithm to produce accurate retinal thickness mapping[45]. However, in order to study a 6 mm by 6 mm area of the macula, nine scans of the eye, with patient fixing nine times the same point, must actually be combined for interpretation, thus resulting in a high coefficient of variability of the retinal thickness values of corresponding points and representing, therefore, a main limitation of this new technique[43].

In conclusion, data from literature highlight that OCT, HRT and RTA scannings represent useful techniques to quantitatively measure macular thickening in DR. However, although the study already published do not recommend, at this time, to replace any other conventional diagnostic tool used to detect DME because of the technical limitations that still affect these novel instruments, they believe that retinal scanning may significantly contribute to early and accurate diagnosis of macular thickening in DR. Further randomised studies with large populations are required to evaluate these new tools for longitudinal monitoring of the disease prognosis and treatment efficacy.

A novel diagnostic approach to the ocular diabetic microangiopathy is also represented by the delivery of ophthalmic services via telemedicine in the context of improving access to eye care for rural or underserved pop-

ulation[46]. In fact, this new technique, already used successfully for guiding an orbital tumor removal[47]. and for glaucoma screening[48], has been recently proposed for identifying DR in remote communities or rural individuals that may have limited access to the needed eye care[49,50]. Considering the few pilot studies already published only, telemedicine seems to allow a satisfactory real-time transmission of digital images, efficient communications with off-site ophthalmologists and good intra- and interreader reliabilities. However, besides the cost-benefit and technical issues, also medicolegal implications of this new technique should be considered, as a result of risks and responsabilities – many of which are as yet unknown – that distant intervention, consultation and diagnosis carry.

Finally, some financial barriers have been recently described in low income-families: e.g. in-office ophthalmoscopy performed by primary care physicians, mainly through undilated pupils and without referring these patients to an experienced ophthalmologist, because the health insurance did not cover such an examination[51]. It is therefore important not only to encourage the development of new diagnostic techniques but also to politically solve any existing economical discrimination in order to ensure the best eye care to all diabetics.

Treatment

Medical treatment

It is now clear that the "core" management of DR is represented by an improved glycemic control[52], even though normalization of glycemia, associated with a combined kidney-pancreas transplantation, did not have a beneficial influence on the progression of advanced DR[53]. The Diabetes Control and Complications Trial (DCCT) Research Group pointed out not only that intensive insulin therapy resulted up to a 76% decrease in progression of retinopathy during a nine-year period in type 1 patients[54] but also that this risk reduction persisted thereafter for at least four years despite increasing hyperglycemia[55]. Although a sight-threatening worsening and a higher frequency of severe hypoglycemic reactions are often observed when this intensive treatment is started after a long-standing poor metabolic control[56], the long-term benefits of this therapy are reported to greatly outweigh these adverse reactions. In particular, early worsening was observed at the 6- and/or 12-month visit in 13.1% of patients assigned to intensive treatment and 7.6% of patients assigned to conventional treatment; recovery occurred at the 18-month visit in 51% and 55% of these two groups respectively. The most important risk factors for early worsening were higher HbA1c level at screening and reduction of this level during the first six months after randomization. No evidence suggesting that a more gradual reduction of glycemia might be associated with less risk of early worsening was found. On the contrary, the large long-term risk reduction with intensive tratment was such that outcomes in intensively treated patients who had early worsening were similar to or more favorable than outcomes in conventionally treated patients who had not[56]. The mechanism behind this so-called "normoglycemic re-entry phenomenon" has yet to be defined. Endocrine and growth factors might play a role as growth hormone (GH) is increased in poorly controlled diabetes and DR correlates with the magnitude of both GH and insulin-like growth factor-1 (IGF-1) hypersecretion. Moreover, elevated GH levels have also been associated with activation of the fibrinolytic and coagulation systems and a variety of haemostatic abnormalities have been demonstrated in diabetic patients, resulting in a state of hypercoagulability[4]. On the other hand, IGF-1, and not GH in itself, is responsible for GH's biological activity. Therefore, it might be possible that hyperglycemia determines the onset of these abnormalities, which might play a crucial role in the pathogenesis of diabetic microangiopathy[57-58].

Similar results to those found in the DCCT were observed for type 2 diabetics in the United Kingdom Prospective Diabetes Study (UKPDS) Group[59-62]. This study, initiated in 1977, was set up to determine whether improved blood glucose control will prevent the onset of the diabetic complications. Moreover, it was also designed to determine whether there were differences between conventional policy (diet therapy) and three different regimens of intensive treatment, based

on sulphonylurea, metformin or insulin[59,60]. Efficacy analyses revealed that intensive policies with sulphonylurea, metformin or insulin were equally effective in reducing fasting plasma glucose concentrations and in decreasing the risk of microvascular complications (e.g. DR) but not macrovascular disease[59]. Metformin appeared to be associated with less weight gain and fewer hypoglycemic attacks than were insulin and sulphonylureas and, therefore, was proposed as the first-line pharmacological therapy of choice in type 2 diabetics[60]. However, in all patients glucose and HbA1c measurements steadily increased with time, reflecting ongoing deterioration of beta-cell function. Associated cardiovascular disease was the mayor cause of complications, and the risk factors observed were: raised LDL and low HDL cholesterol concentrations; elevated blood pressure; elevated HbA1c plasma levels and smoking. Tight blood pressure control in patients with hypertension achieved a clinically important reduction in the risk of diabetes-related deaths and macrovascular complications as well as a significant reduction of DR progression, visual acuity deterioration and risk of retinal photocoagulation[61]. Captopril or atenolol were found to be similarly effective in reducing the incidence of these complications, suggesting that blood pressure reduction in itself might be more important than the treatment used[62].

While studies using aldose reductase inhibitors[63] antihistamines[64] or high-dose vitamin E supplementation[65], enrolled adult type 1 diabetics (over 18 years of age), only recombinant human IGF-1 (rhIGF-1), given as an adjunct to insulin therapy[66-68], has been tested in adolescent diabetics at this time. In fact, in these patients, a good glycemic control may be difficult to achieve, because abnormalities in production of GH or IGF-1 can lead to lower insulin sensitivity. According to these reports, a dose of 40 µg/kg rhIGF-1 may improve HbA1c values without overt toxic effects. However, in other studies a significant relationship was found between high IGF-1 levels and progression on retinopathy in type 1[69] and type 2[58] diabetics and a high prevalence of optic disc swelling was reported among the rhIGF-1 treated subjects[70]. Therefore, the safety and metabolic efficacy of rhIGF-1 cotherapy remains to be established and longer-term trials would be required to determine an acceptable benefit-risk profile.

Some encouraging therapeutic approaches have been performed as pilot studies in type 2 diabetics: for example, defibrotide[71], an interesting drug with antithrombotic, thrombolytic and cytoprotective activities, has been recently highlighted as a possible medical treatment of NPDR. In fact, there are many reports that extensively document the presence of a remarkable endothelium-related dysfunction of the coagulant and anticoagulant pathways in diabetics[4], and defibrotide, due to its manifold effects on vascular endothelia, seems to be an ideal drug. At the same time, acetazolamide (AZM), a carbonic anhydrase inhibitor already found to be helpful in reducing cystoid macular edema and improving visual acuity in patients with chronic iridocyclitis and retinitis pigmentosa, has been recently proposed for treatment of DME[39]. In fact, laser photocoagulation has been proven to reduce blindness due to DME by at least 60%[6]: however, because of its destructive effects, often responsible for a reduction of pericentral sensitivity due to retinal necrosis[6], treatment should also include drugs able to reduce or remove the edema without destroying the retinal anatomy permanently. Facilitated water flow across the RPE has been reported in response to AZM treatment and it might be speculated that the intraretinal edema, arised from a functional damage of retinal capillaries and a serious endothelial alteration, is thereafter removed across the RPE thanks to the AZM therapeutic effect. However, the exact AZM-mediated transport mechanism for water across the diabetes-induced breakdown of the BRB remains obscure. Both pilot studies may not be considered conclusive, because of the small number of patients involved and the short follow-up, and further investigations are required to determine the long-term effectiveness and the exact mechanism of action of both drugs in diabetic patients.

GH and growth factors (e.g. IGF-1) have been implicated in the pathogenesis of DR as strong promoters of vitreoretinal neovascular proliferations and hypophysectomy, pituitary yttrium implantation or pituitary irradiation have been proposed as possible treat-

ments for PDR unresolved by panretinal photocoagulation[4,58]. However, long-term GH replacement therapy, already thought in the past to induce DR-mimicking retinal changes in GH-deficient children, has been found to be safe in a recent clinical trial[72]. Moreover, given the strong evidence that growth factors modulate the severe eyesight-threatening complications, GH inhibitory substances have been studied in diabetic patients and octreotide, a long-acting somatostatin analogue, has been recently found to have various positive effects[73-75]. In particular, it seemed to be able to: decrease thrombomodulin and IGF-1 plasma levels;[73] retard progression of advance DR (severe NPDR or early PDR), delaying the time to laser and surgical treatments[74]; reduce the number of vitreous hemorrhages and the risk of visual acuity loss in advanced PDR after full scatter laser coagulation[75]. In fact, in these cases laser applications are only palliative since vitreous hemorrhages are rarely eliminated in the more advanced stages of DR, and, even though in a small proportion of patients only, retinopathy may remain active. Further studies are necessary to confirm these preliminary data. However, octreotide seemed to be a non-invasive and safe adjunct treatment modality that could be used where a conventional approach has failed, that is in patients with persistence of proliferative characteristics even after a well done panretinal photocoagulation.

Laser treatment

Since a clinically significant efficacy of new drugs has not yet been widely demonstrated, laser photocoagulation is still the first-line treatment of choice for high-risk retinopathy. Despite its permanently destructive effects on the retinal anatomy, photocoagulation has been proven to reduce blindness due to DME or PDR by at least 60% at three years[76-78], but even more patients would benefit if treatment was delivered at an early enough stage. In fact, despite the well standardized techniques (focal, grid, panretinal) that are now available, a significant relationship has been observed between poor clinical outcome and worse initial retinal features[79]. Therefore, an earliest as possible detection of DR is advisable, although laser treatment has been found to be more effective in adult onset than in juvenile diabetics[76]. While in patients with high risk retinopathy laser treatment of the ischemic zones of capillary nonperfusion is indicated, photocoagulation, on the contrary, is not recommended for eyes with mild or moderate NPDR, as the ETDRS data do not indicate that starting laser applications prior to the development of PPDR or PDR will reduce the risk of severe visual loss[76].

Regarding DME, a period of close observation, instead of an immediate treatment, is generally recommended for eyes in which the center of the macula is not yet or not very much involved, especially when most of the leakage to be treated arises close to the fovea. In these cases, photocoagulation may increase the risk of macular damage from direct treatment or subsequent migration of laser scars[77]. On the contrary, clinically significant DME (defined as one of the following conditions: retinal "thickening" 500 µm or less from the center of the foveal avascular zone; hard exudates with associated thickening of the adjacent retina, 500 µm or less from the center of the fovea; one disc area of macular edema, located one disc diameter or less from the center of the fovea) is an indication for focal or grid laser applications[77]. By using these guidelines, photocoagulation was able to reduce the incidence of a 2-line visual acuity loss from 30% to 15% over a 3-year period. However, the beneficial effects seem to be greatest in less advanced conditions, whereas poor prognosis is more likely in patients with diffuse intraretinal edema, macular capillary nonperfusion, cystoid macular edema, intrafoveal hard exudates and poor initial visual acuity (< 20/200)[77].

Surgery

Since the importance of the diabetic abnormal vitreous in determining vitreal fibrovascular proliferations, hemorrhages, DME and/or tractional retinal detachment[80,81], the vitreous removal (pars plana vitrectomy) is a basic surgical procedures for PDR, able to increase the chance of preserving 0.5 vision by 60% after 2 years[82-84]. However, according to the ETDRS data, the vitrectomy cumulative rate could be reduced to a 5.3% at 5 years by starting photocoagulation as soon as high risk PDR is detected[83].

The most common indications for diabetic vitrectomy include: severe vitreal hemorrhage; tractional retinal detachment recently involving the macula; progressive fibrovascular proliferation; rubeosis iridis and vitreal hemorrhage for eyes in which the media opacity has prevented adequate laser photocoagulation. Other less common indications in selected cases include: dense premacular hemorrhage; "ghost cell" glaucoma; DME with premacular traction; cataract preventing treatment of severe PDR; anterior hyaloidal fibrovascular proliferation, and fibrinoid syndrome with retinal detachment[84].

Combined surgical techniques are also routinely performed and of demonstrated clinical efficacy. In particular, in patients with complex tractional retinal detachment, pars plana vitrectomy can be associated with lens extraction (lensectomy), in order to allow a better retinal examination by the surgeon and in consideration of the increased incidence of cataract after surgery. Gas (S3F6, C3F8) or silicon oil retinal tamponade (as vitreal substitutes) and intraoperatively performed laser applications are necessary to reattach and strengthen the retina[85]. Moreover, pars plana vitrectomy-lensectomy combined with transcleral laser applications of the ciliary body (cyclophotocoagulation ab externo) has been found to be effective in the management of diabetic neovascular glaucoma with closed anterior chamber angle. In the cases of open angle neovascular glaucoma, on the contrary, vitrectomy-lensectomy and panretinal photocoagulation may be sufficient[86].

Conclusions

In conclusion, data from literature highlighted: the beneficial effect of near-normal glycemic control (based on the HbA1c value only) on the progression of DR; the importance of including children and adolescents in screening programmes for DR from the age of 10 years; the need for yearly dilated eye examinations, performed by experienced ophthalmologists only, shortly after diagnosis is made in type 2 diabetics and after five or two years of type 1 diabetes in younger children and adolescents respectively. Besides the confirmed effectiveness of early detection and treatment of DME and PDR by laser treatment and pars plana vitrectomy, new diagnostic and therapeutic approaches have been pointed out, whose efficay, if confirmed in further clinical investigations with a longer follow-up and a larger amount of patients, could lead to an earlier diagnosis and a medical treatment of DR.

Moreover, a population-based registry, from which risk factors for the progression of DR could be identified, should be established[87] and the families of diabetic children should be provided with informations about the ocular complications beginning at the time of diagnosis and, thereafter, throughout all the follow-up period[88].

However, a lot of different risk factors, already recognized or still controversial[4], the genetic heterogeneity itself of type 1 diabetes[89-90] and also financial barriers and sociodemographic factors[51] must be taken into account in order to ensure optimal care to all diabetics.

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