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Management of Diabetic Retinopathy

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Short Communication

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ABSTRACT

Management in D.R. through prophylactic treatment (maintaining a glycemic level as close as possible to normal, control hypertension <150/85 mmHg, hyperlipidemia) and curative treatment of D.R. does not cure the disease, but may slow the evolution of D.M. and D.R. AntiVEGF agents are indicated as adjuvant therapy in pan-photocoagulation laser and / or vitrectomy in patients with DR to block angiogenesis by inhibiting VEGF. All antiVEGF agents are an effective treatment for the clinically significant macular edema. Photocoagulation laser is a treatment of choice in preproliferative and proliferative DR and an effective treatment of diabetic macular edema. The indications for laser treatment in diabetic retinopathy are related to the incidence, evolution of neovessels, duration of diabetes, HbA1c level, presence of macular edema, stage of DR. The laser for macular lesions reduces the risk of vision loss in the eyes with incipient and moderate non-proliferative DR and macular edema concomitant; the laser should be applied to all patients with clinically significant macular edema. Vitrectomy in proliferative DR is indicated in vitreous hemorrhage, tractional retinal detachment in order to remove the vitreous hermorrhage and excision of tractional preretinal membranes.

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Keywords: Diabetic retinopathy nonproliferative; proliferative; diabetic maculopathy; antiVEGF agents; laser photocoagulation; panretinal; macular; laser pascal; vitrectomy.

ABBREVIATIONS

D.M.: Diabetes mellitus, D.R.: Diabetic retinopathy, F.A.: Fluorescein angiography, D.M.E.: Diabetic macular edema, O.C.T.: Optical coherence tomography, VEGF: Vascular endothelial growth factor, P.D.: Diameter, V.A.: Papillary visual acuity.

1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease with progressive evolution, which can occur at any age and can be accompanied by systemic complications.

DM is characterized by increased blood glucose > 126mg/dl with hyperglycemia (associated with disorders of lipid and protein metabolism), decreased insulin secretion and varying degrees of insulin resistance. Other reported symptoms include polydipsia, polyphagia, polyuria [1].

The evolution of DM is accompanied by systemic complications with ocular, renal, cardiovascular vascular damage, peripheral neuropathy, and predisposition to infections.

Diabetic retinopathy (D.R.) is the most common ocular complication of diabetes and it affects the retina; it is multifactorial and causes retinal ischemic vascular changes and their consequences, initially characterized by retinal capillary microaneurysms, complicated by retinal neovascularisation and macular edema, which decrease visual function progressively. D.R. occurs in approximately 30% of patients with DM and about 1% has severe forms of D.R. [2].

D.R. is the main complication of DM and the leading cause of blindness in adults aged 20-74 years; the prevalence of D.R. increasing with the duration of diabetes and with age in both forms of DM.

- DM, type 1: insulin-dependent, with rapid-onset, is accompanied by D.R. in 90% of cases after 20 years history of diagnosed DM; monitoring D.R. in the diabetic patient, by rigorous control of eye fundus, FA, OCT allows the prevention, early detection and appropriate treatment of DM
- DM, type 2: non-insulin dependent, is an insidious form of DM, closely correlated to the genetic susceptibility that accompanies D.R. in 20% of cases and in which edematous maculopathy predominates.

Visual symptoms in D.R. are gradual, variable and related to the type and location of retinal lesions, in which the slow loss of vision associated with central visual field amputation is related to the presence of exudates, edema, perimacular microaneurysms; rapid vision loss occurs in complications such as vitreous hemorrhage.

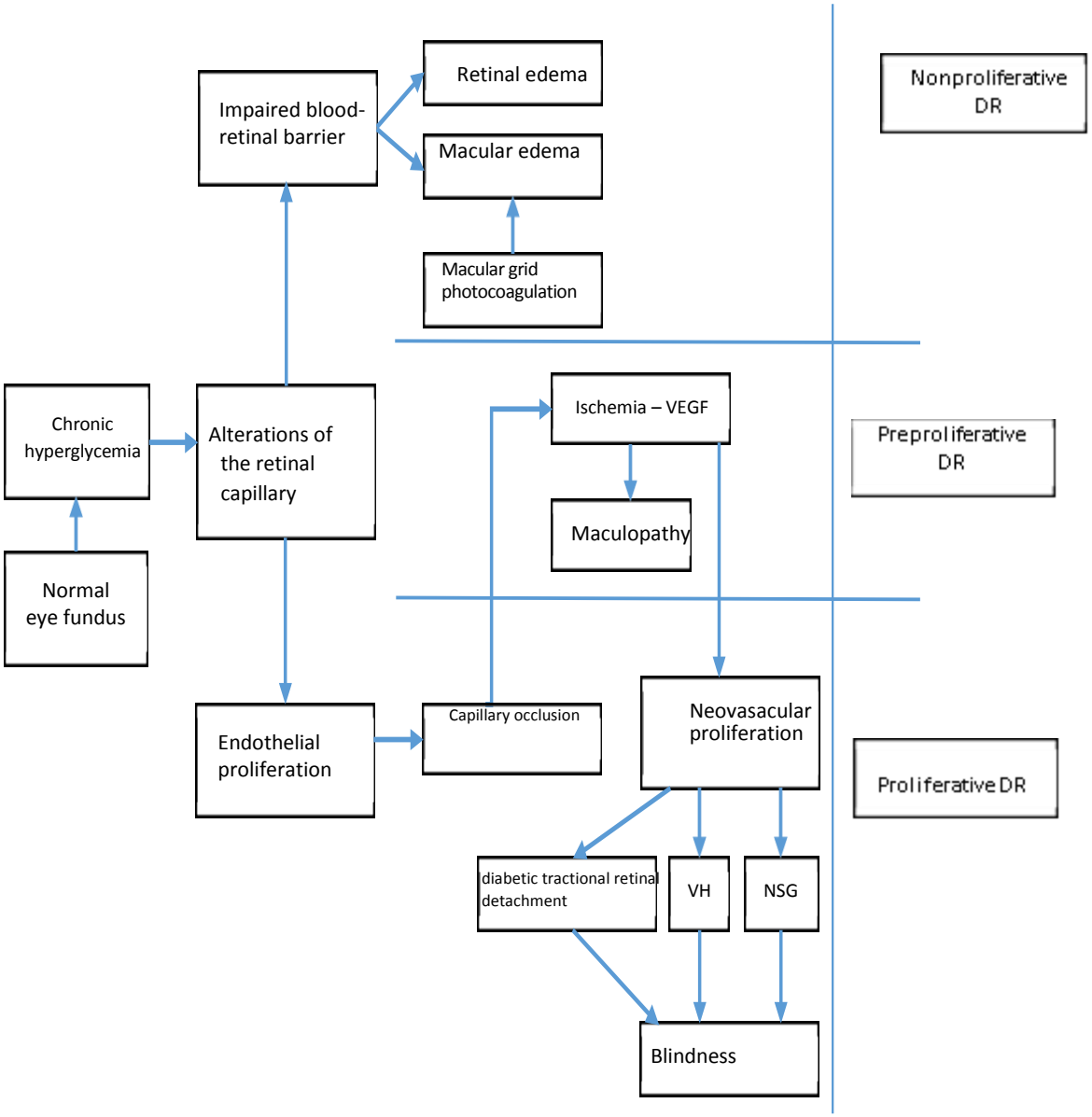
D.R. is a leakage microvasculopathy, through early affected capillary, secondary to increased vascular permeability, parallel to hypoxia that produces VEGF, elements that generate retinal microvascular abnormalities by changes in vascular permeability in the area of leakage, capillary, microaneurysms and proliferative retinopathy [3] Table 1.

In D.R., **edematous capillaropathy** occurs in the posterior and central part of the retina, with capillary hyperpermeability, microaneurysms, hard exudates, intravitreal hemorrhage, intraretinal edema, chronic macular edema and significant vision loss and **ischemic capillaropathy**; it progressively extends to the entire retina, with proliferative retinopathy, preretinal and intravitreal neo-vessels with recurrent hemorrhages, and secondary glial proliferation.

The retinal circulation is unique, and the circulatory bed is directly accessible so that ophthalmoscopic examination, reveals the retinal arteriovenous system, the optic disc, the macula.

Periodic examination of the eye fundus is required in patients with elevated blood glucose to identify D.R.; each patient with D.R. must be followed and subjected to appropriate ophthalmic treatment because he/she is a potential candidate for blindness. Periodic vision control and dilated-pupil ophthalmoscopic examination is necessary because **appropriate early treatment of DR reduces the risk of vision loss by 57%.**

Table 1. The evolution of D.R. after the onset of chronic hyperglycemia in diabetes



Fluorescein angiography (FA) is required for the detection and management of lesions, to establish the treatment protocol by laser photocoagulation in the area of unperfused retina.

OCT measures retinal thickness, highlights retinal structure, cystic spaces, thickened hyaloid, vitreoretinal tractions, intraretinal edema, cystoids macular edema CME, serous neuroepithelial detachment, OCT being necessary to establish the therapeutic conduct and the value of treatment effectiveness.

Clinically, in D.R., the following are present [4]:

- **microaneurysms and punctiform hemorrhages**, in non-proliferative incipient D.R.; their number and evolution are prognostic elements of D.R.
- **retinal hemorrhages,** produced by the rupture of the capillary wall, or of a microaneurysm; they can be: punctiform (dot and blot), in flame, in spot, in clusters (indicator of progression to the proliferative stage of D.R.), diffuse, petaloids.
- individual **hard exudates** or in confluent plaques are risk factors for the development of subretinal fibrosis.
- **soft exudates** - dysoric nodules (cotton wool spots) are elements of unfavourable

prognosis of the advanced D.R. and may be indicators of rapid progression to neovascularisation.

- - **intracellular retinal edema** by capillary occlusion in the unperfused area or extracellular edema by rupture of the hematoretinal barrier, diffusion by microaneurysms or hyperpermeable capillaries.
- **macular edema,** the main cause of vision loss in DM especially in DM type 2, in which the incidence of D.R. increases with duration and severity of DM.
- **cystoid macular edema**, highlighted by FA, OCT.
- **arteriolar changes narrowing**, occlusion and secondary retinal ischemia, source of vasoproliferative factor.
- **venous abnormalities** with venous dilatations, venous loops, beading (successive dilatations and narrowing), are indicators of aggravation of D.R.
- **intraretinal microvascular changes** define the severe stage of D.R.
- **retinal neovascularisation-Fig. 2** that generates severe complications of D.R.: vitreous haemorrhage, diabetic tractional retinal detachment, neovascular secondary glaucoma - NSG, grouped in advanced diabetic eye disease.
- **neovascularisation** located at the level of the optical disc or on the surface of the retina produces preretinal and vitreous hemorrhages.
- **fibrous proliferations**, at the level of the optical disc or in the retina

Major risk in proliferative D.R.:

- -neovascularisation at the level of the optical disc > 1/3 quadrants or
- neovascularisation at the level of the optical disc and vitreous hemorrhage or preretinal hemorrhage or
- neovascularisation in another area larger than half a disc and vitreous hemorrhage or preretinal hemorrhage

Diabetic maculopathy may be present at any stage of D.R. and is the most common cause of vision loss in DR by focal or diffuse edematous maculopathy.

Table 2. D.R. classification [5]

Non-proliferative D.R. (Fig. 1)

Background		**Pre-proliferative D.R.**	
Incipient (minimum)	Moderate	Severe (corresponds to ischemic D.R.	Very severe
-microaneurysms	-microaneurysms	- intraretinal hemorrhages> 20 in each quadrant	- at least two severe criteria
	-hard exudates	-intraretinal vascular abnormalities in at least one quadrant	
	-hemorrhage	-no signs of proliferative DR	
	-vascular anomalies		

Proliferative DR (Figs. 2,3)

Incipient	**Moderate with high risk**	**Severe**	**Complicated**
- isolated preretinal neovessels	- multiple preretinal neovessels	-neovessels prepapillary optical disc, in 1 / 3-1 / 2 of the surface	-vitreous hemorrhage
-requires pan-photocoagulation	- vitreous or preretinal hemorrhage	- preretinal or vitreous hemorrhages	- diabetic tractional retinal detachment
- after the disappearance of the neovessels, semestrial check-up			-neovascular secondary glaucoma

Reserved prognostic factors in DR:

- hard exudates in the macula
- cystoid macular edema
- mixed maculopathy
- severe DR at the time of initial diagnosis of DR

The evolution of DR is slow and progressive and requires ongoing eye supervision. Monitoring the patient with DR requires [6]:

- careful history of the disease with the identification of the following:

➢ blood glucose level, in which a well-monitored glycemic control of HbA1c can delay the onset and progression of DR, nephropathy and neuropathy (with blood glucose dosing, glucose tolerance test),
➢ systemic status, with control of hypertension and serum lipids, because hypertension and hyperlipidemia promote diabetes imbalance and may accelerate the evolution of DR.

- periodic clinical examination depending on the evolutionary stage of DR with: irian biomicroscopic examination, gonioscopy, dilated pupil ophthalmoscopy, indirect ophthalmoscopy for peripheral retinal examination, measuring the visual acuity, visual field, intraocular pressure.
- paraclinical examination, with photographs FO, FA, OCT, which is the most sensitive method to identify the location and severity of DR highlighting retinal thickness, in vitro retinal traction, retinal detachment, the presence of subretinal fluid.
- informing the patient about the evolution of the disease and the possible complications that may occur in diabetic retinopathy: vitreous haemorrhage, tractional retinal detachment, neovascular secondary glaucoma.

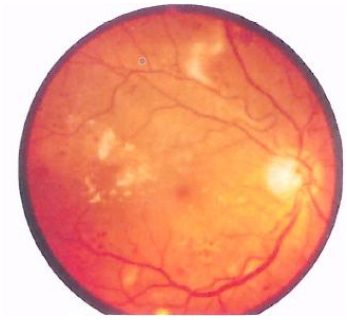


Fig. 1. D.R. background
Microaneurysms, hemorrhages

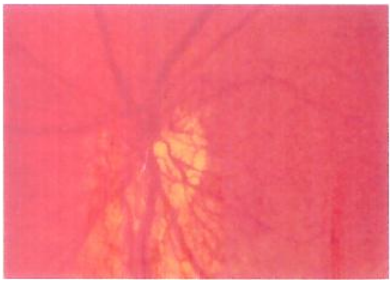


Fig. 2. D.R. new vessels
Retinal optic disc neovascularization

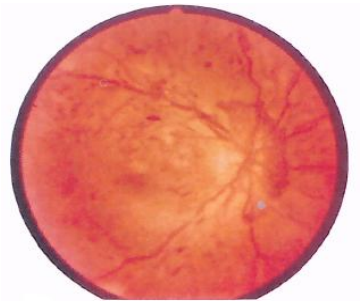


Fig. 3. D.R. proliferative
Prepapillary neovessels]

Table 3. Diabetic maculopathy classification

Edematous maculopathy

diabetic macular edema (DME)-absent	- without retinal thickening or hard perifoveolar exudates		
DME apparently present with non-central involvement	- retinal thickening or hard exudates in the posterior pole, outside the central macular area by Φ 1000 μm.		
	Incipient	Moderate	Severe
	-some areas of retinal thickening	-retinal thickening	-retinal thickening
	-hard exudates at a distance from the centre of the macula	-hard exudates, close to the centre of the macula	-hard exudates, close to the centre of the macula
DME with central involvement	-retinal thickening in the macula in the central area - **it is equivalent to the severe form**		
Cystoid DME	-large decrease in visual acuity - **macular pseudocysts**		

Ischemic maculopathy

With enlargement of the foveal avascular area, by capillary occlusion	Clinically significant macular edema	Mixed forms
-hard exudates, less than 500 μm from the centre of the fovea	-retinal edema with retinal thickening < 500 μm from the centre of the fovea	
- retinal edema at> 1500 μm with retinal thickening at> 1 DP on the surface		
-FA capillary nonperfusion with macular hypofluorescence		

Table 4. D.R. management

no D.R. clinically identified	-check-up at1-3months
incipient non-proliferative D.R.	-check-up at 6 months-1year
moderate non-proliferative D.R.	-check-up at6 months-1 year
severe non-proliferative D.R.	-periodic check-up according to risk factors: HbA1c, severe arterial hypertension, intraretinal microvascular changes, beading in 4 quadrants -lack of risk factors, check-up at 3-4 months
incipient proliferative D.R.	-pan photocoagulation laser therapy -after the disappearance of the neovessels, semestrial check-up

Table 5. Management in diabetic macular edema (DME)

non central DME	- check-up 3-6 months - photocoagulation laser
central DME	- check-up 1-3 months, depending on the evolution of macular edema - photocoagulation laser - antiVEGF - anti-inflammatory steroid – intravitreal injection
stable DME	- check-up 3-6 months

The treatment of DR. does not cure the disease, but may slow the evolution of DM and DR [6] tables [4,5].

Prophylactic treatment of DR requires:

- maintaining a glycemic level as close as possible to normal
  - HbA1c <6.5%
  - Fasting blood glucose 90-130 mg / dl
  - Postprandial blood glucose <180 mg / dl
- permanent check-up of DR by periodic monitoring of the patient, depending on the type of DR, progression of DR, the presence of macular edema
- hypertension check-up; values <150/85 mm HG may limit the progression of DR
- control of hyperlipidemia

2. CURATIVE TREATMENT OF DR

- *antidiabetic drug treatment* with oral and injectable antidiabetics.
- *other drugs:* antioxidants (vitamins C and E), minerals (Zinc and Copper), calcium dobezylate, flavonoids (mirtilene, difebioma), carotenoids (lutein), tarosin, antiplatelet agents, etamsilate, local NSAIDs (bromfenac, nevanac), ruboxistaurin
- *antiVEGF agents* - vascular endothelial growth factor [7,8] -: bevacizumab (avastin), ranibizumab (lucentis), aflibercept (eylea) are indicated as **adjuvant therapy in pan-photocoagulation laser and / or vitrectomy in patients with DR to block angiogenesis by inhibiting VEGF**. All antiVEGF agents are an effective treatment for the **clinically significant macular edema,** the aflibercept having the best results. The use of antiVEGF agents in combination with laser therapy has better results than monotherapy or laser therapy combined with intravitreal injection

of triamcinolone acetonide in the treatment of macular edema.

- *intravitreal corticosteroids* are represented by triamcinolone acetonide which allows the regression of macular edema [9].
- *corticosteroid implant:* detamexazone (ozurdex) active 3-4 months, fluocinolone acetonide (iluvien) active up to 36 months, for the treatment of macular edema in diabetic patients who have been previously treated with intravitreal corticosteroids and did not show increased intraocular pressure.

3. LASER PHOTOCOAGULATION TREATMENT

Laser photocoagulation is the therapeutic method of choice in DR, through confluent photocoagulation of the areas of nonperfusion, in order to inhibit the process of neovascularisation responsible for proliferation.

Photocoagulation laser is a treatment of choice in preproliferative and proliferative DR and an effective treatment of diabetic macular edema [10].

Laser treatment in DR is transpupillary with the help of Yag-Nd laser, doubled in frequency, green argon laser, red krypton laser or with laser diode in case of vitreous hemorrhages or cataracts, the laser treatment aiming to close the leakage areas [11].

Laser impacts produce burns that destroy the ischemic retinal areas and inhibit the process of neovascularisation.

The laser can limit the extension of retinal edema, can promote its resorption and through scars between the retinal pigmented epithelium (PE) and neuroepithelium, it limits the serous detachment of the neuroepithelium.

Laser treatment in DR is a photocoagulator treatment in continuous emission, subliminal regime (subthreshold) micropulse and multispot (laser techniques): Pascal system [10,11,12,13,14].

The indications for laser treatment in diabetic retinopathy are related to the incidence, evolution of neovessels, duration of diabetes, HbA1c level, presence of macular edema, stage of DR.

Focal laser photocoagulation-Fig.4 can be performed directly by microaneurysms and on the microvascular lesions in the centre of the hard exudates, at least 500 μm of fovea with spots 50-100 μm, duration 0.05-0.1s, power 500-750 μm, to obtain a gray colour at the level of microaneurysms in the ischemic territory or in macular edema clinically significant.

The indications for starting laser treatment are:

- disc neovascularisation<of a papillary diameter - PD of the optical disk, at> ¼ PD
- disc neovascularisation<¼ PD, if associated with vitreous or preretinal hemorrhage
- neovascularisation>½ PD or if there is preretinal or vitreous haemorrhage.

Laser treatment can be started in the stages of advanced non-proliferative DR, if there is difficult collaboration with the patient, renal impairment or the presence of cataract.

Grid laser photocoagulation consists in the application of laser points in the macular area, with diffuse edema, not closer to 500 μm of foveola and 500 μm of the optic nerve (OP), with spots 50-100 μm, duration 0.05-0.1s , power 500-750 mw, distance between spots – the diameter of a spot.

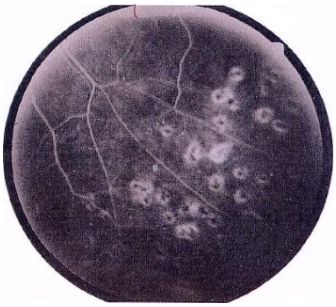


Fig. 4. D.R. focal laser photocoagulation

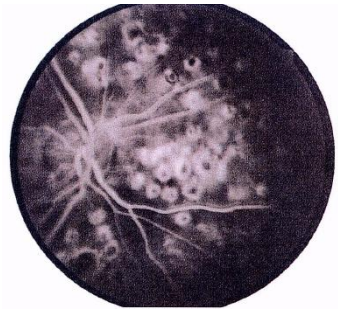


Fig. 5. D.R. panretinal phocoagulation

Diode grid laser photocoagulation with micropulsations.

Pan photocoagulation-Fig.5 is photocoagulation extended to the entire surface of the peripheral ischemic retina outside the macular region, except for the region between the temporal vascular arches, with the destruction of 20-30% of the retinal surface to limit the development of neovascularisation that characterizes the proliferative DR, responsible for the serious complications of DR [6,14,15,16].

The major effect of panretinal photocoagulation is the destruction of neovessels and inhibition of VEGF secretion. Panphotocoagulation is indicated in:

- neovascularisation of the disc > 1/3 above the optical disc surface
- neovascularisation of the disc associated with preretinal or vitreous hemorrhage
- neovascularisation of the disc of the anterior segment

Panretinal photocoagulation is indicated in severe non-proliferative D.R. in all stages of proliferative D.R. and is done in conventional laser photocoagulation, argon laser 1200 impact of 500µm (or more), separated by free intervals of 250µm with a duration of 0.1s, power 250-700 mw in 2-3 sessions, avoiding areas of vascular proliferation, tractional retinal detachment.

The conventional laser treatment alternative is represented by automatic laser photocoagulation that uses wavelengths of 532nm, spot diameter 200µm, duration 20ms, power 300-750nw, in 2 sessions, number of spots 2500-3000.

Pascal multispot laser photocoagulation with non-continuous wave pattern, with short duration pulses brings changes of conventional photocoagulation parameters, with minimal incidence of side effects, comparative efficiency, but better tolerated by the patient [10,11].

The laser for macular lesions reduces the risk of vision loss in the eyes with incipient and moderate non-proliferative DR and macular edema concomitant; the laser should be applied to all patients with clinically significant macular edema [17,18,19].

- no continuous emission laser should be applied for lesions <300-500µm from the centre of the macula
- DME without central involvement requires continuous or micopulse focal photocoagulation
- DME with central involvement requires focal or grid laser treatment, only with micropulse laser if the central retinal thickness is less than 350µm

Laser photocoagulator post-treatment VA remains stable in 70% of cases, improves by 15% or may degrade, the reserved prognostic factors of VA being: macular hard exudates, cystoid macular edema, mixed maculopathy (edematous and ischemic), severe DR.

Photocoagulation may cause complications: cystoid macular edema by worsening of a pre-existing macular edema, may be complicated by serous detachment of the neuroepithelium, subretinal neovascularisation (possible overdose), vitreous hemorrhage, posterior vitreous detachment.

4. SURGICAL TREATMENT [20]

Vitrectomy in proliferative DR is indicated in vitreous hemorrhage, tractional retinal detachment in order to remove the vitreous hermorrhage and excision of tractional preretinal membranes.

Posterior vitrectomy may be indicated for edema refractory to laser treatment, but also as a first-line treatment in edema associated or not with tractions of the posterior hyaloid.

Treatment of neovascular secondary glaucoma, which is produced by neovascularisation of the iridocorneal angle, iris, or both, is done by local and systemic medical therapy, with inhibitors of carbonic anhydrase, topical glycerin; most neovascular secondary glaucomas are refractory to drug therapy and require surgical treatment: trabeculectomy, alcohol injection, enucleation.

5. CONCLUSIONS

In order to limit the progression of diabetic retinopathy to blindness as well as to possibly limit the incidence of severe forms it is essential that patient with diabetes mellitus be followed closely for tight glycemic control and frequent ophthalmologic evaluation. While various treatment of the diabetic retinopathy do exist, best solution is the prevention of its serious form and treatments are not devoid of adverse effects and complications.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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