RECOMMENDED PROCEDURES FOR DIAGNOSIS AND TREATMENT OF DIABETIC RETINOPATHY

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INTRODUCTION

In recent years diabetes mellitus (DM) and its complications have represented a growing society-wide problem in both advanced and developing countries throughout the world. The increasing incidence especially of later complications of DM is a cause of increased morbidity and mortality of the diabetic population, and also determines the main targets of therapeutic-preventive care. The fundamental aim is to reduce the incidence of chronic complications by means of prevention, timely diagnosis and effective treatment. These complications markedly increase the demands for the provided care, as well as the cost thereof. Correct, timely and intensive treatment of DM from the moment of its diagnosis can clearly reduce the risk of complications. Observation of patients and their treatment should be in accordance with the recommended procedures. At present approx. 8-9% of the entire population are registered as diabetics in the Czech Republic (CZ). According to the most recent data from the Institute of Health Information and Statistics of the Czech Republic (IHIS) from 2013, this concerned more than 861 000 patients (8.3%), unfortunately a further number of patients with DM still remain undiagnosed (more than 2% of the population). The incidence of DM increases with age, so in the age group above 65 years it is possible to expect that more than 20% will be diabetic. The number of diabetics is constantly increasing, over the last 20 years their number has doubled, and the current annual increase of registered diabetics is approximately 25 – 30 000. The growing prevalence especially of type 2 DM is leading worldwide to the designation of the incidence of diabetes as an epidemic. According to the World Health Organization, approximately 360 million people worldwide are afflicted with diabetes, and it is expected that by the year 2030 this will increase to more than 550 million. Metabolic syndrome, a component of which is often type 2 DM, may afflict up to 25 – 30% of the adult population. Approximately 5% of the population in CZ suffers from prediabetes, and many of these patients are not aware of their condition whatsoever. With the increase in the number of diabetics within the population there is also a marked increase in the incidence of DR, and even despite continuing primary and secondary prevention, this disease remains a serious social-health problem with significant economic consequences, afflicting approximately 50% of diabetics (1-3).

1. CHARACTERISTICS OF DIABETIC RETINOPATHY

Diabetic retinopathy (**DR**) is a typical microvascular complication of DM. It originates upon a background of specific morphological changes, which are a consequence of a metabolic disorder in patients with types 1 and 2 DM. DR may also accompany other specific types of DM. In advanced countries DR and

its complications represent the most common cause of newly ensuing blindness in persons aged 20-74 years. The risk of blindness in a diabetic is 10-20x higher than in a non-diabetic. Risk factors for the occurrence and development of DR, in addition to the length of duration and the type of DM, are chronic hyperglycaemia (increased level of glycated haemoglobin), hypertension, presence of nephropathy, low socio-economic status and older age. The majority of the data on these risk factors was obtained from large epidemiological studies (WESDR and UKPDS). Further risk factors for the progression of diabetic macular edema (**ME**) are dyslipidemia, microalbuminuria and proteinuria. In addition pregnancy, especially unplanned, may cause progression of ME and proliferative DR, with potential regression after childbirth in certain patients and/or with persistence of ME. Complex preventive and therapeutic procedures reduce the risk of loss of sight by more than 90%. These procedures incorporate intervention in the case of risk factors that can be influenced, active screening for DR and specialised ophthalmology treatment (4, 5).

2. EPIDEMIOLOGICAL CHARACTERISTICS OF DR

Among the observed complications of DM, DR is the most frequently recorded in the Czech Republic. In 2013 this complication afflicted 102 783 persons (11.9%), of whom 27.3% had proliferative form. Of the total number of patients with DR, 2.4% were affected with blindness. The proportion of this advanced form of ocular affliction in diabetics is increasing slightly. The incidence of diabetic maculopathy (**DMP**), the most common cause of deterioration of visual acuity, is not statistically monitored in CZ. Fundamental differences in the incidence and prevalence of diabetic ME, recorded in various epidemiological studies, depend on the type of DM, method of treatment (insulin, PAD or only diet), duration of DM and the age of the patients. ME in diabetics develops in various stages of DR, but appears most frequently in advanced forms of DR.

Prevalence studies of type 2 DM indicate that ME is suffered by 2–8.2 % of diabetics after 5 years' duration of DM, whereas after 20 years' duration this complication afflicts 28% of patients. In the case of type 1 DM the incidence of ME 5 years after determination of the diagnosis of DM is 0%, whereas after 20 years duration of DM it afflicts 29% of diabetics. Patients treated with insulin have a higher prevalence of ME. After 15 years' duration of type 1 DM treated with insulin, ME afflicts 18% of patients, and in the case of type 2 DM 20% of diabetics, whereas in both types of DM without insulin treatment ME afflicts only 12% of patients. The prevalence of ME is directly dependent on the level of glycated haemoglobin(HbA1c) and the presence of nephropathy.

3. PATHOPHYSIOLOGICAL PRINCIPLE AND MORPHOLOGICAL CHARACTERISTICS

Genetic and metabolic factors are applied in the pathogenesis and progression of DR, of which the most important role is played by chronic hyperglycaemia with the connected metabolic pathways (oxidation stress, subclinical inflammation, glycation of proteins, polyol pathway of glucose metabolism etc.). The occurrence of DR and its deterioration is also unfavourable influenced by hypertension. The data about the influence of serous lipids and the mechanism of their applicable effect on the development of DR is not convincing.

As a consequence of haemodynamic, rheological and structural changes in the retinal microcirculation, there is a progressive increase in capillary permeability, obliteration of capillaries and the generation of a region of capillary nonperfusion, with a preference for localisation in the middle periphery of the retina in the case of type 1 DM, and in the region of the posterior pole of the eye in type 2 DM. Chronic retinal hypoxia is a stimulus for the release of inflammation mediators, growth factors, increased permeability and new formation of blood vessels in the retina and along the posterior surface of the vitreous body. A significant element influencing DR is changes of the retinal pigment epithelium and neurodegenerative changes of the retinal nerve cells and glial cells.

4. CLASSIFICATION AND CLINICAL CHARACTERISTICS

On the basis of the dynamics of retinal changes we differentiate between the following clinical stages and forms of diabetic affliction of the eye: **non-proliferative DR (NPDR), proliferative DR (PDR) and diabetic ME.**

Non-proliferative DR (NPDR). The fundamental clinical characteristics of NPDR are microaneurysms, haemorrhages, phlebopathy, intraretinal microvascular abnormalities (IRMA) and cotton wool spots. According to the stage of progression of the changes, it is possible to divided NPDR into incipient [4 – 0 – 0], (numbers in brackets indicate the number of quadrants in which the following clinical progressive characteristics of capillary closure are present: haemorrhage – phlebopathy – intraretinal microvascular abnormalities), medium advanced [4 – 1 – 0] and advanced. Advanced NPDR has a wide range of clinical progressive characteristics of retinal nonperfusion and ischemia, dynamically transforming advanced form [4 – 2 – 1] into very advanced form of NPDR [4 – 4 – 4] (6).

Proliferative DR (PDR). Diagnosis essentially requires the presence of newly formed blood vessels anywhere on the retina and/or disc of the optic nerve, with or without the participation of accompanying fibrous tissue. In addition to a progressive finding of retinal and epiretinal neovascularisations with the presence of fibrous tissue, advanced PDR is also manifested in complications such as preretinal, retrovitreal and intravitreal haemorrhage, tractional and/or rhegmatogenous retinal detachment, and neovascularisation on the iris. According to the dynamics of the pathology we differentiate between incipient and high risk PDR. High risk PDR is defined as the presence of neovascularisation on the disc of the optic nerve within the scope of 1/4 to 1/3 of the papilla and/or new formation of blood vessels anywhere on the retina affecting at least ¼ of the surface of the papilla, accompanied by haemorrhage into the vitreous body.

Diabetic ME (7) originates as a consequence of a breach of the haemato-ocular barrier. It is characterised by abnormal thickening of the retina upon a background of an accumulation of fluid in its anatomically predisposed central

region. The fluid is accumulated in the retina either inside the cells or extracellularly in the external plexiform and internal core layer. Usually an accumulation of proteins and lipids takes place in the form of hard exudates. ME is defined as a thickening of the retina or the presence of hard exudates within the scope of 1 papillary diameter (1500 µm) from the centre of the macula. ETDRS determined the term **clinically significant macular edema (CSME)** in order to determine the degree of severity of ME. According to this key study, ME is considered to be clinically significant if it meets the following parameters: thickening of the retina up to a distance of 500 µm from the centre of the macula and/or hard exudates up to a distance of 500 µm from the centre of the macula if they encroach upon the region of retinal thickening, and/or thickening of the retina by more than the surface of 1 papillary diameter, if part of the saturation is within 1 papillary diameter of the centre of the macula. This edema, defined by specific morphological abnormalities, is an important indicator of the progression of the pathology, with an immediate threat to the the fovea and visual function. This finding requires immediate performance of focal laser coagulation of the retina. ME may occur or persist also as a consequence of vitreomacular (VM) traction.

Classification of ME (8)

a) focal – is characterised primarily by discrete saturation from microaneurysms and capillaries. The areas of focal saturation are frequently bordered by an incomplete or complete ring of hard exudates.
b) diffuse – is caused by extensive damage to capillaries, presence of microaneurysms and pathologically altered arterials and extended thickening of the macula, as a consequence of generalised permeability of the dilated capillary flow.
c) cystoid – is accompanied by regularly diffuse edema and is characterised by saturation into the preformed areas of the deeper layers of the retina, primarily the nerve layers. The presence or absence of cystoid areas does not directly influence the prognosis and treatment of ME.
d) ischemic maculopathy – is characterised by a diminution or death of the perifoleolar capillary network, with a significant to double extension of the foveal avascular zone. FAZ abnormalities include irregular edges and extension of the intercapillary areas. In the case of ischemic maculopathy, hard exudates are mostly absent, we may determine haemorrhage and edema. Ischemic maculopathy significantly damages visual acuity.
e) mixed – in clinical practice a wide range of mixed forms are observed.

DM is a significant risk factor in the **development of postoperative ME**. It develops in diabetics following cataract surgery in up to 81% of cases, and in 25% of cases ME persists for a period of 12 months. ME caused by cataract surgery does not depend on the degree of development of DR.

5. DIAGNOSIS

Diagnostic methods for identifying DR are biomicroscopic examination on a slit lamp, simple photography, photography with colour filter, stereoscopic photography and fluorescence angiography (FAG) of the ocular fundus. These methods are simple, safe and capable of differentiating patients with DR from those without it. All examinations of the ocular fundus are performed following pharmacological dilation of the pupil with the aid of 2.5% phenylephrine (sympathomimetic) and 1% tropicamide (parasympatholytic). For further details see chapter 7.

Biomicroscopic examination on a slit lamp is a sufficiently

Table 1 Treatment of hyperglycaemia

Ukazatel	Požadovaná hodnota
HbA1c (mmol/mol)*	< 45 (< 60)
Glykémie v žilní plazmě nalačno/před jídlem (mmol/l)	£ 6,0 (< 7,0)
Hodnoty glykémie v plné kapilární krvi (selfmonitoring)	
nalačno/před jídlem (mmol/l)	4,0–6,0 (< 8,0)
postprandiální (mmol/l)	5,0–7,5 (< 9,0)
Krevní tlak (mmHg)	< 130/80
Lipidy v krevním séru	
celkový cholesterol (mmol/l)	< 4,5
LDL cholesterol (mmol/l)	< 2,5 (< 2,0)
HDL cholesterol (mmol/l): muži /ženy	> 1 / > 1,2
triacylglyceroly (mmol/l)	< 1,7
Body mass index **	19–25
Obvod pasu: ženy (cm) / muži (cm)	< 80 /< 94
Celková dávka inzulinu/24 hodin/kg hmotnosti (IU)	< 0,6

* HbA_{1c} – glykovaný hemoglobin – podle IFCC s normálními hodnotami do 39 mmol/mol
** u nemocných s nadváhou a obezitou je cílem redukce hmotnosti o 5–10 % a následně ji udržet
() V závorce jsou uvedeny doporučené hodnoty pro diabetiky s vysokým kardiovaskulárním rizikem. Tyto cílové hodnoty stanovujeme individuálně.

sensitive method for determining a diagnosis of DR, newly formed blood vessels on the iris, for determining presence of retinal thickening in the region of the macula and neovascular changes on the papilla or anywhere on the retina. We perform examination with the aid of an aspherical lens with a strength of 90 dioptres or with other types of noncontact and contact lenses.

Stereoscopic photography or digital sterophotography in 7 fields according to the Airlie House Classification is the "gold standard" for evaluation of the degree of DR (ETDRS and EURODIAB studies). Evaluation is performed blind in Retinopathy Grading centres. Colour photo-documentation of the basic two fields (central and disconasal in 40° view) should be performed always and on all risk patients with more advanced forms of DR.

Fluorescence angiography is a supplementary method and is not recommended for the practical purposes of screening. It is not necessary for the diagnosis of CSME or PDR. It may be indicated before laser coagulation of DMP and CSME, in order to determine the scope of macular capillary nonperfusion, fine neovascularisations or for an evaluation of an inexplicable deterioration of visual acuity.

Optical coherence tomography (OCT) is a specialised examination of the macula on the principle of low-coherence interferometry with high resolution. This is the most state-of-the-art method, which enables display of retinal structures with a high resolution capability of up to 3 µm in the form of a cross-section. A classic linear B-scan is available, but also a C-scan, which displays a cross-section of the retina in the frontal plane. The examination is non-invasive and can be performed at high speed without the necessity of dilating the pupil. The method is effective not only upon a qualitative but also quantitative description and evaluation of ME. With the aid of OCT it is possible to observe changes in the macula over time, and to monitor the efficacy of treatment of ME.

6. THERAPEUTIC PROCEDURES

Treatment and prevention of DR rests upon lifestyle and pharmacological treatment of risk factors that can be influenced, in particular treatment of hyperglycaemia and hypertension, as well as specialised ophthalmological treatment. A condition is active ophthalmological screening. At present no specific pharmacological therapy exists (2, 3, 9).

Treatment of risk factors

Good co-operation of the patient, as well as satisfactory compensation of diabetes and other risk factors, are a condition for successful treatment. The target values recommended from the perspective of preventing the occurrence and progression of all micro and macrovascular complications, including DR, in both types of diabetes, are presented in table no. 1. The stated targets are within the normal range of the observed parameter, and in a range of patients we are unable to attain them. We stipulate individual targets of therapy for each patient (10-12).

It is clearly documented that close compensation of diabetes is effective in preventing the development and progression of DR. "Metabolic memory" is applied. We have the greatest demands for closeness of compensation (HbA1c pod 45 mmol/mol) independently of the type of diabetes in the period closely following the identification of the pathology, and in persons with a low cardiovascular risk (patients with a short history of diabetes, without cardiovascular events in anamnesis and current values of HbA1c approx. up to 70 mmol/mol). In persons with associated serious diseases, in which hypoglycaemia increases the risk of cardiovascular complications, we are less stringent (HbA1c pod 60 mmol/mol). A fundamental requirement is safety of treatment (absence of hypoglycaemia). The drop in glycaemia should not be sharp, especially in the case of long-term severely decompensated patients (see risk of early normoglycaemic deterioration). Optimal compensation should be attained gradually over the course of several months.

Each drop in HbA1c, even if we do not attain the target value, is beneficial from the perspective of stabilisation of DR. We usually proceed to a review of hyperglycaemia treatment if HbA1c exceeds 5.3%. In the endeavour to reduce hyperglycaemia the choice of the hypoglycaemic agent is not fundamental, of importance is the attained value of compensation of diabetes (UKPDS, DCCT)(13, 14).

Treatment of hypertension

Normalisation and stabilisation of blood pressure is also unequivocally effective in the treatment of DR. A question remains as to whether individual groups of antihypertensive agents can also have a specific influence on the course of DR. In the treatment of hypertension ACE inhibitors and sartans are the drugs of choice for diabetics. However, the evidence in support of their suitability is based upon their cardioprotective and nephroprotective effects, whilst as regards the progression of retinopathy the choice of pharmaceutical is not decisive according to the current state of the evidence (15, 16).

Treatment of dyslipidemia

Epidemiological studies document significant relationships between the incidence of hard deposits on the retina and levels of LDL cholesterol in serum, relationships of LDL to the severity of DR and associations between DR and the thickness of the media intima measured on the arteria carotis. Similarly levels of triglycerides in serum are associated with the severity of retinopathy, and in prospective studies emerged as an independent risk factor of DR. A sub-analysis of the large mortality study FIELD (17) demonstrated a highly significant reduction in the number of treatments by laser photocoagulation in a group with type 2 DM treated with fenofibrate (by 30%, p 0.005) in comparison with a placebo. Overall the progression of DR was slowed in 79% of cases. Similarly positive results were achieved by the addition of a fibrate to a combination with a statin as opposed to monotherapy with a statin (ACCORD) (18). The group of patients being treated with this combination had a 40% lower relative risk of progression of DR than the placebo group, which is in accordance with the decrease in the level of triglycerides.

Specialised ophthalmological treatment

At present three fundamental options are available in the treatment of DR (19):

a) Focal or grid photocoagulation of the macula

b) Panretinal photocoagulation
c) Pars plana vitrectomy

Laser coagulation of the retina – significantly reduces the risk of loss of visual acuity. Suitably timed treatment of indicated stages of DR and ME is of decisive importance in preventing losses of visual acuity. The effectiveness of laser coagulation is preventive, and as a rule already lost visual acuity cannot be restored. It is difficult to stipulate standards for laser treatment of DR and ME unequivocally, and as a result the presented methodical instructions are general recommendations which ensue from the study DRS (Diabetic Retinopathy Study) and ETDRS. Laser coagulation may be focal, quadrant or panretinal. Of decisive significance in the choice of laser coagulation is not only the severity of DR, but also the presence of other risk factors. At present we use barely visible or invisible (sub-threshold) beams of micropulse lasers with a wavelength of 577nm or 810 nm.

Incipient NPDR – this stage does not require laser treatment.

Medium advanced NPDR – in this stage we do not usually perform laser coagulation of the retina.

Medium advanced NPDR and presence of CSME – in the case of long-term sub-compensated and decompensated diabetics we recommend the use of FAG. In the presence of focal or diffuse saturation in the macula or the region of nonperfusion it is appropriate to commence focal laser coagulation of the macula in order to stabilise visual acuity.

Advanced NPDR – usually requires quadrant/panretinal coagulation of the retina.

Advanced NPDR accompanied by CSME in type 1 diabetic – photocoagulation of the central periphery of the retina or quadrant photocoagulation of the retina is performed, and if CSME does not subside then this is followed by focal, grid or modified grid macular photocoagulation.

Advanced NPDR accompanied by CSME in type 2 diabetic and MODY – laser treatment may be considered, and we recommend commencement of laser photocoagulation of the macula first of all. The benefit of timely panretinal photocoagulation in type 2 diabetics is greater than in patients with type 1 DM.

ME – is a usual indication for photocoagulation. It is necessary to commence treatment promptly. We must inform the patient of the necessity of commencing treatment before visual acuity deteriorates. Statistically visual acuity improves following resorption of edema in only 15% of patients (see combined therapy).

CSME - We always treat this with laser photocoagulation. The choice of the method of laser therapy then depends on the clinical manifestations of edema. This condition requires focal/grid laser photocoagulation either alone and/or in combination with other variants of treatment such as anti-VEGF preparations or steroids applied intravitreally.

PDR – is always an indication for laser therapy. The method of therapy is derived from the type and scope of proliferation.

Retinal neovascularisation (RNV) – type 2 diabetics treated with insulin respond fairly well to focal or quadrant coagulation. In type 1 diabetics panretinal photocoagulation is more appropriate.

Papillary neovascularisation (PNV) – neovascularisation of the optic nerve is virtually always an indication for panretinal photocoagulation.

Persistent newly formed blood vessels may constitute a considerable problem. Targeted coagulation is linked with a relatively high risk of haemophthalmos. It is possible to influence the regression of these neovascularisations by means of intraocular application of anti-VEGF preparations.

Early normoglycaemic deterioration syndrome – in patients with an expected rapid decrease of glycated haemoglobin from levels above 11% we recommend panretinal photocoagulation for advanced forms of NPDR and PDR.

A serious side effect of panretinal photocoagulation is the formation or deterioration of ME. As a result we usually perform panretinal photocoagulation in 4 or 5 separate sessions, with an interval of several days in between.

Pharmacological and combined treatment of diabetic ME

A fundamental advance in the treatment of diabetic ME took place during the course of the last decade with the introduction of pharmacological therapy of retinal complications using VEGF inhibitors and/or steroids applied transconjunctivally and transsclerally into the vitreous body (20, 21). The aforementioned method of local application of pharmaceuticals to the posterior segment of the eye is the most effective approach in the therapy of diseases of this segment. This treatment, in contrast with conventional laser coagulation, is not linked with direct damage to the neurosensory retina.

The method of administration of drugs to the posterior segment of the eye is influenced by the presence of the haemato-ocular barrier (HOB). The HOB may be damaged e.g. by surgical procedure, diabetes, photocoagulation or cryoretinopexy. In the case of a breached HOB pharmaceuticals may enter the eye more easily and quickly, and are also more easily and quickly excreted from the eye. Intravitreal injections have long-term clinical use. This method provides a maximum concentration of pharmaceuticals in the vitreous body upon minimal systemic absorption. It is widely used in the treatment of diabetic ME, in which antibodies against growth factors and/or steroids are applied intravitreally. With regard to the fact that levels of VEGF in the eye correlate with the severity of ME, it is expected that anti-VEGF treatment will lead to a fundamental alleviation of ME. VEGF blockers used in the treatment of diabetic ME include ranibizumab, bevacizumab and aflibercept.

The first registered inhibitor of angiogenic growth factors (VEGF, IGF-1) for the reduction of vascular saturation in the treatment of diabetic ME is ranibizumab. On the basis of an analysis of clinical data from prospective randomised trials (BOLT, RESOLVE, DRCR Net, READ-2, RESTOR) and data from non-randomised trials, it was determined that in the long-term perspective it is not possible to exclude the possibility of a deterioration of macular ischemia, especially in eyes with significant ischemia before treatment and following repeated intraocular applications. It is recommended that prolonged anti-VEGF treatment is proceeded with on an individual basis in order for the therapeutic regime to evalua-

te both the level of ME and the fluoroangiographic scope of macular ischemia in eyes with mixed form of ME.

Contemporary randomised trials have confirmed that repeated intravitreal injections of ranibizumab may significantly improve visual acuity (VA) in patients with diabetic ME, which may fundamentally alter the strategy of treatment of diabetic ME. The efficacy and repeated frequency of treatment are indisputable, nevertheless it remains a contentious issue as to whether intraocular injections of ranibizumab may increase the risk of systemic side effects of treatment. A summary observational non-randomised trial incorporated 6 randomised trials (READ-2, DRCR, RESTOR, RESOLVE, RISE & RIDE and REVEAL), with a total number of 2459 patients. The conclusions of these studies confirmed favourable systemic safety of treatment of diabetic ME with ranibizumab. Ranibizumab is indicated for the treatment of damage to sight caused by diabetic ME in patients with both types of DM (21). It is essential to conduct careful selection of patients with regard to the aforementioned systemic vascular disorders, and it is appropriate to apply a pro re nata therapeutic principle. A prerequisite for treatment is good compliance of the patient and a corresponding diabetological background.

The efficacy and safety of intravitreally applied aflibercept to diabetic ME with affliction of the centre was dealt with by two identical phase III studies (VISTA-ME and VIVID-ME) (22, 23). These studies included 406 and 466 patients respectively, with type 1 or type 2 DM, with clinically significant diabetic ME with affliction of the centre. In the 52nd week of observation the studies demonstrated a significant predominance of favourable functions and anatomical results in comparison with laser coagulation. The total incidence of ocular and serious overall side effects, including arterial thromboembolic events and deaths from vascular causes was the same in all groups. Intravitreally applied aflibercept was very well tolerated. The use of bevacizumab so far remains within an off-label regime in the treatment of diabetic ME in CZ.

Sub-analyses of clinical evaluations of aflibercept document that the effectiveness of intravitreal application of anti-VEGF agents in the treatment of ME is not influenced by the initial values of HbA1c or blood pressure (24).

Biodegradable implants with content of dexamethasone

Dexamethasone is released from a polymer carrier for more than one month, and has a potential therapeutic effect of around 4–6 months. The first extensive trial with intravitreal application of a biodegradable implant (POSURDEX) containing dexamethasone was performed on patients with persisting ME in DR, venous occlusion, uveitis and Irvine-Gass syndrome. According to expectations, an adverse effect was an increase of intraocular pressure. In the observed groups of patients no significant difference was observed in the number of cataracts. Recently results were published from a randomised, controlled, multicentric, double-blind and 12 month trial (PLACID). The number of patients with functional gain was significantly higher in the combined group (laser coagulation plus implant) after 1 and 9 months of observation. The reduction of the region of diffuse saturation, verified angiographically, was also greater in the group of patients with a dexamethasone implant plus laser treatment.

In the recent period two identical randomised, placebo controlled extensive studies entitled MEAD (Macular Edema Assessment of implantable Dexamethasone in diabetes) were completed, the primary aim of which was an improvement of VA in the 3rd year of treatment of diabetic ME from the baseline condition by 15 or more letters on ETDRS optotypes. The improvement of VA in the branches with a dexamethasone implant was statistically significant in comparison with the control group. Dexamethasone was implanted intravitreally every 6 months over a period of 36 months. No systemic adverse effects or cerebrovascular events appeared in connection with this treatment (25, 26).

Pars plana vitrectomy (PPV)

This concerns a microsurgical procedure in the vitreous body and on the retina, with the option of endolaser panretinal photocoagulation. The principle of the operation is removal of a turbid and pathologically altered vitreous body and the severance of vitreoretinal adhesions, preparation and removal of epiretinal and subretinal membranes and reattachment of the retina in the case of its detachment, and performance of laser coagulation of the retina. The introduction of OCT as a routine examination method for ME represented a significant advance in the diagnosis and differential diagnostics and in the evaluation of the treatment of these pathologies. Imaging with the aid of OCT also enables effective evaluation of the vitreomacular interface and the tractional forces leading to structural changes in the retina. Through the separation of the posterior hyaloid membrane, PPV positively influences diabetic ME which has not responded to laser therapy, and VA improves after surgery.

Basic indications for pars plana vitrectomy in the case of DR and their complications can be divided into a number of groups:

- non-reabsorbing vitreous haemorrhage
- tractional retinal detachment threatening macula
- combined tractional and rhegmatogenous retinal detachment
- advanced progressive fibrovascular proliferation
- florid PDR not responding to laser photocoagulation
- neovascularisation of iris in connection with vitreous haemorrhage
- dense, non-reabsorbing premacular haemorrhage
- macular edema not responding to laser coagulation diffuse and/or cystoid without vitreomacular (VM) traction and/or with VM traction

The procedure is performed at specialised centres and vitreoretinal centres. The final decision on indication for vitrectomy is made by a vitreoretinal surgeon, especially with regard to the feasibility of improvement of the patient's visual functions. In this decision it is necessary to consider a whole range of factors, such as visual functions of the other eye; finding of hard ischemic changes on the retina of the other eye signals that we may expect a similar finding also on the eye which is to be operated on due to a turbid vitreous body, and here even despite a successfully performed operation there is often no improvement in the patient's vision. In indicated cases of PDR preoperative preparation with intraocular application of an anti-VEGF preparation is used to advantage, reducing the risk of perioperative and postoperative haemorrhage, and increasing the chance of a better postoperative result.

Further pharmacological treatment

Causal pharmacological treatment of clinically developed DR is not known. To date no drug has been confirmed to be effective in specifically acting upon the origin and progression of DR. At present the administration of substances such as vasodilators, antiaggregants, vitamins, calcium dobesilate and others, from the perspective of prevention or treatment of DR, is not justified.

Antiaggregant and anticoagulation treatment upon DR

It has been demonstrated that the administration of acetylosalicylic acid in a standard dose (75-150 mg/den) does not increase the risk of haemorrhage into the vitreous body upon DR, which is not a contraindication for the administration of acetylosalicylic acid within the framework of secondary prevention of ischemic heart disease (27). The subject of the discussion is the degree of risk of anticoagulation therapy or fibrinolytic therapy upon myocardial infarction, pulmonary embolisation and other vital indications. In these vital cases DR should not represent a contraindication for the administration of the above-stated preparations. It is obvious that in non-vital indications such as heparinisation upon haemodialysis, upon venous thromboses, we proceed very cautiously under careful control of haemocoagulation parameters, especially in the case of high risks forms of PDR. Unless this concerns a vital indication we do not apply anticoagulation therapy in the early period following fresh haemorrhage into the eye.

Early (transitory) normoglycaemic deterioration syndrome (normoglycaemic re-entry phenomenon)

This concerns a temporary deterioration of DR, which may occur after a rapid improvement of compensation for diabetes in patients suffering from type 1 and 2 diabetes, for example following the commencement of insulin therapy, the introduction of an intensified insulin regime, transition to therapy by insulin pump or transplantation of the pancreas. A rapid progression of advanced forms of diabetic retinopathy and maculopathy takes place on the fundus due to the impact of an increase in the levels of growth factors. This condition is characterised by severe hypoxia, edema and the formation of soft exudates. A risk factor is a high level of HbA1c and severity of DR. This is not a fatal complication, but the clinical course is not necessarily always benign.

Recommended procedure upon expected rapid decrease of glycaemia:

Medium advanced NPDR – ophthalmological examination every 2-3 months
Advanced NPDR and developing PDR – panretinal photocoagulation
ME – perform FAG and if applicable subsequent laser photocoagulation

If possible, attempt to compensate long-term decompensated patients more gradually (over the course of several months)! Under no circumstances should the risk of normoglycaemic re-entry phenomenon be a cause for deferring intensified therapy!

Pregnancy and childbirth

If a patient with DR decides to become pregnant, it is necessary to warn her of the risk of acceleration of the ocular finding. Examinations are necessary before conception and subsequently in each trimester. Stabilisation of DR by the available means is an essential requirement. Pregnancy is not a contraindication for laser therapy. NPDR is not a contraindication for spontaneous childbirth. PDR is not an indication for Caesarian section. However, cautious management of childbirth is recommended.

Table 2 Extraordinary appointments for examination and screening of DR

Clinical manifestations of DR	Nález na očním pozadí	Frequency of examinations
Neproliferativní DR počínající	mikroaneuryzmata mikrohemorhagie intraretinální hemorhagie	6–12 months
středně pokročilá	venózní abnormality cévní změny v oblasti makuly tvrdé exsudáty vatovité exsudáty	6–12 months
pokročilá	intraretinální mikrovaskulární abnormality (tRMA) ischemie sítnice	months
Proliferativní DR počínající	neovaskularizaci na sítnici (epiretinální)	dle oftalmologa
vysoce riziková	neovaskularizace na papile (epipapilární) trakční amoce sítnice intravitreání krvácení	
Diabetická makulopatie	makulární edém klinicky signifikantní makulární edém	dle oftalmologa

Peroral antidiabetic agents – glitazones

An adverse side effect of glitazones such as rosiglitazone and pioglitazone is retention of fluid in tissues. Exacerbations of macular edemas have been observed in approximately 5-15% of cases. After discontinuation of pharmaceutical therapy and treatment of diffuse edema with laser the condition was corrected. However, exacerbation occurred immediately following repeat application of remedies (28).

Cataract surgery

There remains a certain degree of doubt as to whether cataract surgery worsens the course of DR and ME. It has been demonstrated that poor monitoring of the blood sugar level, male sex and longer duration of the operation cause progression of retinopathy. Longer operations are linked with more pronounced postoperative inflammation, which may lead to a breach of the haemato-ocular barrier, leading to a progression of retinopathy and edema. By contrast, stabilisation of DR by laser reduces the risk of acceleration of DR (29).

7. PREVENTION, SCREENING

Prevention of the occurrence and progression of DR may be implemented upon the precondition of professional co -operation of diabetologists, internists, general practitioners and ophthalmologists. The aim of diabetological treatment in patients with DM in relation to prevention and stabilisation of DR is timely (risk of metabolic memory), long-term and satisfactory compensation of DM, control of hypertension and other risk factors. The diabetologist recommends patients with DM for an examination by an ophthalmologist at the time of determination of diagnosis of both types of DM (characteristics of DR and DMP may already be present), and further at minimum 1x per year. The ophthalmologist is then responsible for the timely identification of DR, records diabetics with DR, calls upon them to attend regular examinations and ensures specialised ophthalmological treatment.

Screening of retinopathy is performed by an ophthalmologist on children and adolescents once per year from the age of 10 years, regardless of the duration of diabetes (30). The frequency of examinations on diabetics with clinical manifestations of DR and DME is more frequent (every 3 to 6 months), primarily depending on the degree of DR and development of DME, with application of an individual approach. The clinical stage of diabetic retinopathy and the frequency of checks are summarised in table no. 2.

Change of classification of DM, also commencement of insulin therapy, intensified regime, treatment by insulin pump, commencement of dialysis, pregnancy all require extraordinary examination of the ocular fundus. In these cases it is necessary to contact a diabetologist together with an ophthalmologist. Other extraordinary appointments necessary in the case of advanced forms of DR should be clearly indicated by an ophthalmologist.

Examination and screening methods

Examination of the ocular fundus of a diabetic patient should be unconditionally performed in broad artificial mydriasis. Screening examination by ophthalmoscope is reserved only for bedridden patients. The optimal method of examination can be considered to b only biomicroscopic examination on a slit lamp. A whole range of noncontact aspherical and contact lenses with high resolution capability can be used for this purpose. At present all hospitals and also some private ocular outpatient clinics are equipped with digital cameras for photographing the ocular fundus. It has been demonstrated that red-free photography in a 50o angle demonstrates almost 98% sensitivity as against colour digital photography in two fields and at an angle enlargement of 50o. A question remains concerning the suitability of use of "non-mydriatic cameras" in the screening of DR. Their use without artificial mydriasis cannot be considered to be correct, since due to the narrow and reacting pupil the quality of the images is not sufficient.

8. ASSESSMENT PERSPECTIVES IN OCULAR COMPLICATIONS OF DR

Advanced stages of DR which significantly reduce visual acuity or limit the scope of the visual field are indications for acknowledging partial or full invalidity with reference to specific circumstances in individual patients according to the relevant decrees.

Practical blindness in both eyes is visual acuity of 1/60 with best possible correction or 1/50 to light sense or limitation of visual field up to 5 degrees around central fixation, even if central sharpness is not affected. Complete blindness in both eyes is loss of sight covering states from absolute loss of light sense to preservation of light sense with faulty light projection.

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