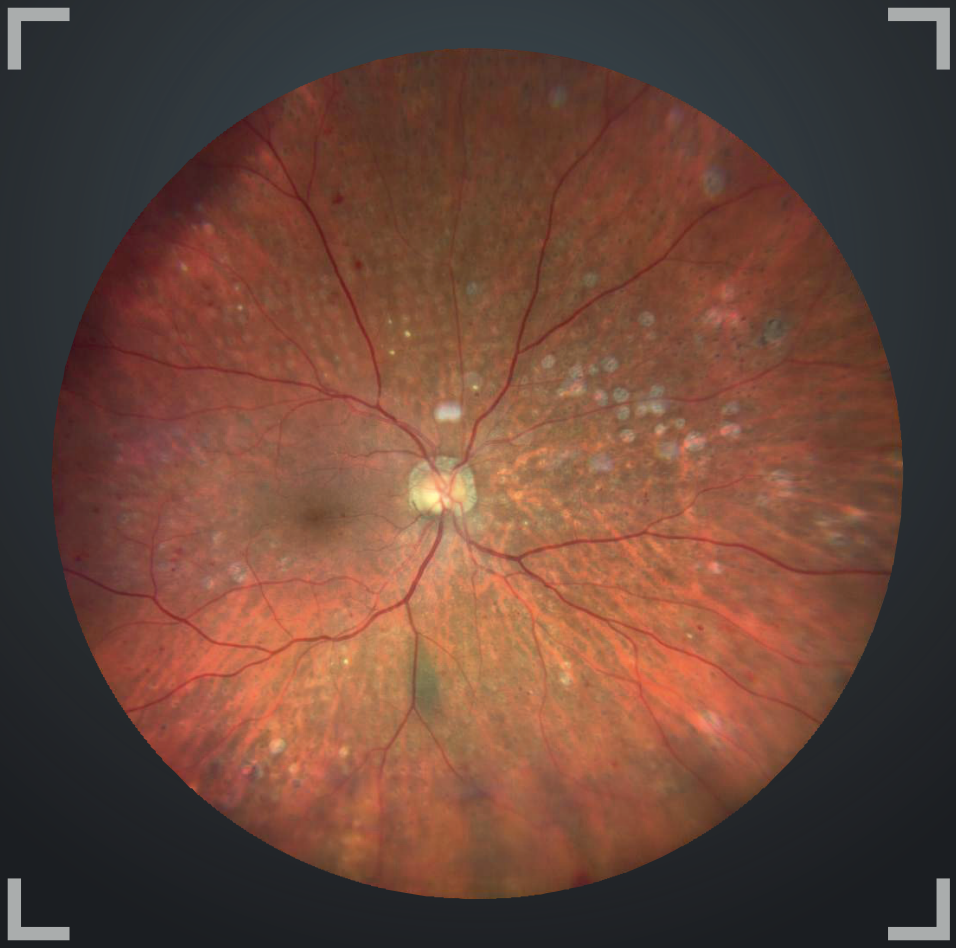
Diabetic Retinopathy

Maciej Gawęcki



Théa
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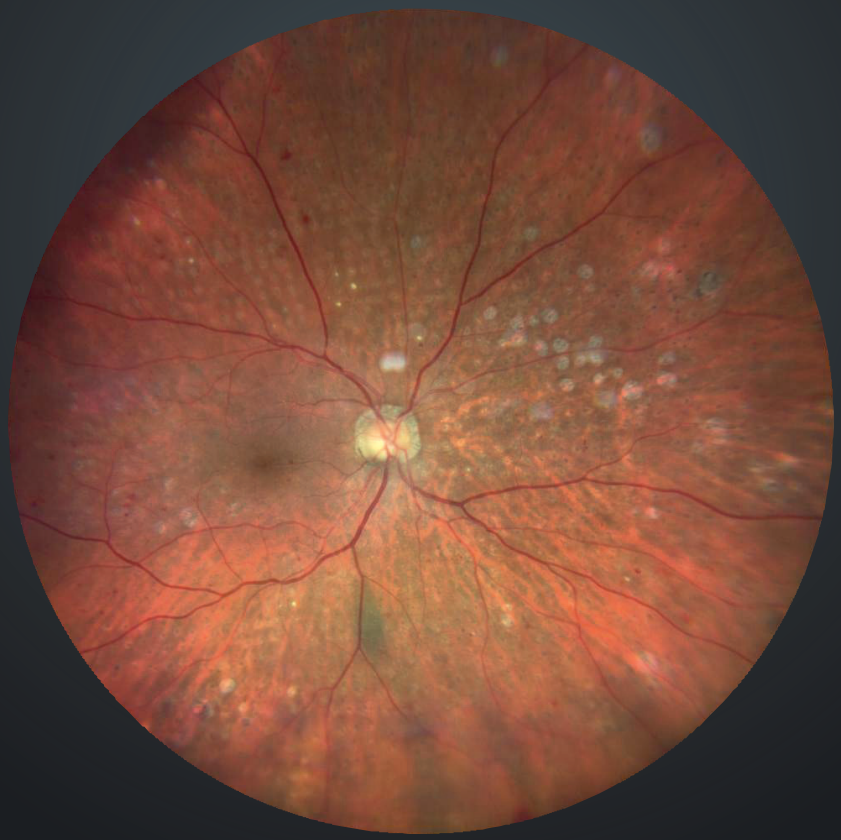

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Maciej Gawęcki

Diabetic Retinopathy

A Practical Manual for Ophthalmologists, Diabetologists and Internists

translated by Stephen Dersley

To my students and colleagues

Preface

Dear Readers

This book is intended as a compendium of knowledge on the pathomechanism, diagnostics and treatment of diabetic retinopathy. I focus on current imaging methods and contemporary treatment methods of that disorder. In addition, I indicate the likely directions that the diagnosis and treatment of diabetic retinopathy may take in the near future. The publication contains numerous illustrations and images, most of which derive from my own practice, but some were also kindly made available to me by colleagues and medical companies. Some of the photographs were taken especially for this book by Anna Rezulak.

The manual is intended for ophthalmologists, diabetologists and general practitioners interested in diabetic retinopathy, as well as medical students. Considering this wide audience, I tried to present some issues in a very simple way, so that the text will be comprehensible for representatives of many specialties. Some passages may seem too rudimentary for specialists in particular fields. However, I am of the view that using simple language is always better than artificially complicating the topics under discussion. The chapter on the influence of systemic treatment on the development of diabetic retinopathy was written by Monika Łukaszewicz, MD, a specialist in diabetology. It is always a good idea to use the help of experts in a given field.

Since every textbook should be convenient, I have compiled a compendium of practical knowledge and algorithms of management at the end of the book, which should be helpful in day-to-day medical practice.

At the same time I would like to thank all my co-workers at Dobry Wzrok Clinic, the Specialist Hospital in Chojnice, as well as my family and friends, especially Katarzyna, my wife and best friend. Without your work, support and inspiration this book would not have been written.

Maciej Gawęcki

Foreword

This excellent book accurately prepared by Dr. Maciej Gawęcki addresses diabetic retinopathy, which is one of the most important causes of vision loss.

The text is organized to thoroughly cover all the aspects of the disease by describing classification, epidemiology, pathophysiology, clinical findings, and therapeutic management. *Diabetic Retinopathy* offers a complete and updated overview of the disease to address both the current clinical practice and the future research purposes regarding diabetic retinopathy. In addition to a clearly-written text, many illustrations complete the book to make the understanding of each topic easier.

Diabetic Retinopathy will be especially useful for students, ophthalmolgists, diabetologists, and researchers.

I wish the author the best personal success.

Maurizio Battaglia Parodi, MD
Associate Professor
Department of Ophthalmology
Vita-Salute San Raffaele University
Milano, Italy

Foreword

Doctor Gawęcki is to be congratulated for this excellent concise but comprehensive primer on diabetic retinopathy for healthcare providers. In it are outlined and described the current understanding of the pathogenesis, key clinical manifestations and disease management of diabetic retinopathy. Throughout the text Dr. Gawęcki displays the most important attribute of a true scientist: curiosity. Why is this important?

Skepticism has become the pervading attitude of modern science. While is usually dressed in the fine robes of priestly intellectual purity, the skeptic risks nothing, discovers nothing, creates nothing, and can learn nothing new. Anyone, high or low, can play the skeptic. For how many years did Gullstrand deny Einstein the Nobel Prize? The crime is not that he did; it is that he could. Skepticism in full-flower.

Despite the excellence of Dr. Gawęcki's book, it is important to understand that everything in it will, in 10, 20, or 50 years-time, be considered either obsolete or simply in error. This is the price of progress. It is the reason we should never defend too strongly the status quo and the "current consensus": it is wrong. We just don't know it yet. If you don't believe me, take a moment to reflect on the past. Despite our earnest efforts to be as correct as possible in our moment in time, the future will likely view us with either horror, or amusement – and most likely both. If we're lucky, compassion as well.

Dr. Gawęcki's curiosity, evident throughout his current book, is an antidote to our culture of skeptical arrogance, and an invitation to progress; to new and better information, and new and better practices. Another step in the endless journey. Such a book has an important place in our library. I am sure you will enjoy reading it and find it useful, as I have.

Jeffrey K. Luttrull, MD
Ventura County Retina Specialists
Ventura, California

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List of abbreviations

AAO – American Academy of Ophthalmology
AAP – American Academy of Pediatrics
FDA – Federal Diabetic Association
ISPAD – International Society for Pediatric and Adolescent Diabetes
NICE – National Institute for Health and Care Excellence
RCO – Royal College of Ophthalmologists
PTD – Polskie Towarzystwo Diabetologiczne (Polish Diabetes Society)
PTO – Polskie Towarzystwo Okulistyczne (Polish Ophthalmological Society)

*

ACE – angiotensin-converting enzyme
AGE – advanced glycation end products
AI – artificial intelligence
AMD – age-related macular degeneration
angio-OCT – see OCTA
AR – aldose reductase
ATP – adenosine triphosphate
BCVA – best corrected visual acuity
bFGF – basic fibroblast growth factor
BMI – body mass index
CI DME – center-involved DME (Br. Eng. CI-DMO)
CME – cystoid macular edema (Br. Eng. CMO – cystoid macular oedema)
CNV – choroidal neovascularization
COAG – chronic open angle glaucoma
COST – cone outer segment tips
CRT – central retinal thickness
CRTA – central retinal thickness average
CS – contrast sensitivity
CSCR – central serous chorioretinopathy
CSME – clinically significant macular edema (Br. Eng. CSMO – clinically significant macular oedema)
CV – cube volume
DAG – diacylglycerol
DCP – deep capillary plexus
DD – disc diameter
DM – diabetes (Lat. *diabetes mellitus*)
DM1 – type 1 diabetes
DM2 – type 2 diabetes
DME – diabetic macular edema (Br. Eng. DMO – diabetic macular oedema)
DMI – diabetic macular ischemia
DR – diabetic retinopathy

DRIL – disorganization of inner retinal layers
DRSS – diabetic retinopathy severity scale
DVC – deep vascular complex
EBM – evidence-based medicine
EGF – epidermal growth factor
ELM – external limiting membrane
EpM – endpoint management
ERG – electroretinography
ERM – epiretinal membrane
EZ – ellipsoid zone[1] (cf. abbreviations **IS** and **OS**)
FA – fluorescein angiography
FAF – fundus autofluorescence
FAZ – foveal avascular zone
GCL – ganglion cell layer
GHIH – somatostatin
GLP-1 – glucagon-like peptide
HbA1 – glycosylated (glycated) hemoglobin
HIF – hypoxia inducible factor
HR PDR – high risk proliferative diabetic retinopathy
HRF – hyperreflective foci
HSP – heat shock proteins
ICAM – intercellular adhesion molecule
ICP – intermediate capillary plexus
IGF – insulin-like growth factor
ILM – inner limiting membrane
INL – inner nuclear layer
IOP – intraocular pressure
IPL – inner plexiform layer
IRC – intraretinal cysts
IRMA – intraretinal microvascular abnormalities
IS – internal segments (cf. abbreviation **EZ**)
IVA – intravitreal aflibercept
IVB – intravitreal bevacizumab
IVR – intravitreal ranibizumab
IVTA – intravitreal triamcinolone
IZ – interdigitation zone

1. Formerly defined as the junction between inner and outer segments of photoreceptors (IS and OS). Despite the change in nomenclature, both the newer term “ellipsoid zone” and the term from the older literature on the subject are used in practice: “junction between inner photoreceptor segments and outer photoreceptor segments”, and consequently the corresponding abbreviations: EZ, IS/OS. The same term variation occurs in this book.

LPC – laser photocoagulation
LTFU – lost to follow up
ME – macular edema (Br. Eng. MO – macular oedema)
mfERG – multifocal electroretinography/multifocal electroretinogram
MV – macular volume
MVL – moderate visual loss
MZ – myoid zone
NADPH – nicotinamide adenine dinucleotide phosphate (reduced form)
NAD – nicotinamide adenine dinucleotide
NADH – reduced form of NAD
NADP – nicotinamide adenine dinucleotide phosphate
NADPH – reduced form of NADP
nAMD – neovascular AMD
NCI DME – non-center-involved DME (Br. Eng. NCI DMO)
NFL – nerve fiber layer
NFLVP – nerve fiber layer vascular plexus
NPDR – non-proliferative diabetic retinopathy
NRT – non damaging retinal therapy
NSAID – non-steroidal anti-inflammatory drugs
NV – neovascularization
NVA – neovascularization of the angle
NVD – neovascularization/new vessels at the disc
NVE – neovascularization/new vessels elsewhere
NVG – neovascular glaucoma
NVI – neovascularization of the iris
OCT – optical coherence tomography
OCT EDI – optical coherence tomography enhanced depth imaging
OCTA – OCT angiography
OLM – outer limiting membrane
ONL – outer nuclear layer
OPL – outer plexiform layer
OS – outer segments (cf. abbreviation EZ)
PCO – posterior capsule opacification
PDGF – platelet-derived growth factor
PDR – proliferative diabetic retinopathy
PEDF – pigment epithelium-derived factor
PIGF – placental growth factor
PKC – protein kinase C
POAG – primary open angle glaucoma
PPV – pars plana vitrectomy
PR – photoreceptor
PRN – as required (Lat. *pro re nata*)
PRP – panretinal photocoagulation

PVD – posterior vitreous detachment)
RAAS – renin-angiotensin-aldosterone system
RAGE – receptors for AGEs
RAS – renin-angiotensin system
RNFL – retinal nerve fiber layer
ROS – reactive oxygen species
RPE – retinal pigment epithelium
RVO – retinal vein occlusion
SCDME – subclinical diabetic macular edema (Br. Eng. SCDMO – subclinical diabetic macular oedema)
SCP – superficial capillary plexus
SH – subhyaloid hemorrhage
SMPLT – subthreshold micropulse laser treatment
SD-OCT – spectral domain optical coherence tomography
SRF – subretinal fluid
SS OCT – swept source OCT
SSADA – split spectrum amplitude decorrelation angiography
SVC – superficial vascular complex
SVL – severe visual loss
SVP – superficial vascular plexus
TGF – transforming growth factor
TSCPC – transscleral cyclophotocoagulation
UWF – ultra wide field (in relation to angiography)
VA – visual acuity
VCAM – vascular cell adhesion molecule
VEGF – vascular endothelial growth factor
VH – vitreous hemorrhage
VL – visual loss
VMA – vitreomacular adhesion
VMT – vitreomacular traction
VTDR – vision threatening diabetic retinopathy

List of studies and research groups cited

ACCORD – Action to Control Cardiovascular Risk in Diabetes
APOLLON – Routine Clinical Practice for Use of Intravitreal Aflibercept Treatment in Patients with Diabetic Macular Edema
AQUA – Investigation of the Change of Vision-related Quality of Life in Subjects Treated with Aflibercept According to EU Label for DME
BOLT – Bevacizumab or Laser Treatment in the Management of Diabetic Macular Edema
BOULEVARD – Simultaneous Inhibition of Angiopoietin-2 and Vascular Endothelial Growth Factor-A with Faricimab in Diabetic Macular Edema

CATT – Comparison of Age-related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial
CHROME – A Retrospective Chart Review of OZURDEX® in Patients with Macular Edema
CLARITY – Intravitreal aflibercept Compared with Panretinal Photocoagulation for Proliferative Diabetic Retinopathy)
CURES – Chennai Urban Rural Epidemiology Study
DCCT – Diabetes Control and Complications Trial
DIEP – Diabetes in Early Pregnancy Study
DiRECT – Diabetes Remission Clinical Trial
DiVFuSS – Diabetes Visual Function Supplement Study
DRCR.net – Diabetic Retinopathy Clinical Research network
DRS – Diabetic Retinopathy Study
DRVS – Diabetic Retinopathy Vitrectomy Research Study
ETDRS – Early Treatment Diabetic Retinopathy Study
EUROCONDOR – European Consortium for the Early Treatment of Diabetic Retinopathy
FAME – Fluocinolone Acetonide in Diabetic Macular Edema Extension Study
FIELD – Fenofibrate Intervention and Event Lowering in Diabetes
LEADER – Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation
MAPASS – Manchester Pascal Study
MEAD – A Study of the Safety and Efficacy of a New Treatment for Diabetic Macular Edema
MESA – Multi-Ethnic Study of Atherosclerosis
OZLASE – A Prospective Randomised Controlled Trial of Intravitreal Ozurdex and Macular Laser Therapy versus Macular Laser Therapy only in Diabetic Macular Oedema
PANORAMA – Study of the Efficacy and Safety of Intravitreal (IVT) Aflibercept for the Improvement of Moderately Severe to Severe Non-proliferative Diabetic Retinopathy (NPDR)
PRIDE – Multicenter 12 Months Clinical Study to Evaluate Efficacy and Safety of Ranibizumab Alone or in Combination with Laser Photocoagulation vs. Laser Photocoagulation Alone in Proliferative Diabetic Retinopathy
PROTEUS – Prospective, Randomized, Multicentre, Open-label, Phase II/III Study to Assess Efficacy and Safety of Ranibizumab 0.5 mg Intravitreal Injections Plus Panretinal Photocoagulation (PRP) Versus PRP in Monotherapy in the Treatment of Subjects with High Risk Proliferative Diabetic Retinopathy
RASS – Renin Angiotensin System Study
READ-2 – The Ranibizumab for Edema of the mAcula in Diabetes: a Phase 2 Study
RELDEX – Real-Life Study in Diabetic Macular Edema Treated with Dexamethasone Implant
RESOLVE – Safety and Efficacy of Ranibizumab in Diabetic Macular Edema with Center Involvement
RESTORE – A 12 Month Core Study to Assess the Efficacy and Safety of Ranibizumab

(Intravitreal Injections) in Patients with Visual Impairment Due to Diabetic Macular Edema and a 24 Month Open-label Extension Study

RETAIN – Ranibizumab 0.5 mg treat-and-extend regimen for diabetic macular oedema

REWIND – Researching Cardiovascular Events with a Weekly Incretin in Diabetes

RIDE/RISE – A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema (ME) with Center Involvement Secondary to Diabetes Mellitus

SUSTAIN-6 – Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes

TREX-DME – A Safety and Efficacy Trial of a Treat and Extend Protocol Using Ranibizumab with and Without Laser Photocoagulation for Diabetic Macular Edema

UKPDS – United Kingdom Prospective Diabetes Study

UKPMESG – United Kingdom Pseudophakic Macular Edema Study Group

VIVID/VISTA – A Randomized, Double Masked, Active Controlled, Phase III Study of the Efficacy and Safety of Repeated Doses of Intravitreal VEGF Trap-Eye in Subjects with Diabetic Macular Edema

WESDR – Wisconsin Epidemiological Study of Diabetic Retinopathy

YOSEMITE – A Study to Evaluate the Efficacy and Safety of Faricimab (RO6867461) in Participants with Diabetic Macular Edema

Chapter 1: Epidemiology of diabetes, diabetic retinopathy and diabetic macular edema

Introduction

The readers of textbooks and studies tend to skip over the sections containing the epidemiological data associated with various diseases. However, let me encourage my readers to get to grips with the contents of this chapter. We can draw many practical conclusions from epidemiological data, which can help us in the day-to-day treatment of our patients. Patients with diabetic retinopathy (DR) are no exception: the analysis of epidemiological data allows us to estimate the following factors and events:

1. the risk of DR incidence,
2. the risk of DR progression,
3. the risk of transformation of non-proliferative diabetic retinopathy (NPDR) to proliferative (PDR),
4. the risk of severe vision loss.

This, in turn, allows us to plan the treatment and monitoring of a given patient, depending on the baseline condition, both local and general.

The epidemiology of diabetes

According to the International Diabetes Federation, there are currently over 425 million people with diabetes mellitus (DM), which amounts to approximately 8% of the adult population. This means that one in eleven people has diabetes. Moreover, 90% of all patients with diabetes are patients with type 2 diabetes (DM2)[1]. Somewhat surprisingly, every second person with diabetes is not aware that they have developed this condition.

In Poland, the number of people with diabetes is estimated at 2, 235,000[2]. In the years 2010–2014, the percentage of people diagnosed with diabetes ranged from 3.5% to 5.5% (depending on the province), i.e., 4.47% on average. In turn, between 2010 and 2014, the percentage of people who collected prescriptions for diabetic medications or glucometer strips was 5.88%. Diabetes morbidity has been steadily increasing in Poland year after year[3].

The prevalence of diabetic retinopathy

A great deal of research has been conducted on the prevalence of retinopathy in diabetic patients (the number of DR patients relative to the population of diabetics, expressed as a percentage). The data are not always consistent, however, because the results depend on the population studied (ethnicity, age, the type and duration of diabetes). A large meta-analysis of 35 studies on DR from the 1980s to 2008 estimated the prevalence of any retinopathy (NPDR or PDR) in patients with diabetes to be at the level of 35.4%, and the prevalence of PDR at 7.5%[4]. The frequency of the occurrence of any retinopathy was higher in patients with type 1 diabetes (DM1) than in patients with DM2 (77.3% for DM1, 25.2% for DM2). For PDR, these proportions were respectively 32.4% and 3%. It is necessary to emphasize that the above data are averaged and therefore must be treated with due caution.

In the analysed studies, there was a significant spread in the frequency of DR occurrence in different populations. For example, in European and US populations, the prevalence of any retinopathy in DM1 patients has been reported to range from 36.5% to 93.6%, and with vision-threatening diabetic retinopathy (VTDR) from 6.7% to 34.9%[5, 6, 7, 8, 9, 10, 11] – hence the term VTDR usually refers to PDR and diabetic macular edema (DME). Data discrepancies may be due to differences between the

studied populations and dissimilarities between healthcare systems in individual countries. Additionally, they can also be attributed to methodological differences in the way that epidemiological studies are conducted[12].

Risk factors for retinopathy in patients with diabetes

Factors affecting DR prevalence

- ethnicity,
- the socioeconomic level of the country and the healthcare system,
- lifestyle and education,
- gender,
- type of diabetes (DM1 or DM2),
- insulin dependence,
- the duration of diabetes,
- the patient's age,
- the age when diabetes is diagnosed.

Ethnicity, socioeconomic level, lifestyle and the prevalence of DR

The prevalence of DM1 in Asian countries is low, therefore population studies in this region focus on the patients with DM2. This means that epidemiological comparisons between Europe, the USA, and Asian countries are only valid for the group of DM2 patients. In this respect, there is a higher DR prevalence DR among patients from Europe and the USA have as compared to patients from Asian countries (28.5–40.3% versus 12.1–23%). A similar relationship is evident for VTDR (4.4–8.2% versus 4.3–4.6%)[13, 14, 15, 16]. An exception in this regard is Singapore, where the prevalence of DR is much higher (33.9%) than, for example, in the Chinese population (25.4%)[17]. This is most likely due to the ethnic structure of the society, since in Singapore there is a significant proportion of Malays and Indians, in whom DR occurs more frequently.

In the countries of the Middle East, the prevalence of DR is comparable to that of Western European Countries and fluctuates at around 30% (36.8% in Saudi Arabia, 29.6% in Iran)[18, 19]. However, attention is drawn to the higher percentage of VTDR in these countries (10.6–17.5%). This is most likely due to the fact that in this region DR is only diagnosed at a very advanced stage. This situation can perhaps be attributed to the quality of the healthcare system and the education of the general public. For the sake of comparison: in highly developed Asian countries (Hong Kong, South Korea) the prevalence of DR in diabetic patients is very low (12.1% and 15.8%, respectively).

A country's economic level and the general level of education in the society are also likely to influence the results of epidemiological studies. A case in point is the difference in DR prevalence between rural and urban communities in China[13]. In urban communities, where healthcare and education are at a higher level, the prevalence of DR in diabetic patients is 18.1%, compared to 29.1–43.1% in rural areas. On the other hand, the effect of migration to the city may have the opposite effect. In India, DR is clearly more prevalent in the inhabitants of cities than villages[15]. Researchers attribute this fact to changes in lifestyle and diet after moving to the city (a sedentary lifestyle, fast food). This has also been put forward as an explanation for the high prevalence of DR in Indians living in Singapore[17].

Data on Hispanic populations seem to be discrepant. For example, Esteves et al. showed the frequency of DR in patients with DM1 in Brazil to be at 44.4%, which is a high value compared to other populations[20]. However, in the San Louis Valley Diabetes Study, Varma et al. reported a lower prevalence of DR in the Hispanic population compared to the white population[21].

The conclusion to be drawn here is that there are no clear trends in the relationship between ethnicity and the occurrence of DR. High prevalence of DR in a particular ethnic group may be due to many factors, such as the organization and provision of healthcare and the socioeconomic level.

Gender and the risk of developing DR

Data on the effect of gender on the prevalence of DR are inconclusive. Many studies do not find any such relationship, while others show a strong relationship between the lifestyle of a given gender in a specific country and the occurrence of DR[22].

One recent major study conducted among the Chinese population showed a higher prevalence of DR in men with DM2[23, 24]. Similar data were found for the diabetic population over the age of 40 in the USA[25]. In turn, the data relating to the Japanese population show a higher prevalence of PDR in women with DM2[26]. The study in question identifies the female gender as a risk factor for the development of DR. However, many other epidemiological studies have failed to establish a relationship between gender and the prevalence and/or incidence of DR (i.e., the number of new DR cases within a specified period of time)[15, 21, 27, 28].

Type of diabetes and the prevalence of DR

At the time of diabetes diagnosis, retinopathy is significantly more common in DM2 than in DM1 (6.7–38% and 0–3%, respectively)[9]. In contrast, the statistic data on the frequency of DR without reference to the duration of diabetes indicate that DR is more common in DM1 patients[8, 29]. If the duration of diabetes is included in the statistical analysis, the differences between the prevalence of DR in DM1 and DM2 are not statistically significant[30].

Insulin dependence and the prevalence of DR

There is a clear relationship between the prevalence of DR and insulin dependence. Among patients with diabetes which began to develop in advanced years, the occurrence of DR is significantly more common in people taking insulin (70% versus 39%)[31]. When analysed for the entire group of patients with diabetes, the risk of DR is 5.79 times higher in those taking insulin[15]. It is worth emphasizing that insulin dependence is almost always present in the late phase of DM2. Starting insulin treatment early may delay the development of complications[32].

Diabetes duration and the prevalence of DR

The duration of diabetes mellitus is one of main factors influencing the prevalence of DR. Longer duration of diabetes is associated with increased DR incidence and prevalence[15, 23, 29, 30, 31]. This also applies to advanced forms of retinopathy[27, 29].

Age and the prevalence of DR

Overall, the prevalence of DR grows with age – this has been confirmed in many studies[12, 21, 33]. (Interestingly, however, this pattern does not apply to the population in Barbados[34]). In the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) conducted in the USA, in non-insulin-using diabetic patients with onset at older ages, the prevalence of DR was 30.5% for the 40–49 age group, and 36.5% for the 60–69 age group. In the case of insulin-dependent diabetes mellitus with onset in older age, it was 64.6% and 67.4%, respectively[31].

The age of the patient at the time of diabetes diagnosis

The occurrence of DR depends on the age at which the patient develops diabetes. This fact is confirmed by the results of the WESDR[31, 35]. Thus, DR, PDR and DME were more frequent in patients who were diagnosed with diabetes before the age of 30. DR was least frequent in patients who were diagnosed with diabetes at an older age and who did not take insulin. It is interesting that the early onset of DM2 represents a strong risk factor for the development of DR, which is independent of other factors[36].

Risk factors for DME

The prevalence of DME in the population of diabetics is estimated at 4.2–7.9% for DM1 and 1.4–12.8% for DM2[6, 8, 14, 18, 25, 37, 38]. WESDR states that DME most frequently affects older onset patients with insulin-dependent diabetes – 12% (with the frequency of 6% in patients with younger onset diabetes and 4% in older onset non-insulin-using diabetic patients)[31, 35].

The incidence of DME is closely related to the duration of the diabetes, which is confirmed by the majority of epidemiological studies[19, 33, 39, 40]. In both younger onset diabetes and older onset diabetes, the prevalence of DME after 20 years of diabetes is about 30%[41]. Also, the prevalence of DME depends on the duration of the underlying disease. For both younger onset diabetes and older onset diabetes, the graph of the ten-year incidence of DME has a parabola shape: the incidence increases with the duration of the disease, culminating in the range of 10–12 years, and then decreases[42].

Risk factors for PDR

WESDR provides data on the prevalence of PDR in various types of diabetes: 23% for younger onset diabetes, 14% for older onset insulin-dependent diabetes, and 3% for non-insulin dependent older onset diabetes[31, 35]. In turn, the ten-year incidence of PDR (progression to PDR) was 30% for younger onset diabetes, 24% for insulin-dependent older onset diabetes, and 10% for non-insulin-dependent older onset diabetes[43]. The incidence of PDR increases with the duration of the diabetes[15, 21, 31, 35]. It should be emphasized that the risk of progression to PDR also depends on the duration of the diabetes. For example, in DM1, the risk of progression to PDR is close to zero for the first years of the disease, then increases over several years, reaching a stable level[37, 44]. Interestingly, PDR is more common in men with younger onset diabetes than in women with younger onset diabetes[31].

Major systemic risk factors for the development of diabetic retinopathy

Systemic risk factors for the development of DR[45]

Modifiable factors:

- high levels of glycosylated hemoglobin (HbA1c),
- high systolic blood pressure,
- hyperlipidemia,
- high body mass index (BMI).

Non-modifiable factors:

- puberty,
- pregnancy.

Hyperglycemia

Hyperglycemia increases the risk of the onset and progression of DR. This fact was confirmed by high-quality studies conducted by the two largest research groups: the United Kingdom Prospective Diabetes Study (UKPDS) and Diabetes Control and Complications Trial (DCCT)[46, 47]. Intensive glycemic control in patients with DM1 (median value HbA1c = 7.2%) in DCCT studies allowed the prevalence of DR to be reduced by 76% and for the progression of DR to be reduced by 54% when compared to conventional glycemic control[48]. Lowering the HbA1c value by 1% resulted in a reduction of DR development by 40%, a reduction in the progression to VTDR by 25%, and a 25% reduction of the need for retina laser therapy[49]. Additionally, the four-year prevalence of DR was reduced by 58% when intensive glycemic control was applied[38].

Studies show that the use of intensive glycemic control has a long-lasting effect, even despite later fluctuations in blood sugar levels[50]. It is believed that early normalization of glycemic levels prevents the long-term effects of oxidative stress and excessive glycation at the cellular level[51]. The main danger of such therapy is that there is a possibility of a temporary exacerbation of retinopathy and hypoglycemic episodes at the beginning the treatment process[40].

Hypertension

The relationship between DR progression and hypertension is not straightforward. There are studies that show no exacerbation of DR with uncontrolled hypertension[52, 53]. However, the UKPDS study has shown the benefit of blood pressure control for reducing the severity of DR[18]. Patients with well-controlled blood pressure (less than 150/85 mmHg) showed lower progression of DR (a 34% reduction in the risk of progression) compared to patients with blood pressure maintained below the value of 180/105 mmHG. In contrast, the WESDR study showed that the risk of DR progression is associated with elevated diastolic pressure, and the presence of hypertension clearly increases the risk of PDR[54].

Hyperlipidemia

The results of research into the relationship between plasma lipid levels and DR progression are contradictory. Some studies do not confirm a positive relationship[55, 56], but the DCCT indicates that the prevalence of retinopathy is proportional to the level of plasma triglycerides and inversely proportional to the levels of HDL[57]. Furthermore, taking fenofibrate, which reduces plasma lipid concentration, decreases the need for DR patients with DM2 to have laser therapy, although the mechanism of this effect it is not fully understood and does not ultimately depend on plasma lipid concentrations[58].

Nevertheless, the large Multi-Ethnic Study of Atherosclerosis (MESA) and the Chennai Urban Rural Epidemiology Study (CURES) did not report a correlation between total cholesterol levels and the promotion of DR[59, 60].

BMI

Most studies show a relationship between high BMI and an increased risk of the development and progression of DR[61, 62, 63, 64]. However, there are also large studies that do not confirm such a relationship[65]. Despite the many controversies over the impact of being overweight on the development of DR, proper weight control is recommended by the majority of the authors who have published on this subject.

Puberty and pregnancy

The details of DR development during the puberty and pregnancy are provided in Chapter 11: *Ophthalmic care for special diabetic patients: children, adolescents and pregnant women* (pp. 209–216). At this point, it is necessary to emphasize, however, that during both pregnancy and adolescence DR can undergo rapid progression[66, 67, 68]. For this reason, in the case of diabetes, both of these groups of patients should be closely supervised by an ophthalmologist. Individuals diagnosed with diabetes during adolescence are at a higher risk of developing DR compared to people who were diagnosed earlier[69]. Patients with diabetes and retinopathy should plan their pregnancy in such a way that at the time of conception DR is stable.

Practical considerations

- DR occurs in about ⅓ of all diabetic patients.
- DR is more common in patients with DM1 than with DM2.
- PDR is the most common in DM1 and the least frequent in non-insulin-dependent DM2.
- The longer duration of diabetes increases the risk of developing DR, including its advanced forms such as PDR.
- A younger age of diabetes diagnosis is a risk factor for DR development.
- DME most often affects DM2 patients who are taking insulin.
- The prevalence of DME increases with the duration of diabetes.
- The most important modifiable risk factors for the development of DR are hyperglycemia and hypertension.
- The most important non-modifiable risk factors for DR progression are pregnancy and puberty.

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Chapter 2: The pathomechanism of diabetic retinopathy

Introduction

Current knowledge unequivocally links the development of diabetic retinopathy (DR) with elevated blood glucose concentrations, however, the exact pathomechanism of these changes is still debated. For many years, the pathomechanism responsible for the development of retinopathy were predominantly explained through the vascular theory, according to which microangiopathy is the main cause of DR. Nowadays, the discussion is increasingly focused on the neurodegenerative basis of ophthalmic changes in diabetes mellitus (DM), which may theoretically precede the onset of vascular changes. These two main pathogenetic theories of DR will be presented below.

Vascular theory – microangiopathy in diabetic retinopathy

The large, randomized studies conducted by the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) have shown a clear association between blood glucose concentration and the development of retinal microangiopathies[1, 2]. The dependence between the occurrence of changes in microvessels and high plasma glucose is also confirmed by studies on animals[3].

The pathogenesis of angiopathy in DR has its origins in the two major disorders that accompany diabetes. These include:

1. changes in the structure of vessel walls,
2. changes in blood flow and the quality of morphotic elements in the blood (erythrocytes, leukocytes, platelets).

Under normal conditions, the capillary wall is composed of mesenchymal cells – pericytes, which form the outer structure of the vessel (the tunica adventitia), and endothelial cells, which form the inner wall of the capillary. Approximately one endothelial cell corresponds to each cell of the tunica adventitia. Between these two layers of cells is located the basement membrane. The main early disorder that occurs in DR is the loss of pericytes. In laboratory studies, rats have shown such changes in the capillaries just weeks after the induction of hyperglycemia. The loss of adventitia cells was accompanied by the emergence of microaneurysms.

The laboratory model was confirmed in the histopathological examination of human tissue. Loss of pericytes results in a disturbance of the capillary structure. The outer scaffolding disappears, which leads to the formation of bulges – microaneurysms, which become a source of fluid exudation swelling and hemorrhage.

Endothelial cells are also affected by the changes. Pericyte atrophy leads to endothelial cell apoptosis. Moreover, as a result of a number of biochemical processes, the cells junctions in this layer open and vascular permeability increases as a consequence.

In addition, the basement membrane of the cells that make up the vessel wall stiffens and thickens. This means that the vessel becomes less flexible and more prone to thrombotic lesions in certain sections. This is especially significant in the context of changes in blood composition and quality. In a rigid and inflexible vessel, platelet aggregation is more frequent, especially with increased blood viscosity. Changes in the shape of blood morphotic elements are also important: erythrocytes lose flexibility and the ability to bend, which leads to the closure of small vessels (micro-clots).

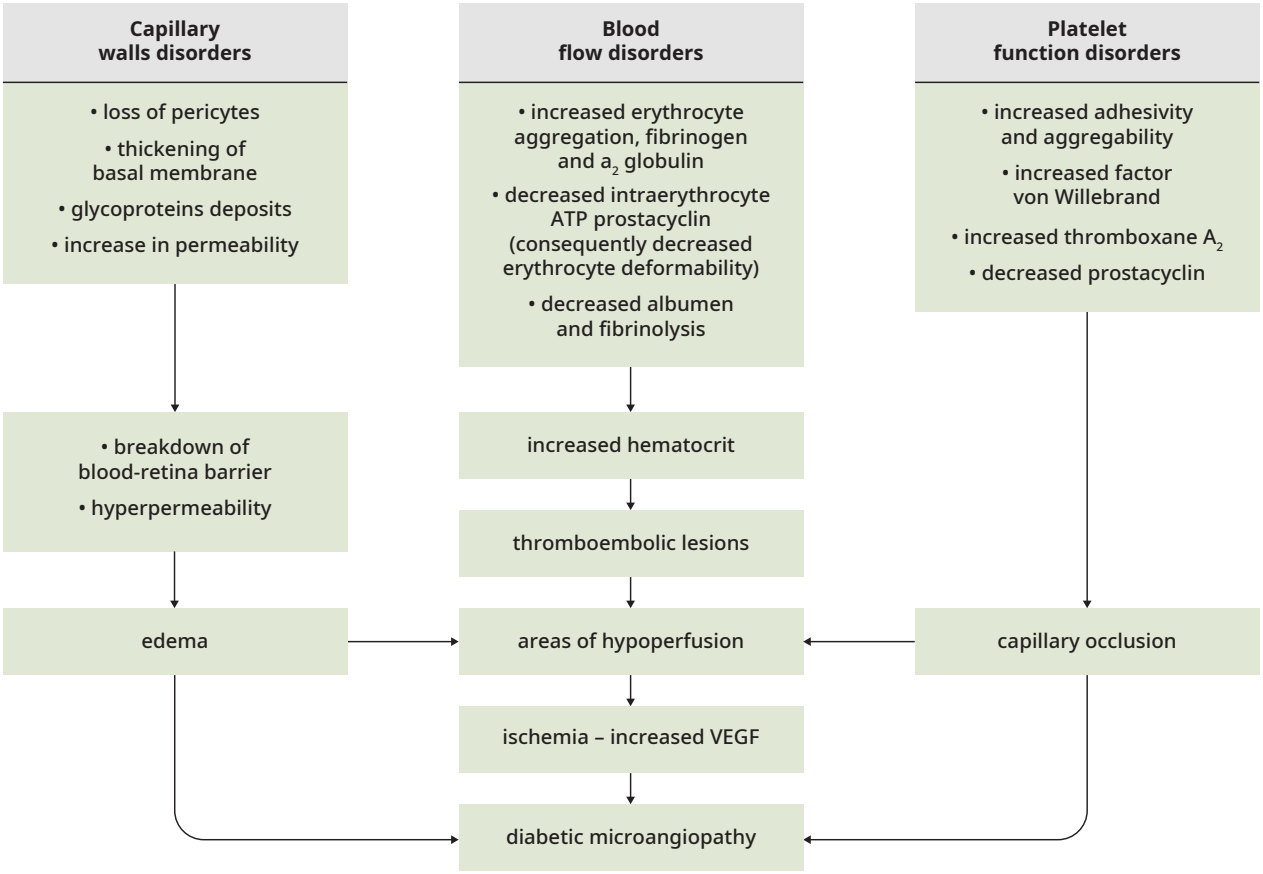

Figure 1. Diagram of the pathogenesis of diabetic retinopathy according to the vascular-hemorheological theory. | ATP – adenosine triphosphate, VEGF – vascular endothelial growth factor

Due to the local inflammatory process, the number of leukocytes increases, leading to leukostasis, i.e. the blockage of small blood vessels by white blood cells[4]. Consequently, tissue hypoxia occurs, which results in the production of vasoproliferative factors. Vascular permeability increases, edema intensifies, and neovascularization develops. The pathomechanism of vascular DR is presented in Figure 1.

It is necessary to stress that vascular changes in DR do not have a purely mechanical basis. Abnormal capillary structure and function result from numerous biochemical processes, such as effect of reactive oxygen species (ROS) and vascular endothelial growth factor (VEGF), the accumulation of advanced glycation end products (AGEs), and subclinical inflammatory processes, all of which mutually escalate. The basic biochemical processes relevant to the pathogenesis of DR will be discussed later in this chapter.

Diabetic retinopathy is progressive, especially with poor glycemic control. The pattern of lesion development in DR is shown in Figure 2. Significant tissue ischemia induces proliferative changes, neovascular growth, blood extravasation and glial proliferation. In extreme forms of proliferative diabetic retinopathy (PDR), retinal detachment develops due to traction through the fibrous-vascular tissue or only fibrous tissue. Proliferation in the iridocorneal angle leads to the development of neovascular glaucoma (NVG). Both conditions can cause practical blindness.

If there is no significant retinal hypoxia, DR can involve edematous processes. They lead to the development of

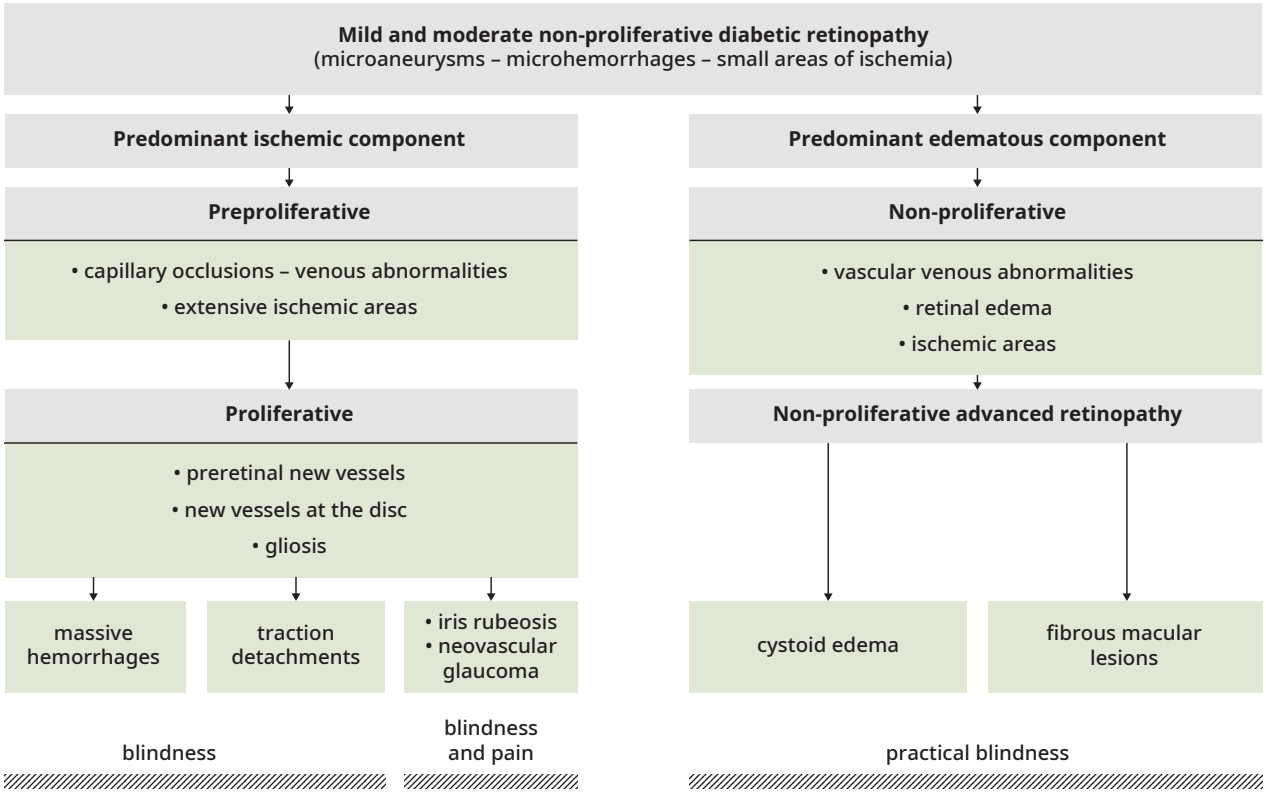

Figure 2. Diagram of the progression of diabetic retinopathy.

cystoid macular edema (CME), which may be accompanied by glial proliferation (fibrosis) due to inflammatory reaction. These changes also lead to severe vision loss and may end in practical blindness.

The neurodegenerative theory

Nowadays, it is widely believed that vascular lesions in DR are accompanied by neurodegenerative changes that affect nerve cells and glial cells[5]. These neurodegenerative processes primarily include the increased apoptosis of neuronal cells, increased glial cell reactivity, the activation of microglia (immune response cells residing in the retina), and disturbances in glutamic acid metabolism[6]. According to some theories, neurodegenerative changes in DR are forerunners of microvascular changes[7]. This theory is supported by some experimental studies and research on animals. Reactive glial activation may be a factor that links neurodegenerative and microvascular changes. This is because astrocytes and Müller cells play a key role in the regulation of blood flow and water management in the retina, and in maintaining normal blood-retinal barriers. The increased gliosis in Müller cells entails increased VEGF expression and, consequently, the production of proinflammatory cytokines and damage to the blood-retinal barrier[8]. In turn, microglia activation stimulates the activation of subclinical inflammatory processes in the retina.

In the early stages of DM there is a balance between pro and anti-inflammatory signals, however with DR progression there is a predominance of pro-inflammatory factors and an increase in chronic inflammation[9].

In addition, diabetes impairs the expression of neuroprotective factors – including the retinal pigment epithelium-derived factor (PEDF), somatostatin (GHIH),

and glucagon-like peptide (GLP-1) – and this impairment exacerbates the process of nerve cell damage[10]. These findings have therapeutic implications. Experimental studies show that the application of PEDF, GHIH, GLP-1 and erythropoietin has positive neuroprotective effects[11]. However, treatment or supplementation protocols focusing on this group of substances have yet to be developed for clinical practice. For example, the European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR) has not confirmed the neuroprotective effect of brimonidine or somatostatin administered in eye-drops[12].

These neurodegenerative processes are reflected in changes in the morphology of individual retinal nerve layers, which are visible, for example, in spectral domain optical coherence tomography (SD-OCT). They can manifest as a thinning of the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL) and the inner plexiform layer (IPL). Such abnormalities have been reported in the very early stages of mild retinopathy[13, 14]. Studies also show the progressive atrophy of retinal neurons in diabetic patients, even in the absence of retinopathy[15].

Anatomical changes result in functional impairments. According to many studies, such impairments become evident even before retinopathy is confirmed. This applies, for example, to ERG recording abnormalities[16]. The extent of abnormalities in ERG correlates with the duration of the diabetes. Functional impairments also include problems with colour vision and contrast sensitivity, and increased time required to adapt to darkness[17, 18].

The debate over whether neurodegenerative alterations precede microvascular lesions in DR is ongoing. There are analyses that do not confirm this sequence of events[19]. Possibly, in some diabetic patients, detected neurodegenerative changes are linked to an increased risk of retinopathy. In other cases, we may be dealing with two independent processes.

Such considerations also have diagnostic implications. In the process of testing/screening patients with diabetes for retinopathy, not only vascular studies (fluorescein angiography – FA, optical coherence tomography of the retina – OCT), but also analysing the thickness of individual retinal layers may be important in determining the risk of DR onset or progression. Precise protocols are yet to be develop and require further investigation.

Analysis of the pathogenetic processes leading to the emergence of diabetic retinopathy

The exact mechanism behind the development of retinopathy as a result of high blood glucose concentrations has yet to be established. The following have been discussed: the impairment of various biochemical pathways, hemodynamic disturbances, subclinical inflammatory processes, the role of oxidative stress, and abnormal levels of vascular growth factors.

Polyol pathway disorders

In diabetes, excess glucose accumulated in tissues is metabolized to sorbitol (and then to fructose) through the action of two enzymes: aldose reductase (AR) and sorbitol dehydrogenase (SDH). Both enzymes are present in the retina. The consequence of high levels of blood glucose is its intensive transformation to sorbitol, which accumulates in cells (cell membranes are impermeable to sorbitol). It is believed that the accumulation of sorbitol in the cells of the retina causes their direct damage (Fig. 3), mainly by an osmotic mechanism[20].

A consequence of high glucose concentration is increased AR activity in retinal cells: pericytes, pigment epithelium, Müller or ganglion cells[21, 22]. Studies show that AR inhibitors have a positive effect on inhibiting DR progression[23, 24].

Additionally, the transformation of glucose to sorbitol produces large amounts of the cofactor for aldose

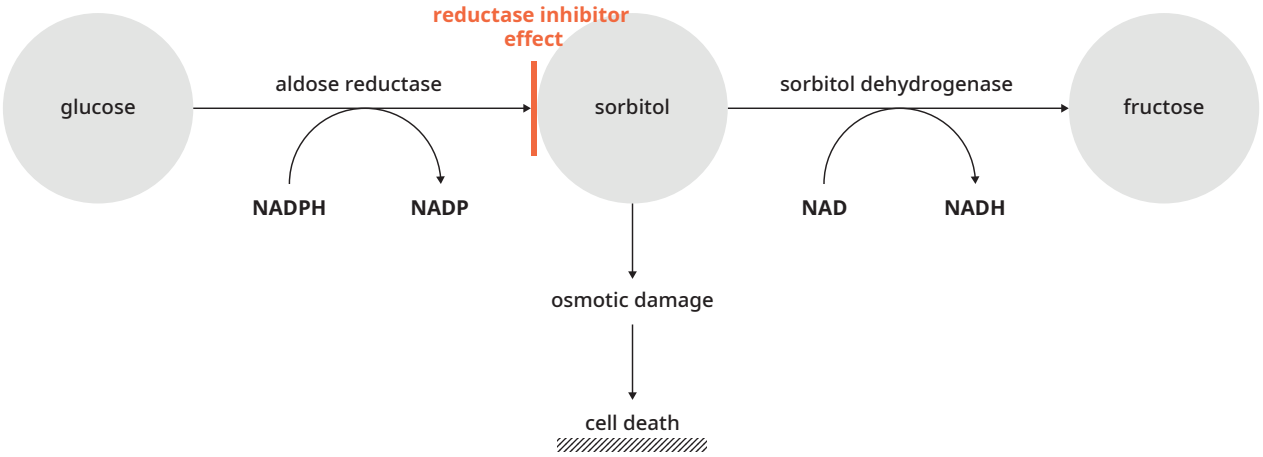

Figure 3. Schematic diagram of the polyol pathway. | NADP – nicotinamide adenine dinucleotide phosphate, NADPH – a reduced form of NADP, NAD – nicotinamide adenine dinucleotide, NADH – a reduced form of NAD

reductase – a reduced form of nicotine adenine dinucleotide phosphate (NADPH). Since NADPH is also a cofactor for glutathione reductase, the generation of reduced glutathione in the cell is hindered. Glutathione, on the other hand, has a strong antioxidant potential. As consequence of the described cell processes, a patient with diabetes is deprived of this antioxidant benefit.

The accumulation of advanced glycation end products in retinal cells

Glycation is a non-enzymatic process involving the reaction of sugars with amino groups – mainly proteins and lipids. The phenomenon of increased glycation is naturally associated with the aging process[25]. In the case of diabetes, the process of natural cell function loss, which is typical of an aging organism, occurs much earlier.

In a living organism, glycation occurs very slowly (over many weeks). This is because a small amount of glucose exists in its open form – that is, with the free aldehyde group reacting with the amino group of proteins and lipids. In diabetes, glycation is intensified due to the high level of glucose in the cells. The final effect of the intensified glycation is the AGEs – advanced glycation end products, i.e. highly reactive chemical compounds. They bind among themselves, and also with intracellular proteins, thus disturbing the functions of cells and tissues. Additionally, AGEs bind with the corresponding receptors on cell membranes, causing the formation of reactive oxygen species and the activation of transcription factors. As a result, the cell is subjected to oxidative stress and is damaged. High levels of AGEs have been found in vessels, cells nerves and connective tissue in the retina of diabetic patients[26, 27].

Collagen glycation and the formation of cross-links lead to the disruption of collagen structure, and to the loss of its flexibility. This process affects vessel walls (the basement membrane), causing them to stiffen[28]. The processes associated with increased protein glycation also cause damage to the vascular endothelium and loss of connections between endothelial cells and the inner vessel membrane. Studies on laboratory animals have shown the accumulation of AGEs in pericytes[29]. The reactions described above induce the development of diabetic microangiopathy, and lead to vessel wall damage, microaneurysm formation, and increased vascular permeability.

The loss of pericytes also results in impaired hemostasis, as well as susceptibility to thrombogenesis and angiogenesis. A correlation has also been shown

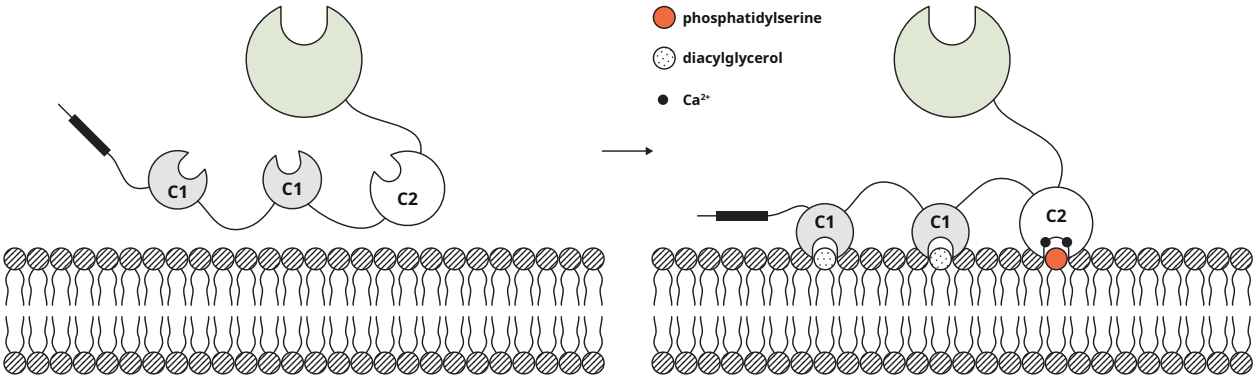

Figure 4. The activation of protein kinase C due to binding of the C1 domain with diacylglycerol, and the C2 domain with phosphatidylserine.

between the accumulation of AGEs in the human retina and the expression of VEGF[30].

Laboratory findings also suggest that AGEs are responsible for stimulating the inflammatory process in vessels[31, 32]. In addition, the upregulation of the receptors for AGEs (RAGE) located in the endothelium intensifies the inflammation process and oxidative stress[33].

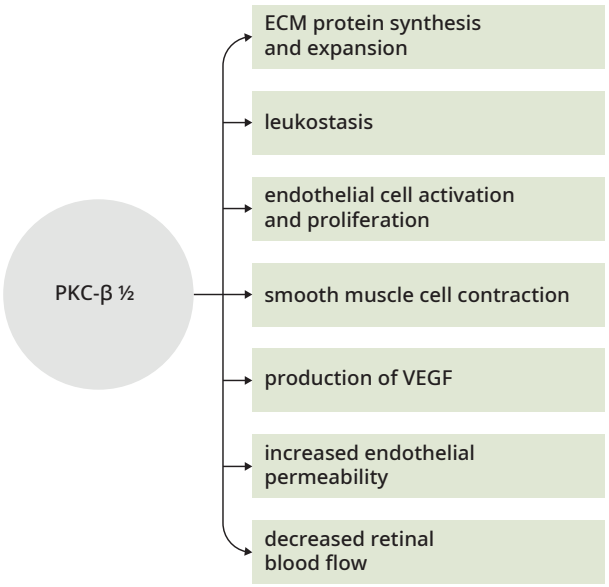

Figure 5. The regulation of pathophysiological processes in diabetic retinopathy due to protein kinase C (PKC). | ECM – extracellular matrix, VEGF – vascular endothelial growth factor

The role of AGE accumulation in the development of DR has specific therapeutic consequences. In studies on laboratory animals, AGE inhibitors such as aminoguanidine significantly reduced retinal complications[33]. Other studies have shown the beneficial effects of lipoic acid and benfotiamine in inhibiting the effects of AGE accumulation[34, 35, 36].

Protein kinase C activation

Hyperglycemia leads to increased diacylglycerol (DAG) synthesis, the levels of which directly affect protein kinase C (PKC) activation. PKC is a family of enzymes located, in an inactive form, in the cytoplasm of the cell. In the structure of PKC there is the C1 domain, which allows the enzyme to bind to diacylglycerol, and the C2 domain, which binds to phosphatidylserine (Fig. 4). The binding of the C1 and C2 domains to cell membrane structures leads to a complete change in the spatial structure of the protein and to the release of the catalytic center, i.e. activation of the enzyme[37].

The role of PKC in the body is multifaceted, but generally it is involved in the regulation of transcription, mediating the processes of immune response, the regulation of cell growth, and influencing learning and memory processes. However, the function depends on the type of cell in which PKC activation occurs, as its effects are described as cell-specific[38].

In the pathogenesis of diabetic retinopathy, changes in the PKC-β½ isoform are significant[37]. The activation of this enzyme triggers a cascade of biochemical processes which lead to changes typical for DR (Fig. 5).

Trials focused on using PKC-β½ inhibitors in the treatment of diabetic retinopathy have yielded positive results in laboratory conditions, but as yet have not led to the use of such a drug in clinical practice[39]. PKC is involved in numerous physiological processes, so simply inhibiting it may result in a range of side effects.

Hemodynamic changes

The Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) and UKPDS confirmed the importance of monitoring blood pressure as DR progresses[40, 41]. On the other hand, patients with diabetes often also suffer from arterial hypertension[42]. Nowadays, it is believed that hypertension contributes to the development DR via two mechanisms. The first is vascular endothelial damage due to the direct stress associated with elevated vessel pressure. When combined with increased blood viscosity, this mechanism leads to endothelial dysfunction[43].

The second mechanism involves a disturbance within the endocrine system, particularly in the renin-angiotensin-aldosterone system (RAAS), which directly controls correct blood pressure[44]. Studies show that in PDR there is increased expression of renin, angiotensin converting enzymes I and II (ACE), and angiotensin receptors[45]. The changes in receptor and molecule expression occur independently of actual blood pressure levels. This also means susceptibility to vasoconstriction and high blood pressure (Fig. 6). In vitro studies show that ACE inhibition prevents retinal neovascularization[46]. Blocking the receptors for angiotensin and ACE in diabetic patients resulted in a lower incidence and a slower progression of retinopathy. The results were confirmed in large clinical trials: the Diabetes Remission Clinical Trial (DiRECT) and the Renin Angiotensin System Study (RASS)[47, 48].

Subclinical inflammatory processes

The role of inflammatory processes in the pathogenesis of DR has been known for many years and has been confirmed in clinical trials[49, 50]. It should be borne in mind that the biochemical processes that occur in the tissues in the course of diabetes – such as

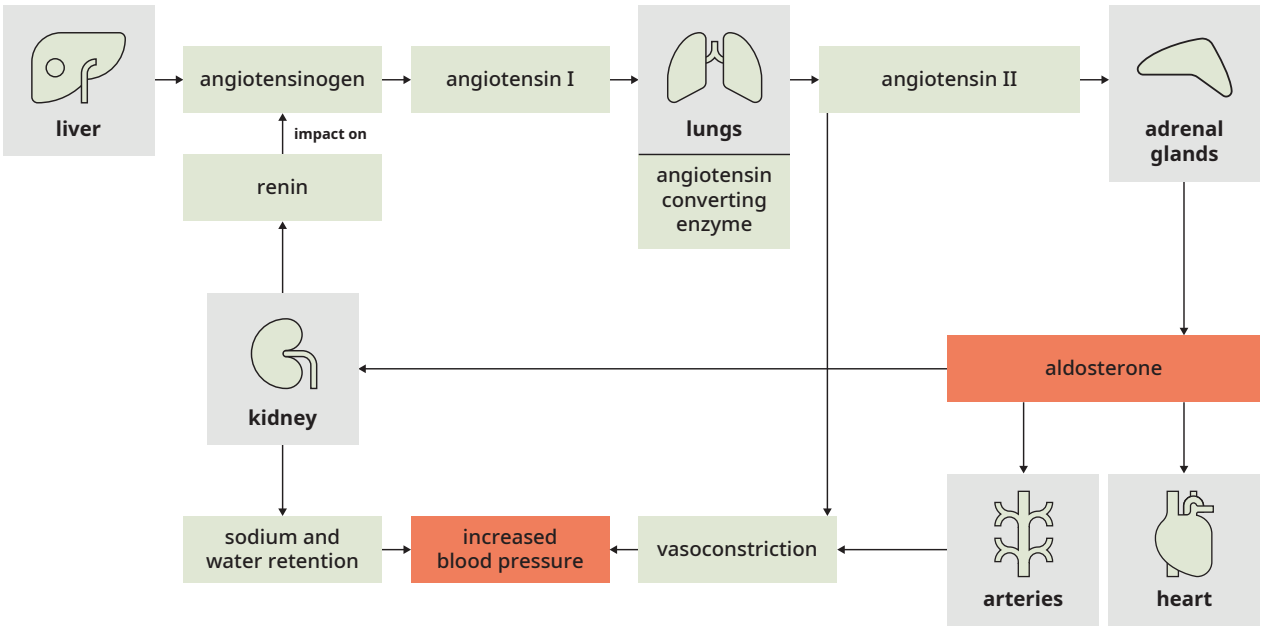

Figure 6. The role of the renin-angiotensin-aldosterone system in blood pressure regulation.

hyperglycemia and glucose metabolism via the sorbitol pathway, advanced glycation and AGE formation, oxidative stress, and arterial hypertension – trigger the activation of cascades of inflammatory mediators. In turn, inflammation mediators induce further pathochemical pathways, causing VEGF production, the increased expression of RAGE, or a change in the regulation of nitric oxide levels.

Studies indicate increased pro-inflammatory cytokine concentrations, as well as activated adhesion molecules and immune cell response in DR patients[51]. In turn, increased levels of these factors correlate with the progression of retinopathy[52]. High levels of inflammatory mediators contribute to an increase in leukocytes levels. The simultaneous increased adhesion of these of these cells to endothelium leads to leukostasis[53].

The use of anti-inflammatory drugs to treat DR has been investigated in large clinical trials. The effectiveness of intravitreal steroid therapy has been repeatedly confirmed, but this is only appropriate for advanced stages of DR, i.e. diabetic macular edema (DME)[54, 55]. Moreover, the way in which these drugs are administered precludes their use in DR prevention. Some studies show a beneficial effect of the topical application of non-steroidal anti-inflammatory drugs (NSAIDs), such as nepafenac, in slowing the development of microvascular lesions in DR[56]. Thus far, however, no NSAIDs have been registered for prolonged use in the treatment of DR. So far, these drugs are applied in DR only for DME prevention after cataract surgery.

Oxidative stress

Oxidative stress can be defined as an imbalance between the production of reactive oxygen species (ROS) and the body's ability to eliminate them through its natural defence systems. Under physiological conditions, ROS are neutralized when bound with thioredoxin, glutathione or tocopherol (vitamin E), for instance, or they are eliminated by enzyme systems, for example, dismutase superoxide, catalase, peroxidase glutathione, and thioredoxin reductase. In diabetes, the body's defence mechanisms against ROS are notably impaired[57].

In diabetic patients, oxidative stress is induced by activation of the previously described biochemical pathways: the polyol pathway, AGE accumulation, and PKC activation. Studies show that there is a strong

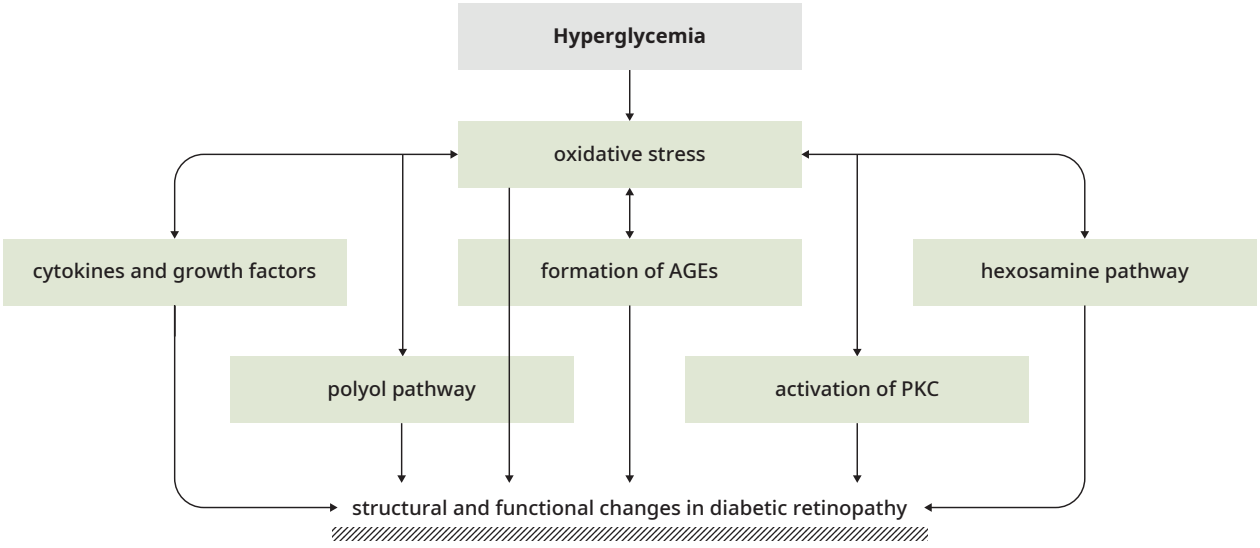

Figure 7. The role of oxidative stress in the pathogenesis of diabetic retinopathy. | AGE – advanced glycation end products, PKC – protein kinase C

association between the development and progression of retinopathy and increased levels of ROS[58, 59]. Furthermore, research on animals show that oxidative stress is responsible for the lack of regression of DR even after glycemic stability has been achieved[60].

Oxidative stress appears to be the DR pathogenesis mechanism that connects all the other biochemical pathways. Disturbances at the level of chemical reactions result in increased ROS production at the cellular level (Fig. 7) and induce epigenetic changes occur, such as damage to cell DNA, the formation of non-coding RNA, and histone modifications. DNA changes are followed by enzymatic disorders that lead to AGE accumulation, PKC activation, and disturbances in the polyol pathway[61]. Cell membrane lipids are also directly damaged. When damage resulting from excessive ROS production affects cells in the vessel walls, microangiopathy develops. Moreover, oxidative stress is also responsible for neuronal apoptosis in diabetes[62].

The overall processes associated with oxidative stress also exacerbate inflammatory processes. Hence, we are dealing with a feedback mechanism: oxidative stress – subclinical inflammatory processes. These mechanisms trigger each other, resulting in the progression of retinopathy.

Growth factors

The course of DR depends on the level of growth factors. Research on their role has been conducted for decades. Studies from the 1970s showed that pituitary ablation slowed DR progression[63]. Research on DR shows that many growth factors play a role in its development, such as: fibroblast growth factor (bFGF), insulin-like growth factor (IGF-1), epidermal growth factor (EGF), transforming growth factor beta 2 (TGFβ2), platelet-derived growth factors (PDGF), erythropoietin, angiopoietin 1 and 2, as well as others. Nowadays, VEGF is considered to be the most important growth factor in the pathogenesis of DR. It exists in four monomeric forms with different numbers of amino acids (VEGF-A, VEGF-B, VEGF-C and VEGF-D). The placental growth factor (PIGF) also belongs to the VEGF family.

Under physiological conditions, VEGF has important functions in maintaining the homeostasis of retinal nervous tissue (Müller cells and photoreceptors)[64]. It is also important for the proper functioning of the choroid, and especially the choriocapillaris[65].

Hypoxia and inflammation induce VEGF-A upregulation[66, 67]. VEGF-A binds to the tyrosine kinases of cell membranes, thereby activating several transduction cascades that promote vascular proliferation and an increase in vascular permeability. VEGF-A is a very powerful mitogenic agent, primarily for endothelial cells. The multiplication of these cells results in vascular proliferation.

As VEGF-A binds to receptors in the vascular endothelium, intercellular junctions open and fluid leaks out of a vessel. Moreover, under the influence of VEGF-A, vascular endothelial proliferation occurs, and this promotes the formation of microaneurysms in a situation of pericyte deficit, which is typical of diabetic retinal capillaries[68]. Taken together, these processes lead to the breakdown of the blood-retinal barrier.

VEGF also stimulates the expression of adhesion molecules – vascular cell adhesion molecules (VCAM) and intercellular adhesion molecules (ICAM), which contributes to an increase in leukocyte adhesion to the endothelium and leukostasis. In turn, these processes exacerbate hypoxia and thus stimulate the production of even more VEGF.

Therapeutic consequences of the pathogenetic mechanisms of diabetic retinopathy

Understanding the pathogenetic mechanisms of DR has implications for planning the appropriate therapy for this medical condition.

Anti-VEGF therapy, i.e. blocking the vascular growth factor function, is commonly used today. The goal of this treatment is to reduce retinal edema and to inhibit the neovascularization (the details of this therapy are discussed in later sections, see especially pp. 147–157, 188–192). It should be noted that anti-VEGF therapy involves administering multiple intravitreal injections and following a strict regimen of ophthalmologic supervision, which is a significant burden for the patient.

Another group of drugs used intravitreally are steroids (dexamethasone, fluocinolone, triamcinolone), i.e. anti-inflammatory drugs. These agents have been used in the treatment of DME, most often with cases that do not respond well to anti-VEGF therapies (the details of this therapy are discussed in later chapters, see pp. 144–147). The use of steroid injections is associated with some side effects: cataracts and increased intraocular pressure. Therefore they are usually not the first-line medication used in the treatment of DME.

Antioxidants, primarily alpha-lipoic acid, are used as supplements in the treatment of DR. Alpha-lipoic acid reduces oxidative stress and the expression of RAGE, and inhibits the formation of cell-free capillaries and the production of VEGF[69, 70, 71]. Combining alpha-lipoic acid supplementation with vitamin B1 seems to be beneficial, since the latter has strong antioxidant properties (it inhibits the polyol pathway, PKC activation, and AGE accumulation). It should be emphasized that the use of supplementary antioxidants has an auxiliary role and should be used in the initial phase of DR, or even in diabetic patients without DR.

There is ongoing research on drugs targetted at blocking other biochemical pathways leading to the development of DR. This applies primarily to anti-inflammatory agents (broadly conceived). The problem is selectively blocking specific biochemical pathways and minimizing the side effects caused by such blocking.

Researchers have focused on the following anti-inflammatory agents in ongoing clinical trials:

1. Adenosine kinase inhibitor (ABT-702) – inhibits inflammatory processes in the retina. Research on mice showed a positive effect of this agent[72].

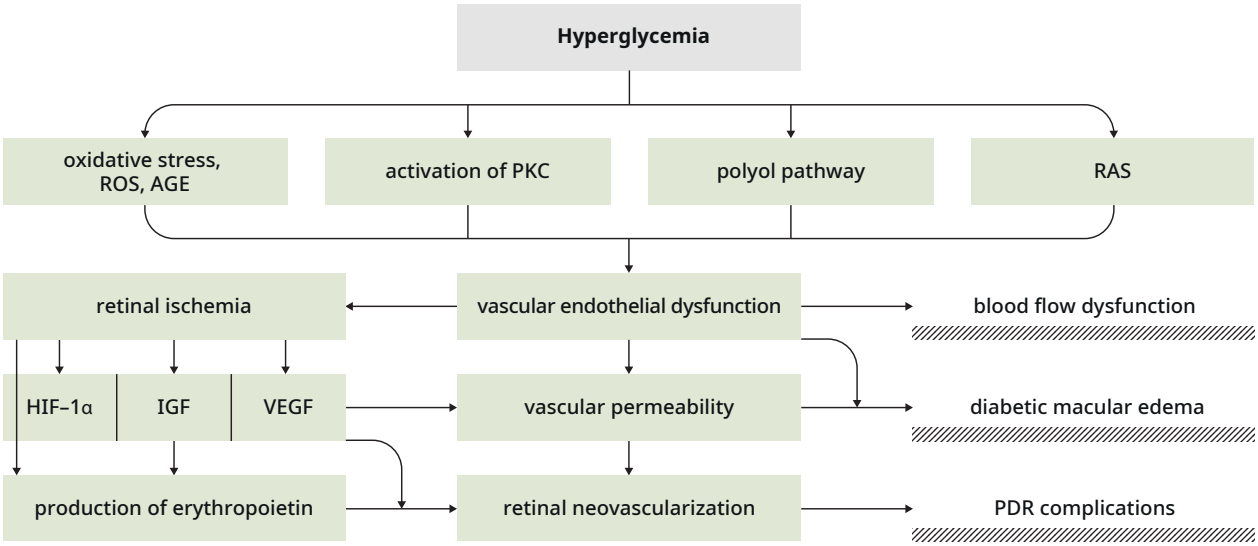

Figure 8. Diagram of the processes occurring in cells under the influence of hyperglycemia – a summary. | AGE – advanced glycation end products, HIF-1 – hypoxia induced factor 1, IGF – insulin-like growth factor, PDR – proliferative diabetic retinopathy, PKC – protein kinase C, RAS – renin-angiotensin system, ROS – reactive oxygen species, VEGF – vascular endothelial growth factor

2. Angiopoietin 2 inhibitors – inhibit inflammatory processes, reduce vascular permeability and pericyte atrophy. Research is directed towards developing one agent targeting both VEGF and angiopoietin 2 pathways or using a combination of agents with such effect (the clinical trials BOULEVARD, RUBY and YOSEMITE)[73, 74, 75].
3. Inhibitors of proteins causing vascular adhesion, tested orally in DME treatment (VIDI study)[76].
4. Phospholipase A2 inhibitor associated with lipoprotein (LP-PLA2: darapladib) – the substance reduces blood-retinal barrier damage in animal model studies[77].
5. RHO-kinase inhibitor (fasudil) – prevents leukocyte adhesion and endothelial damage by neutrocytes. The substance is being tested in the treatment of refractory DME in conjunction with bevacizumab[78].
6. iCo-007 oligonucleotide – a substance that blocks the signalling effects of protein kinase. In the IDEAL study on the use of iCO-007 in DME treatment, in monotherapy or combined with ranibizumab or laser, the preliminary results were encouraging[79].
7. Luminate (ALG-1001) – a substance that blocks integrins (transmembrane receptors) and inhibits angiogenesis. Initial research results show the effectiveness of luminate in the treatment of DME after intravitreal injection[80].
8. Kallikrein inhibitors (proteolytic enzymes) – their upregulation in DME has been confirmed, which resulted in increased vascular permeability. Oral kallikrein inhibitors are tested as monotherapy or combination therapy with anti-VEGF agents in the treatment of DME resistant to anti-VEGF monotherapy[81].

Summary of mechanisms leading to the development of diabetic retinopathy (Fig. 8)

Factors causing direct damage to the vessel wall:

- high blood glucose levels,
- the production of sorbitol and AGEs,
- the formation of microaneurysms – edema, hard exudates.

Changes in blood viscosity in diabetic patients – erythrocyte and leucocyte aggregation:

- thrombotic changes – edema, hemorrhages,
- embolic changes – edema, soft exudates.

Retinal hypoxia – increased production of growth factors:

- formation of pathological vessels – hemorrhages,
- increase in vascular permeability – edema, hard exudates,
- changes in venous vessels – beading, reduplication, loops, stasis.

Neurodegenerative changes:

- apoptosis of nerve cells – thinning of individual layers of the retina,
- glial and microglial activation,
- intensification of inflammatory processes and oxidative stress,
- exacerbating microangiopathy.

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Chapter 3: Anatomical aspects of diabetic retinopathy

Introduction

This chapter covers basic information on the anatomy and physiology of the eyeball, with particular attention paid to the pathomechanism of diabetic retinopathy (DR). Some of this information may seem too rudimentary for ophthalmologists, but please bear in mind that this book is also intended for diabetologists and general practitioners, who rarely encounter ophthalmic problems in their everyday practice.

The anatomy of the eyeball

The eye is one of the most complicated organs of the human body. The elements of its construction are replicated, to some extent, in the construction of cameras: the iris – aperture, lens – component lens, retina – light-sensitive matrix.

Roughly speaking, the eyeball structure contains two balls: a smaller, transparent ball, with a radius of curvature of 8 mm, and larger, opaque one, with a radius of curvature of approximately 12 mm[1]. The surface of the smaller ball corresponds to the cornea, while the larger one corresponds to the sclera. The axial dimension of the eyeball ranges from 21 mm to 26 mm, on average 24–25 mm, and the transverse dimension is approximately 24 mm[2]. The volume of the eyeball is approximately 6.5 cm^3, on average.

The wall of the eyeball is made up of collagen fibers of irregular arrangement, and is called the sclera. Due

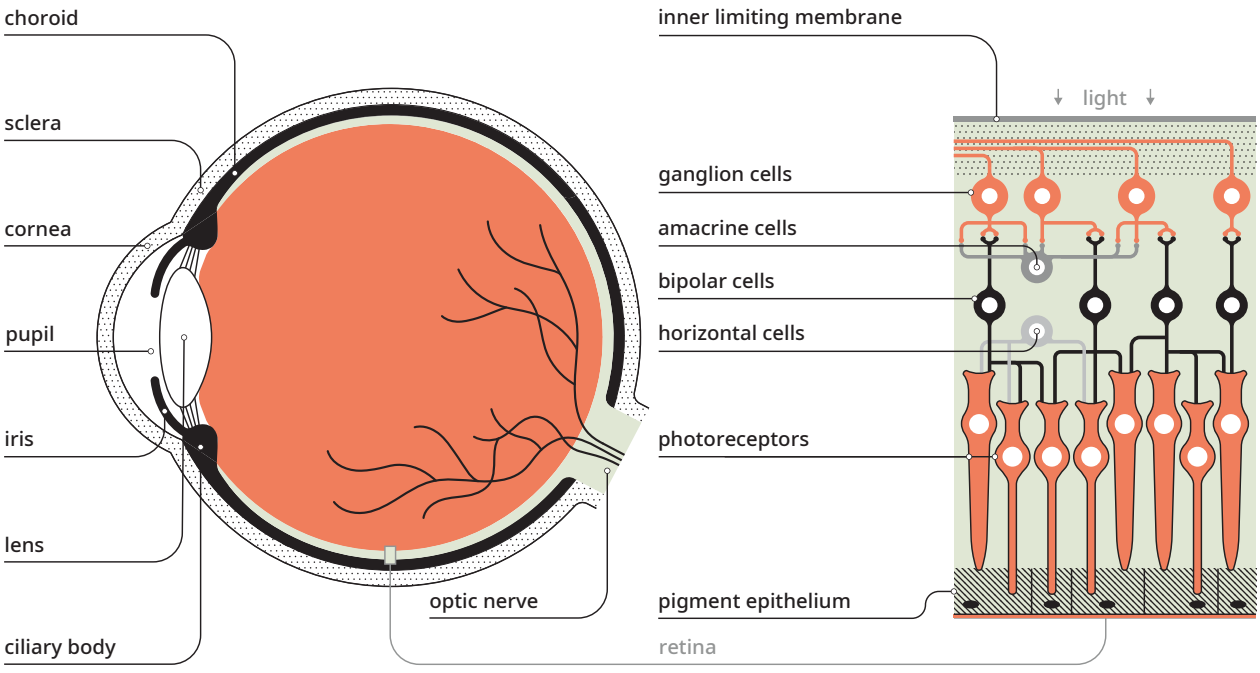

Figure 1. A cross-section of the eyeball.

to the irregular arrangement, the sclera is opaque and white.

At the front of the eyeball, the sclera transitions to the transparent cornea. Its translucency is determined by the change of the irregular arrangement of collagen fibers into a regular arrangement. The cornea is the basic refractive element in the optical system of the eye. In the posterior part of the eyeball, the sclera is continuous with the dura mater, which covers the optic nerve.

The transparent cornea makes up the most anterior part of the eyeball. The space behind it is the anterior chamber, which is closed by the corneal endothelium, the iridocorneal angle, the iris and the lens. In turn, the posterior chamber occupies the area between the back of the iris, the lens and the vitreous membrane. Both the anterior and posterior chambers are filled with the aqueous humor.

The aqueous humor is secreted from the ciliary body and under normal conditions flows freely from the posterior chamber to the anterior chamber. The site of the aqueous humor outflow from the eyeball is in the iridocorneal angle, located between the cornea and the iris. In this way, the aqueous humor is discharged from the eyeball to the episcleral venous circulation. Impairment in this outflow results in increased intraocular pressure and damage to the optic nerve, i.e. glaucoma.

The pigmentation of the iris determines the colour of a person's eyes. Most of its volume is made up of muscles that originate in the ciliary body. By contracting and relaxing, these muscles determine the size of the pupil, which is the opening in the centre of the iris. The function of the iris is often compared to the diaphragm in a camera. It controls the quantity of light penetrating the eye.

The lens is located directly behind the iris. The lens is held in place by ligaments that extend between the ciliary body and the lens capsule. The ciliary body also changes the shape of the lens by contracting and relaxing. The lens may take on a spherical or flatter shape, depending on the location of the object to which gaze is directed. This process is called accommodation. Along with the cornea, the lens, which is responsible for accommodation, is the most important optical element of our visual system.

Most of the area of the posterior part of the eyeball is filled with a gel-like, collagenous, transparent structure – the vitreous body, located behind the lens. The posterior part of the eyeball is lined with a layer consisting of the choroid and retina. The choroid, a layer resting directly on the sclera, is a dense network of vessels that nourishes the outer layers of the retina. The choroid transitions into the ciliary body and the iris. These three structures are collectively referred to as the uvea or the vascular layer of the eyeball.

The inner surface of the choroid is covered by the retina, which is made up of cells and photoreceptors that receive light stimuli. Towards the anterior aspect, at the point where the ciliary body begins, the retina loses its light-sensitive elements. The junction between the light-sensitive retina and the ciliary body is called the ora serrata. A diagram of the structure of the eyeball and retina is shown in Figure 1.

Light has to pass through several anatomical structures before it reaches the retina and the optic nerve. The correct reception of light stimuli depends on the transparency of the individual elements of the eyeball: the cornea, aqueous humor, the lens, and the vitreous body.

The path of the light stimulus in the eye is as follows: a ray of light passes through the transparent cornea, where it is refracted for the first time; it then passes through the anterior chamber of the eyeball, which is filled with aqueous humor. Next, it reaches the lens through the pupillary aperture, where the second refraction of the light ray takes place. From there,

passing through the vitreous body, it reaches the retina and the optic nerve. The optic nerve is the part of the brain that receives light stimuli.

The anatomical component that receives visual stimuli is the retina. It is a collection of cells and receptors that generate visual impulses which are transmitted to the brain via the optic nerve. Because of its rich vascularization, it is also the site where changes associated with the microvascular comorbidities of diabetes are observed. Examining the fundus can provide a great deal of information about the progression of these changes, which are referred to as diabetic retinopathy.

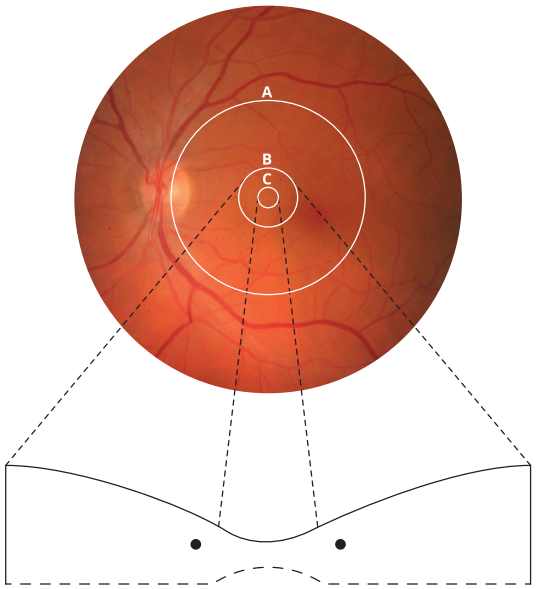

Figure 2. Anatomical diagram of the fundus superimposed on an ophthalmoscopic image. The diagram shows the relationship between the size of the foveola (C), approximately corresponding to the avascular zone, and the fovea (B) and macula (A).

Retinal anatomy and optic fundus topography

Introductory remarks

The basis for any classification of lesions is establishing their precise location. That is why anatomical knowledge of the retina is so important.

In the most general terms, the topography of the retina is described by the following concepts[3]:

1. the posterior pole (macula) – the posterior part of the retina, contained between the main temporal vascular arcades, 5–6 mm in diameter; in practical terms, it corresponds to the anatomical term macula lutea;
2. the optic nerve disc – located in the nasal part of the posterior pole, with a diameter of about 1,500 µm (1 DD); its size is a common reference for determining the size of other structures visible on the fundus;
3. the fovea centralis – a retinal depression in the centre of the posterior pole, about 1,500 µm in diameter; in young people, a characteristic reflection from the internal limiting membrane is visible in ophthalmoscopic examination, marking the borders of the fovea;
4. the foveal avascular zone (FAZ) – the central area of the macula, usually 350 µm to 500 µm in diameter, devoid of a capillary network, made of cones and their nuclei; in clinical practice this area is referred to as the foveola;
5. the umbo – a small depression in the centre of the fovea, the source of the characteristic point-like light reflex in ophthalmoscopic examination;

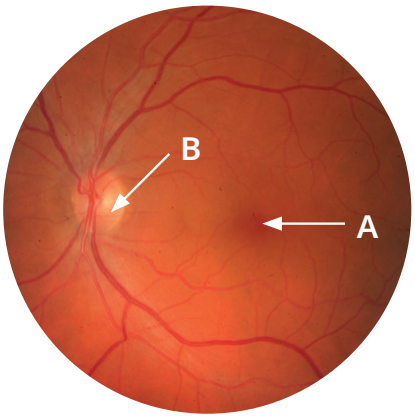

Figure 3. Ophthalmoscopic image of the fundus. The photo shows the fovea (A) and the optic nerve (B).

6. the diameter of the venous vessel at the rim of the optic disc is about 125 μm; this value is important as a reference for determining the size of fundus lesions.

The architecture of the retina

It is important to bear in mind that the terms defined above apply to a relatively small area of the entire retina. They were created for the purpose of describing ophthalmoscopic images, which, depending on the lens used for the examination, cover an area ranging from a few to several millimeters in diameter. When unfolded, the entire retina, is a disk of 30 to 40 mm in diameter.

Figure 4 shows a cross-section through the retina. Its thickness is on average about 0.5 mm. The innermost layer of the retina consists of the axons of the ganglion cells, which reach the brain in the optic nerve (nerve fiber layer, NFL). Central retinal artery and central retinal vein, whose branches supply blood to the inner retinal layers, also reach the retina through the optic nerve.

There are three layers of cell nuclei in the retina: the ganglion cell layer (GCL), which is the innermost layer, the inner nuclear layer (INL), and the outer nuclear layer (ONL). The inner nuclear layer is composed of the nuclei of bipolar, amacrine, and horizontal cells. The outer nuclear layer, on the other hand, is made up of the cell bodies of the cones and rods. The nuclear layers are divided by plexiform layers – inner (IPL) and outer (OPL), made up of cell synapses and axons.

When looking at the cross-section of the retina, it should be borne in mind that light must pass through all the layers of the retina before it reaches the photoreceptors, i.e. cones and rods. A visual impulse is generated in the photoreceptors, i.e. in the outermost layer of the retina, and only from there, through two neurons, does it reach the brain through the optic nerve.

The architecture of the retina varies depending on the location on the fundus. The differences are determined by factors such as the distribution of photoreceptors. The central part of the retina is dominated by cones, which are absent in the peripheral retina – here there are only rods. The cones require more cells to conduct impulses, which results in the significant thickness of the inner nuclear layer, the inner

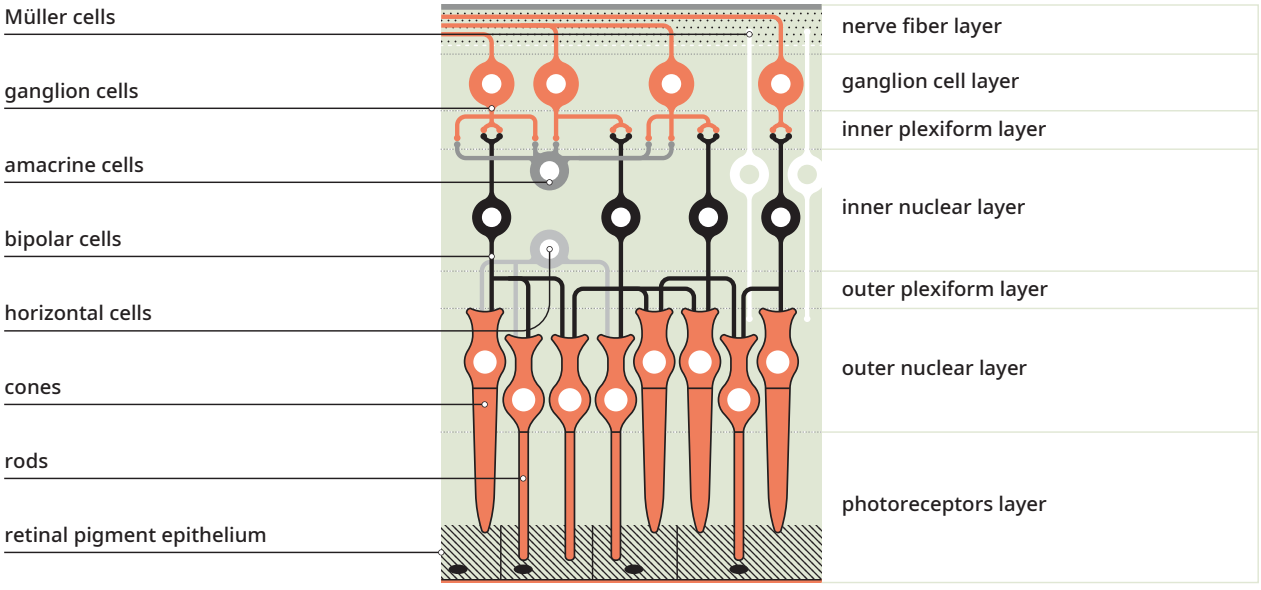

Figure 4. A cross-section of the retina.

plexiform layer, ganglion cell layer and nerve fibers in the fovea area. In contrast, they are thinner in the peripheral layer of the retina.

The axons of the cone cells follow an oblique course and, together with the processes of Müller cells, they form their own layer within the outer plexiform layer, referred to as the Henle layer[4]. This layer is absent in the peripheral retina.

The fovea also has a different anatomical structure than the rest of the retina. This central part of the macula is occupied by cones only. These photoreceptors are concentrated in a very small space (an area with a dimension of about 300 μm), which is facilitated by their arrangement in the form of a hexagonal mosaic[5]. Here, the remaining retinal layers are shifted to the sides (Fig. 5).

Differences between the architecture of the central and peripheral parts of the retina are also determined by the presence of carotenoid pigments, i.e. xanthophyll, lutein, and zeaxanthin, which are found within the retinal cells, mainly bipolar and ganglion. The concentration of these pigments is considerably higher in the macular area, which causes the slightly yellowish macular glare that is visible during funduscopic examination. Carotenoids have a protective function with regard to visible light. They work like a filter, protecting the retina from oxidative stress[6].

The perifoveal area is characterized by a predominance of ganglion cells and bipolar cells, which are most abundant in this area (12 and 7 layers, respectively). Towards the periphery of the retina there are fewer photoreceptors, and the individual retinal cell layers fuse together. Eventually, the sensory retina turns into a single layer of elongated cells, which transform into the pigment-free epithelium of the ciliary body. The retinal pigment epithelium (RPE) layer passes continuously into the ciliary body pigment epithelium, and the inner retinal limiting membrane passes into the ciliary body limiting membrane. The anatomical boundary of the sensory retina is assumed to be the ora serrata, located approximately 5 mm anterior to the equator of the eyeball[7]. In the location of the ora serrata and about 2 mm behind it, there is strong adhesion between the vitreous body and the retina.

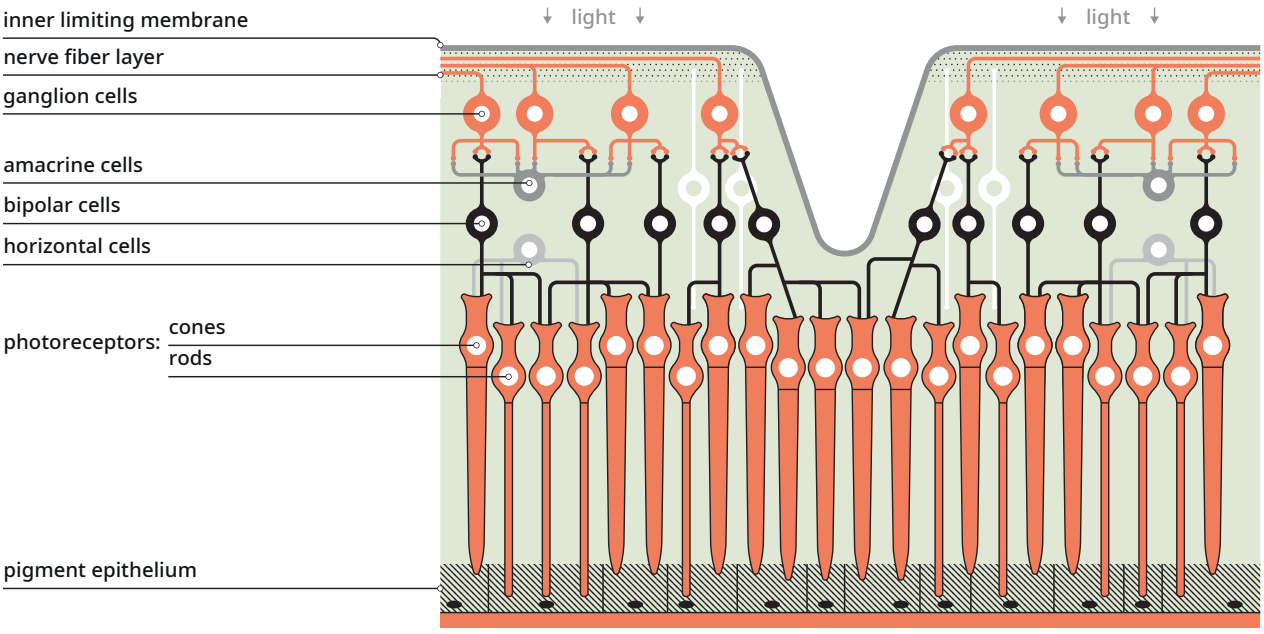

Figure 5. A cross-section the fovea centralis. Visible concentration of cones in the central part of the fovea.

The optic nerve

The optic nerve disc is the area where the ganglion cell axons leave the eyeball. It is the part of the nerve visible on the fundus of the eye, usually slightly oval, larger vertically than horizontally. For the purpose of clinical practice, it is assumed that the diameter of the optic nerve disc is on average 1.5 mm. After leaving the eyeball, the diameter of the nerve increases. The number of nerve fibers decreases with age.

There is a physiological depression (cupping) in the centre of the optic nerve head, which is where the branches of the central retinal artery and vein exit to the retinal surface. The size of the cupping is subject to quite a lot of individual variability, but it is estimated that in most individuals the ratio of the diameter of the depression to the diameter of the nerve disc is between 0.35 and 0.55[8].

There are no photoreceptors within the optic nerve, so its counterpart in the visual field is a blind spot.

Retinal pigment epithelium

The outermost layer of the retina is the RPE. This is a single layer of hexagonal cells closely connected to each other (the so-called zonula occludens of pigment epithelium). These tight intercellular junctions form the blood-retinal barrier and prevent the free flow of substances from the choroidal space to the retina. The RPE cells are flat on the outside and rest on the basement membrane, a component of Bruch's membrane. On the inner side, they contain numerous apical microvilli that wrap around the photoreceptors.

RPE cells contain numerous pigment granules, the most important being melanosomes and granules containing lipofuscin, a degradation product of photoreceptors[9]. One of the main functions of RPE is the metabolism of photoreceptor outer segments (Fig. 6). In the course of a single day a single RPE cell is able to metabolize over 2000 of these segments[10]. The elements that are not degraded are deposited in the cells matrix as lipofuscin deposits. This process increases with age and leads to impaired cell function and degenerative changes, such as age-related macular degeneration (AMD). The density of pigment varies in accordance with the location in the retina – the highest concentration is observed in the macular region. Here, the RPE cells are also significantly higher compared to the peripheral retina. Consequently, in ophthalmoscopic examination, the fovea itself appears darker than other areas of the retina.

RPE and photocoagulation

The presence of pigment in the RPE cells is important for laser photocoagulation of the retina. It is the RPE cells that are the target of laser photocoagulation, and because of the presence of the pigment that significantly absorbs light, the main effect of thermal laser therapy occurs there.

Properly functioning RPE cells form a tight barrier between the retina and the choroid (the outer blood-retinal barrier)[11]. In normal conditions there is no blood exchange between these two structures. The supply of nutrients from the choroid to the retina and the elimination of metabolites from the retina to the choroid is selective, and takes place through the RPE cells, mainly by means of active transport[12].

Functions of RPE cells

- formation of the blood-retinal barrier,
- phagocytosis of the outer segments of photoreceptors,
- active transport of nutrients from the choroid to the retina,
- elimination of metabolites from retina to the choroid,
- production of growth factors (among others VEGF) and anti-angiogenic factors (PEDF),
- storage and metabolism of vitamin A,
- absorption of excessive light – protection against oxidative stress.

RPE cells also have secretory functions and are a source of growth factors and vascular growth inhibitory

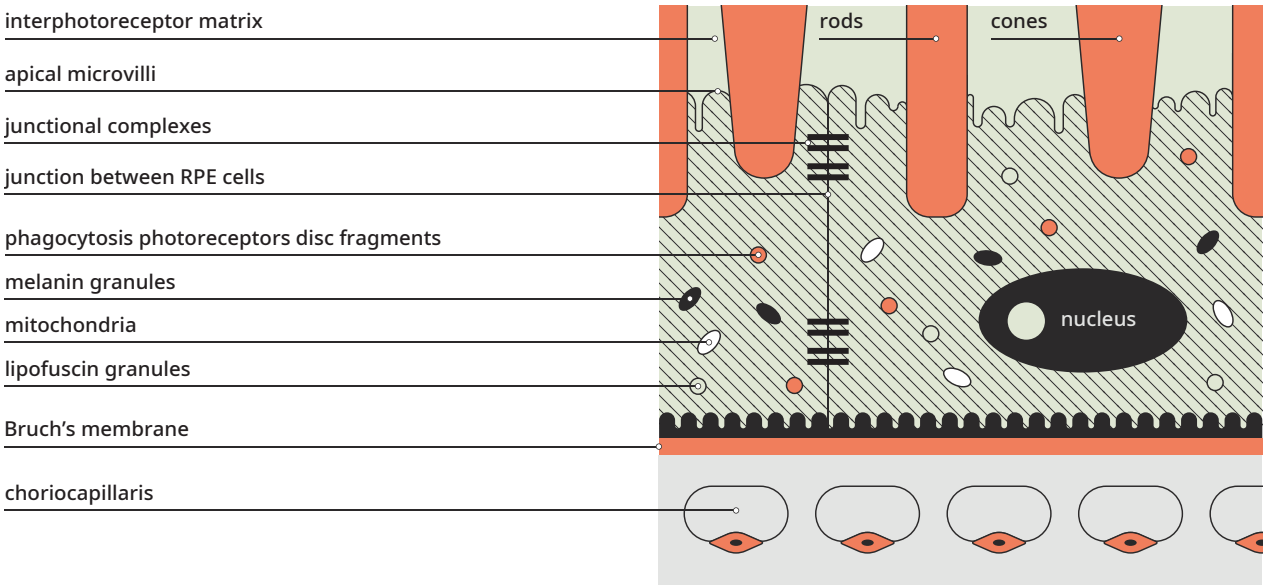

Figure 6. Retinal pigment epithelium – a cross-section and anatomical structure.

factors. Balance between them is necessary for the proper functioning of the retina and choroid, and its disruption may lead to neovascularization[13].

Retinal blood supply

The retina is nourished from two sources: retinal circulation (the inner ⅔ of the retina) and choroidal circulation (the outer ⅓ of the retina). The central retinal artery enters the optic nerve about 1 cm behind the eyeball and enters the eye through it. The division into two large branches takes place within the optic nerve. On the surface of the retina, there is a further division of the arterial branches into superotemporal and superonasal branches and inferotemporal and inferonasal branches, which supply individual quadrants of the retina (Fig. 7). Further subdivisions into smaller branches occur in

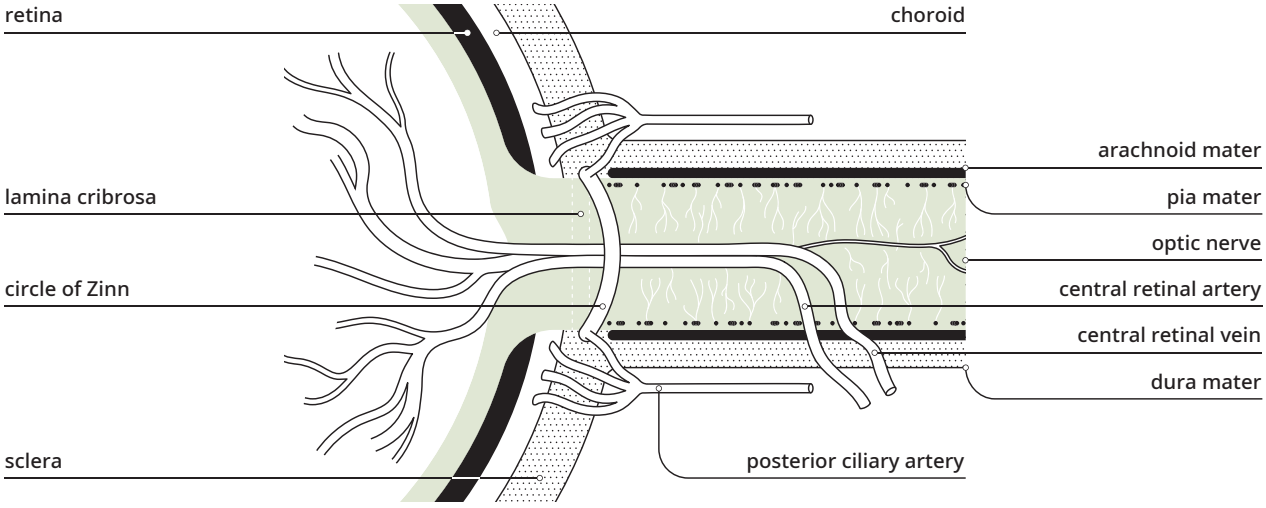

Figure 7. Diagram of eyeball vascularization.

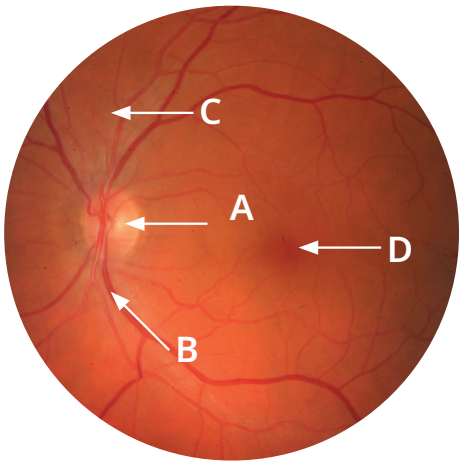

Figure 8. Retinal vessels. Visible: A – optic nerve cup, B – venous vessel, C – arterial vessel, D – foveal avascular zone.

the peripheral course of the arterioles. The vascular system reaches the ora serrata, where it becomes a venous system and then returns to the central retinal vein in the optic nerve. This blood supply system is so – called “end artery” system – it has no communication with any other arterial system (Fig. 8).

Consequently, any closure of the vessel results in a form of retinal infarction.

There are two capillary plexuses in the retina, formed by branches of the retinal vessels. The first, more superficial, is located in the nerve fiber layer. The second, deeper, extends between the inner nuclear and outer plexiform layer, mainly in the inner nuclear layer (Fig. 9)[14]. Detailed images of retinal vasculature also show the intermediate capillary plexus, located on the border of the inner plexiform and inner nuclear layers (see Chapter 4: *Diagnostic techniques for diabetic retinopathy*, pp. 73–77).

Capillary plexuses and symptoms of DR at the fundus

The location of capillary plexuses in the retina is important for the symptoms observed in fundus in DR. Microcirculatory abnormalities located in the nerve fiber layer, such as hemorrhages, assume a shape that follows the course of the nerve fibers, that is, flame-shaped. In contrast, damage to the deep capillary network results in petechiae with a dot or blot-like shape.

Source of supply	Capillary plexus
retinal circulation	superficial
	deep
choroidal circulation	

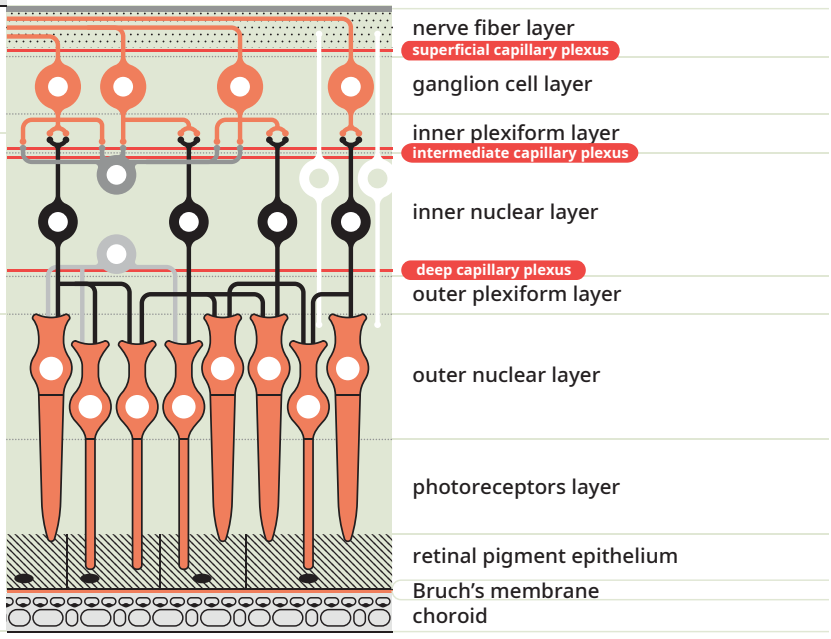

Figure 9. Diagram of the extent of retinal vasculature.

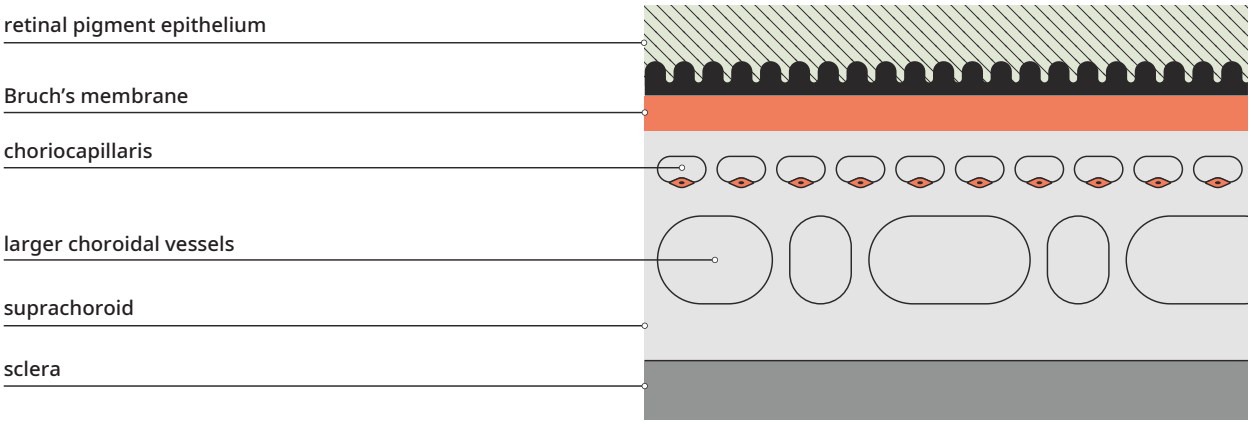

Figure 10. A cross-section through the choroid.

Moving out from the outer plexiform layer, retina remains avascular and receives nutrition from the choroid. Neither capillary plexus extends into the fovea. This central zone of the retina, 300 µm to 500 µm in diameter, is referred to as the foveal avascular zone (FAZ)[15]. As described earlier, in practical terms this area only contains cones, which are nourished from the choroidal circulation. The second place without capillaries are the zones along the arterioles – perivascular avascular zones.

Key features of retinal capillaries

- There is a only a single layer of endothelial cells on the basement membrane.
- Tightly connected endothelial cells (zonula occludens) form an inner blood-retinal barrier[16].
- Pericytes, which surround the capillaries, have the ability to contract, due to their processes and contribute to the autoregulation of microcirculation.

The second source of blood supply to the retina is the choroid, located between the sclera and the retina (Fig. 10). This highly vascularized structure is supplied by the long and short ciliary arteries (which are branches of the optic artery) and by the branches of the vascular circle of Zinn. The choroid receives 65–85% of the blood reaching the eyeball (to compare: retinal circulation provides 20–30% of the blood). The choroid connects to the retinal pigment epithelium by means of Bruch's acellular membrane.

As mentioned earlier, both Bruch's membrane and the zonula occludens of endothelial cells form a tight blood-retinal barrier. Therefore, the exchange of nutrients and metabolites between choriocapillaries and RPE cells is not mediated by vessels, but is a consequence of active transport through Bruch's membrane.

Most of the choroid is taken up by blood vessels arranged in a lobular pattern. Large vessels are located closer to the sclera, smaller ones – choriocapillaries – are located near Bruch's membrane. The characteristic feature of the choriocapillaries are fenestrations, which allow the flow of macromolecules into the extravascular area.

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Chapter 4: Diagnostic techniques for diabetic retinopathy

Basic ophthalmologic examination

Every patient with diabetic retinopathy (DR) should undergo a complete basic ophthalmologic examination, including a visual acuity test, measurement of intraocular pressure, and the examination of the anterior segment and the fundus.

Visual acuity test

The patient's distance and near visual acuity should be tested, with optical correction. Best corrected visual acuity (BCVA) is the basic measure of macular function. This test is performed with the use of Snellen charts (Fig. 1) or ETDRS charts (Fig. 2).

Figure 1. Visual acuity panel with Snellen optotypes.

Figure 2. ETDRS chart.

ETDRS charts were developed for research purposes of clinical studies on diabetic retinopathy, which required this procedure to be standardized[1]. They can be reported as a fraction (as with Snellen charts) or as a logMAR value, where 0 corresponds to a visual acuity of 1.0 (for example, a value of 0.3 corresponds to 0.5 on the Snellen scale). The logarithmic scale of visual acuity testing is used in clinical research because the resulting BCVA values given in logMAR can be calculated and averaged mathematically, which is not correct with fractions from Snellen charts.

A characteristic feature of ETDRS charts is that each line contains the same number of letters – five. Therefore the ETDRS chart can provide the BCVA letter score, which is the most common form of analysing changes in visual acuity in clinical trials[2]. Letter score testing is a separate, rather lengthy procedure and this tends to be performed for the purposes of research rather than in daily medical practice. The relationships between the BCVA values of the Snellen scale, logMAR and letter score are shown in Table 1.

Any decrease in BCVA in a patient with DR calls for further diagnosis. Changes in BCVA may indicate the progression of diabetic maculopathy (DME), including the development of macular ischemia. The progressive deterioration of vision in diabetic patients may also be caused by lens opacity, or cataracts. In diabetes mellitus

Table 1. Relationships between best corrected visual acuity (BCVA) values in Snellen fractions, LogMAR scale, and ETDRS letter score.

Snellen fraction	LogMar scale	ETDRS letter score
20/800	1.6	5
20/640	1.5	10
20/500	1.4	15
20/400	1.3	20
20/320	1.2	25
20/250	1.1	30
20/200	1.0	35
20/160	0.9	40
20/125	0.8	45
20/100	0.7	50
20/80	0.6	55
20/63	0.5	60
20/50	0.4	65
20/40	0.3	70
20/32	0.2	75
20/25	0.1	80
20/20	0.0	85
20/15	-0.1	90
20/12	-0.2	95

(DM) patients, cataracts develop approximately 10–15 years earlier than in the healthy elderly population.

A change in BCVA is especially significant for patients undergoing certain therapies, such as retinal laser therapy or intravitreal injections. A decrease in visual acuity after retinal laser photocoagulation may be related to the increase in macular edema or vitreous hemorrhage, and less often to accidental damage caused to the fovea during the procedure[3]. In the case of treatment involving intravitreal injections, a significant decrease in visual acuity may indicate a complication in the form of intraocular inflammation. This serious condition must be urgently treated in the ophthalmology department.

The most common causes of visual impairment in patients with diabetes

- significant macular edema,
- epiretinal membranes,
- ischemic maculopathy,
- cataracts,
- vitreous hemorrhage – an emergency,
- an acute angle-closure glaucoma (in the course of secondary neovascular glaucoma) – an emergency,
- retinal detachment (in advanced proliferative diabetic retinopathy) – an emergency,
- complication related to ongoing therapy (macular damage in the course of laser photocoagulation, intraocular inflammation in the case of intravitreal injections) – an emergency.

Practical remarks

Visual acuity testing alone is not a sufficient measure of DR progression.

Despite the absence of deterioration of central vision, patients with DR need regular ophthalmologic follow-up.

Attention should also be paid to situations in which the patient has normal visual acuity but develops advanced retinopathy. This most often occurs in young patients with type 1 diabetes (DM1)[4]. It is possible that in such cases the macula has not been damaged, but areas of ischemia and vascular proliferation develop on the periphery of the retina.

Consequently, regular ophthalmic consultations are necessary for diabetic patients, even if there are no

Figure 3. Non-contact "air puff" tonometer.

Figure 4. Handheld applanation tonometer (Tono-pen).

signs of visual deterioration. In such cases, the role of diabetologists and general practitioners is crucial as they should refer their patients to an ophthalmologist. Since they do not experience any deterioration of vision, diabetes patients often disregard such indications, and this significantly delays the start of ophthalmic treatment.

Tonometry

Tonometry is a test that measures intraocular pressure. Such measurements are made with tonometers (Figs. 3 and 4). Nowadays, non-contact "air puff" tonometers are usually used. Increased intraocular pressure tends to indicate glaucoma. Although tonometry is a standard examination used with all ophthalmic patients, it is particularly important for DR patients. Proliferative diabetic retinopathy (PDR) may be accompanied by the development of neovascular glaucoma[5] (see Chapter 12: *Ophthalmic conditions associated with diabetic retinopathy*, pp. 220–226). It leads to the proliferation of vessels in the iridocorneal angle, followed by iris neovascularization. In patients with an early diagnosis of neovascular glaucoma, prompt panretinal photocoagulation can be effective, sometimes in combination with anti-VEGF therapy.

In patients who fail to comply with recommendations and who do not attend regular ophthalmic consultations, increased intraocular pressure may be the first sign of PDR. In addition, it should be borne in mind that, according to some results from clinical studies, open-angle glaucoma is statistically more frequent in patients with diabetes than in the healthy population[6, 7].

Slit-lamp examination of the anterior segment

Anterior segment examination is a component of basic ophthalmologic examination (Fig. 5). In diabetes, the most common changes affect the iris and the lens. Advanced DR with significant ischemia may result in iris neovascularization, or rubeosis iridis. Additionally, neovascularization can be observed in the iridocorneal angle with the use of a gonioscope. Both of these signs indicate the need for panretinal laser photocoagulation, sometimes combined with anti-VEGF intravitreal therapy.

The second important anatomical element examined in diabetes is the lens. In diabetes, it is not uncommon to have secondary cataract, associated with a different lens metabolism in the state of hyperglycemia. In patients with diabetes, cataracts occur much earlier than in the healthy population[8, 9]. This condition often affects very young people with DM1[10].

Figure 5. Slit-lamp examination. An image of the anterior segment of the eye is visible on the display.

Figure 6. Slit-lamp fundus examination with a Volk lens.

The presence of a cataract not only causes vision impairment but also makes fundus examination difficult and often prevents effective laser therapy. Cataract treatment is exclusively surgical.

Funduscopic examination

Funduscopic examination is a routine tool for diagnosing and monitoring patients with DR. If retinopathy is suspected, stereoscopic images should be taken when the pupils are dilated. The examination usually involves the use of a slit lamp and a +90D or +78D focusing lens (Volk lens, Fig. 6). In patients who have blepharospasm in reaction to the microscope light, the examination should be performed with a contact fundus lens – the same as that used for retinal laser therapy. Examination with a contact fundus lens is carried out under corneal anesthesia.

The fundus image should be analysed for the presence of macular edema and assessment of severity of retinopathy. A stereoscopic image is necessary for the examination of the macula, as this is the only way to detect retinal thickening[11]. Once this is confirmed, thorough morphological and quantitative assessment of the edema is recommended so the patient should be referred for further diagnostic tests, primarily for optical coherence tomography (OCT, see pp. 67–70).

The use of focusing lenses for fundus examination provides the opportunity to evaluate other regions on the periphery of the retina. The distal periphery can be best assessed with the fundus contact lens which is used for panretinal laser photocoagulation, because the examination angle of this lens is very

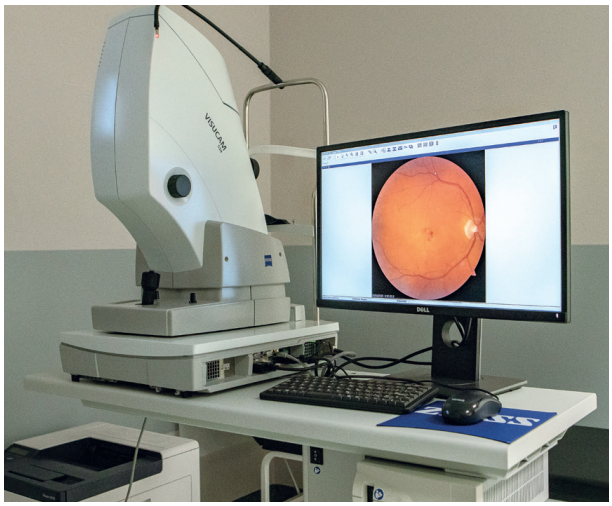


Figure 7. A fundus camera for taking fundus images and fluorescein angiography.

wide – usually 150–160 degrees. If there is doubt about the nature of the retinopathy (proliferative or not) or difficulty in assessing retinal vascular perfusion, the patient should be referred for fluorescein angiography of the fundus (Fig. 7).

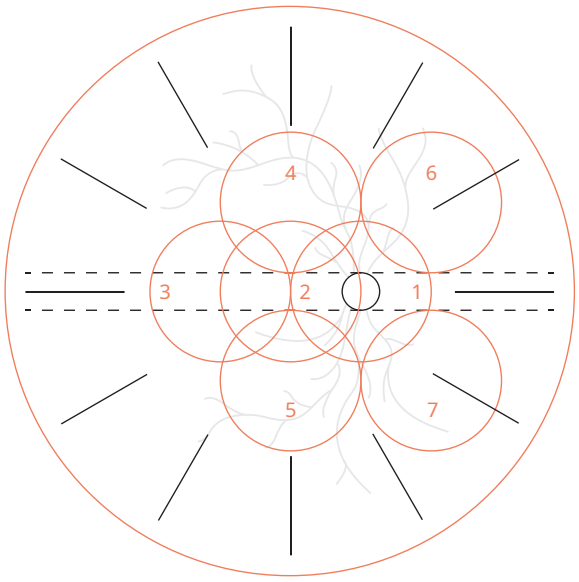
Fluorescein angiography

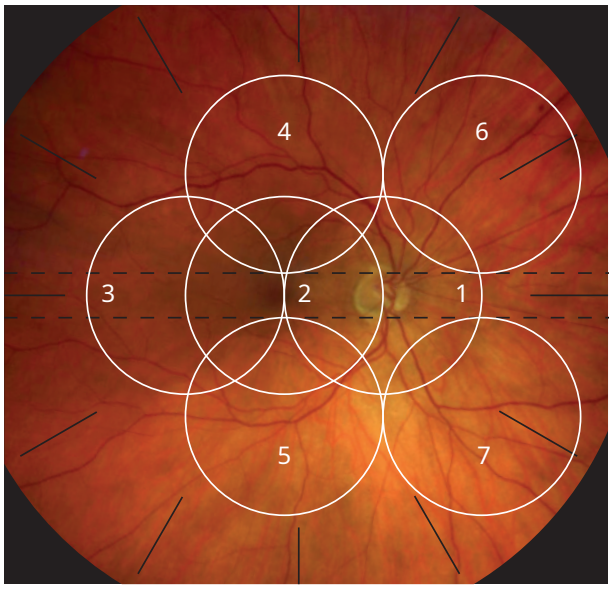
General remarks

Fluorescein angiography (FA) is one of the basic tools for the analysis of retinal and choroidal vascular pathologies. As in other angiographic examinations, i.e. vascular examinations, fluorescein angiography requires a contrast agent, in this case fluorescein[12].

FA involves the use of fluorescein sodium, which has a molecular weight of 376.67 Da. The characteristic feature of this substance is its ability to fluoresce, i.e. to emit light of a specific wavelength after stimulation with a light beam of a shorter wavelength. In the case of fluorescein, the absorption peak occurs at 465–490 nm (blue light) and the emission peak at 520–530 nm (green light)[13, 14].

Typically, 2.5–5 ml of 10% fluorescein solution is injected into the antecubital vein. Then about 60–80% of fluorescein combines with plasma proteins, mainly albumin. The remaining amount, called “free fluorescein”, can





Figures 8–9. The seven standard ETDRS fields used in the classification and diagnosis of diabetic retinopathy and their projection onto the fundus. Field 1 is centered on the optic nerve disc, Field 2 center is the foveola, and Field 3 is located in the temporal area of the macula. The radius of each standard field equals the distance between the center of the optic disc and the center of the fovea.

penetrate some anatomical barriers, especially in pathological states. The elimination of the dye takes 24 to 36 hours and takes place primarily through the kidneys.

The toxicity of the dye is low. The main side effects after administration include yellow skin and orange urine, which last for about one day. Nausea is less common. It occurs in about 10–15% of patients 30–60 seconds after intravenous administration of the dye. Mild allergic reactions (urticaria) are rare, and severe allergic reactions (anaphylaxis, cardiac arrest or bronchospasm) are very rarely reported[15]. FA is contraindicated in patients with a documented allergic reaction to fluorescein, patients with multifactorial allergic history, severe renal insufficiency and pregnant women[16].

Examination equipment and technique

Angiographic imaging uses a fundus camera for observing the fundus and the anterior segment of the eye in magnification, and digital image recording.

Filters, i.e. a blue excitation filter and a green barrier filter, are the essential elements of the device. During the examination, the fundus camera emits a flash which passes through the excitation filter and enters the eyeball. The light emitted by the excited fluorescein molecules returns to the device, passes through a green barrier filter and is then recorded by a digital camera or a camcorder.

The first images usually appear 10 to 15 seconds after the contrast agent is administered. During the early phases, images are taken every second, and later at a slower frequency. Images should be taken in all retinal sectors, in accordance with the ETDRS recommendations (Figs. 8–9).

The benefits of fluorescein angiography in the diagnosis of diabetic retinopathy

FA can be used to:

1. determine the type of diabetic retinopathy[17];
2. locate the neovascularization foci and assess their area to potentially refer the patient for panretinal laser photocoagulation (in some situations it is difficult to detect neovascularization in funduscopic examination, particularly in the case of neovascularization located outside the optic disc (NVE); FA facilitates such a diagnosis and the patient's qualification for laser therapy);
3. locate the areas of hypoperfusion, mainly in the periphery of the retina to identify patients potentially at risk of developing PDR and qualify them for laser therapy[18];
4. assess the severity and nature of macular edema, in particular distinguish focal and diffuse edema;
5. locate leaking microaneurysms in the perspective of focal or GRID laser therapy[19, 20];
6. identify and assess macular ischemia (by detecting the foveal avascular zone (FAZ) enlargement)[21];
7. identify iris neovascularization, especially if it is dark brown[22].

A normal fluorescein angiography and the basis for its interpretation

A properly performed fluorescein angiography should record six phases[23]. They are presented in Figure 10 and described below:

1. The pre-arterial (choroidal flush) phase – a very short phase (lasting about one second) when fluorescein reaches the choroidal circulation. Fluorescein leakage from the choriocapillaries prevents accurate visualization of the choroidal vessels. It is, however, possible to visualize the lobular structure of the choroid – its irregular filling in the form of hyper- and hypofluorescence patches. From this moment on, we can observe the superimposed image of choroidal and retinal fluorescein circulation. The fluorescence from the choroid is referred to as background fluorescence. The intensity of fluorescence decreases after the intermediate phase of angiography.
2. The arterial phase – from the moment when dye appears in the arteries until the arteries are completely filled.
3. The arteriovenous phase – complete filling of the arteries and laminar flow in the veins; in this phase,

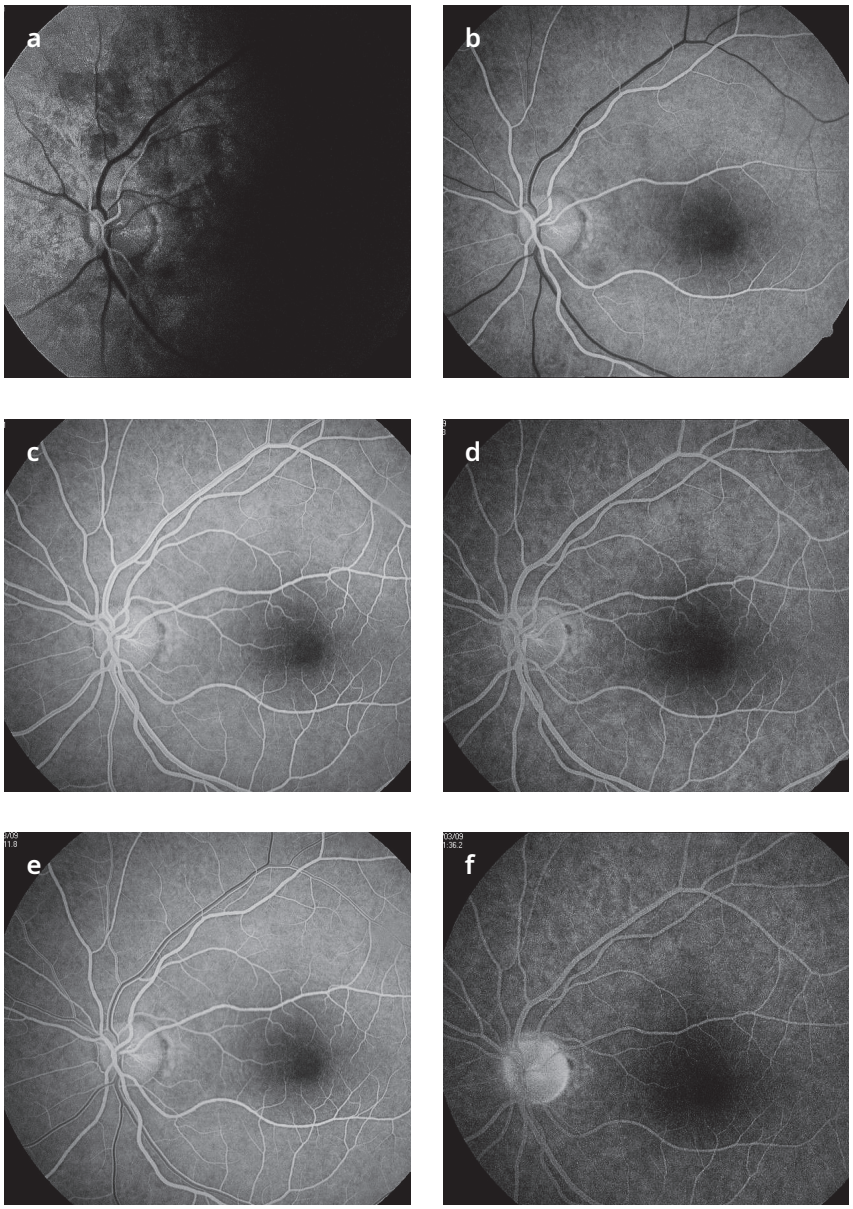


Figure 10. Phases of Fluorescein Angiography:
a. the pre-arterial phase,
b. arterial phase,
c. arteriovenous phase,
d. venous phase,
e. recirculation phase,
f. late phase.

the network of peripapillary capillaries and the network of capillaries around the FAZ are visible.

4. The venous phase – lasts about 10–15 seconds on average: from the moment of laminar flow in the veins to the moment of complete filling of veins and the fading of the contrast agent in the arteries.
5. The recirculation phase – starts about one minute after contrast administration. A gradual weakening of the fluorescence is observed. In this phase, background fluorescence from the deeper layers of the choroid and sclera visibly fades, and the optic disc is hyperfluorescent.
6. Late phase – is noted after 20–30 minutes of contrast administration. Very weak background fluorescence is visible, and choroidal vessels are visible as shadows. There is a distinct hyperfluorescence of the nerve disc.

The main signs observed in FA:

1. hyperfluorescence – an increase in the intensity of fluorescence;
2. hypofluorescence – a decrease in the intensity of fluorescence;
3. a window defect, resulting from atrophy of the

retinal pigment epithelial cells (RPE) and/or their thinning, which causes increased intensity of choroidal fluorescence (background fluorescence); it has the following characteristic features:
   a. it is visible as an area of hyperfluorescence,
   b. its margins are well-defined and static in all phases of the angiogram,
   c. fluorescence intensity at the defect site decreases over time;
4. leakage – occurs when the outer or inner blood-retinal barrier is broken (leakage to a specific anatomical region is referred to as pooling, for example in RPE detachment); it has the following characteristic features:
   a. it is visible as an poorly defined area of hyperfluorescence,
   b. the area of hyperfluorescence distinctly increases over time,
   c. the intensity of hyperfluorescence in this area distinctly increases over time;
5. staining – occurs when fluorescein penetrates the tissues; it has the following characteristic features:
   a. it is visible as an area of hyperfluorescence,
   b. the intensity of the hyperfluorescence increases slightly over time,
   c. the boundaries of the lesion are usually blurred and may slightly increase over time, while maintaining the same shape;
6. a filling defect – occurs as a result of a defect in the vascular filling, for example in embolism or thrombosis of the retinal vessels; it has the following characteristic features:
   a. it is visible as an area of hypofluorescence,
   b. a visible delay in the vessels filling in the area, or no filling occurs
7. a blocked fluorescence – an area of hypofluorescence due to the formation of a physical barrier between the area of fluorescence and the fundus camera (for example, blood, exudates, pigment or intraocular foreign bodies etc.); it has the following characteristic features:
   a. it is visible as an area of mostly uniform hypofluorescence,
   b. static and distinct margins correspond to the lesion margins that are visible in an ophthalmoscopic examination.

Fluorescein angiography and lesions typical for diabetic retinopathy

Fluorescein angiography allows the visualization of lesions typical for all stages of DR.

1. Microaneurysms (Fig. 11) – in FA, they are visible as punctate foci of hyperfluorescence. Angiography usually reveals a larger number of such lesions than ophthalmoscopy and OCTA. Microaneurysms can leak, which, however, is not inevitable. Microaneurysm leakage manifests in the late phase of the angiogram as retinal edema or staining.
2. Dot and blot or flame hemorrhages (Fig. 12) – in FA, they are visible as areas of hypofluorescence (a blocked fluorescence).
3. Hard exudates (Fig. 12) – in FA they cause moderate blockage of background fluorescence, i.e. exhibit hypofluorescence. The choroidal pattern is blurred, and the intensity of hypofluorescence is not as high as in the case of hemorrhages.
4. Cotton wool spots (CWSs) (Fig. 12) – as areas of hypoperfusion are hypofluorescent. There is no capillary perfusion in such areas.
5. Venous anomalies (Fig. 13) (beading, constrictions, dilations, reduplications, loops) – are sometimes more distinct in FA, although they should be detected in routine ophthalmoscopy.
6. Areas of hypoperfusion (Fig. 14) – in FA, these are visible as hypofluorescent areas without capillary perfusion. Angiography makes it possible to assess their localization and extent, thus clarifying the risk of retinopathy progression.
7. Areas of neovascularization (Figs. 14–15) – in FA are seen as spots of intense leakage, which increase over time.

   In the case of neovascularization at the disc (NVD), it is possible to detect early changes, visible as a small area of hyperfluorescence in the center of the disc. In contrast, neovascularization

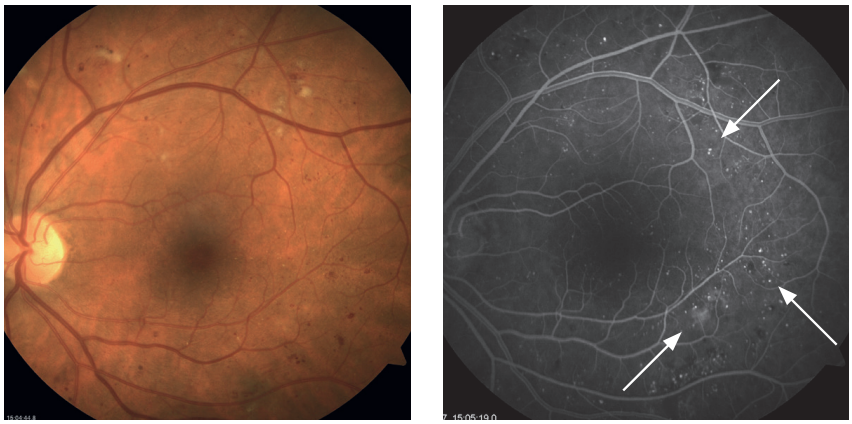


Figure 11. Mild non-proliferative diabetic retinopathy. The angiographic image shows multiple punctate foci of hyperfluorescence corresponding to microaneurysms (indicated by arrows).

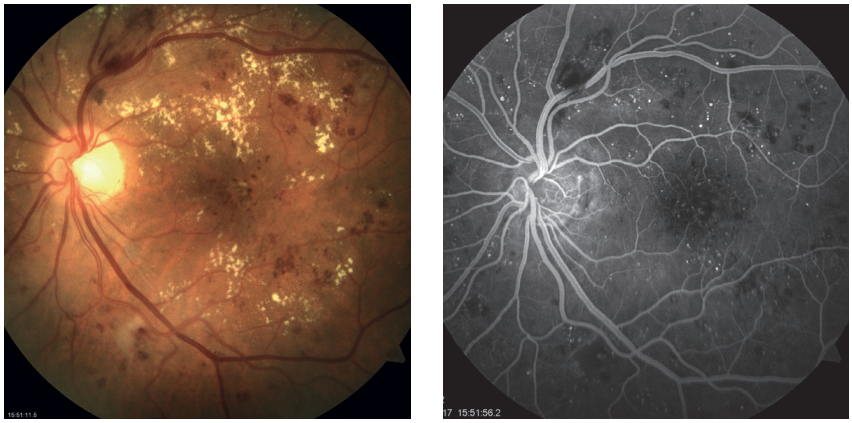


Figure 12. Severe non-proliferative diabetic retinopathy. Multiple dot and blot hemorrhages (blocking fluorescence), hard exudates in the macular area (weak background fluorescence in their projection) and cotton wool spots outside the macular center (impaired capillary perfusion in their projection).

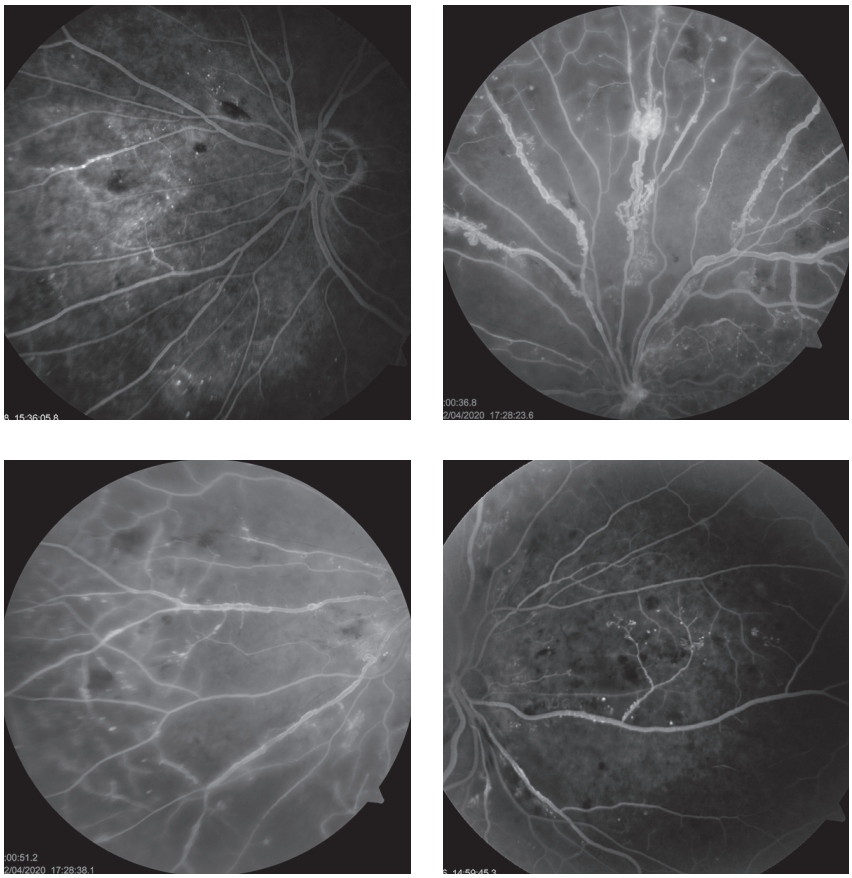


Figure 13. Retinal venous anomalies: venous dilations, constrictions and beading, associated areas lacking capillary perfusion, and intraretinal microvascular abnormalities.

elsewhere (NVE) may not be detected in routine ophthalmoscopic examination. In FA, we obtain evidence of a clear leakage presenting as an area of hyperfluorescence, so diagnosis is more straightforward.

8. Iris neovascularization (Fig. 16) – usually seen in slit-lamp anterior segment examination, does not require angiography. If there are diagnostic doubts (dark irises) FA can be helpful.

Wide-field fluorescein angiography

Wide-field or ultrawide-field angiography is a method that allows for capturing images of the retinal area up to 200 degrees (for comparison: classical angiography usually shows the retinal area in the range of 45 degrees, and obtaining a wider field of fundus examination requires the assembly of several images of the retinal periphery – see Fig. 17).

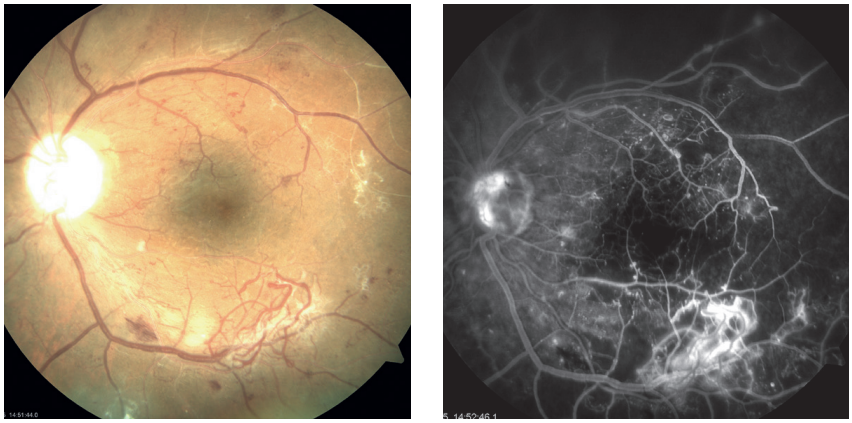


Figure 14. Advanced proliferative retinopathy. The colour photograph shows extensive vascular proliferation outside the optic nerve disc. The angiographic image reveals leakage from neovascularization at the disc and from extensive neovascularization elsewhere. Visible areas of hypoperfusion in the temporal retina and ischemic changes in the macula.

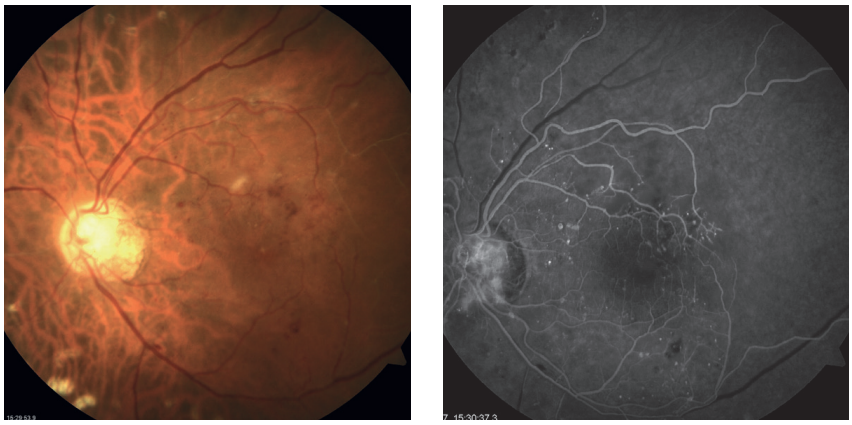


Figure 15. Proliferative retinopathy with neovascularization at the disc. The colour photograph shows pathological vessels on the disc. Fluorescein angiography confirms leakage from pathological vessels at its early stage.

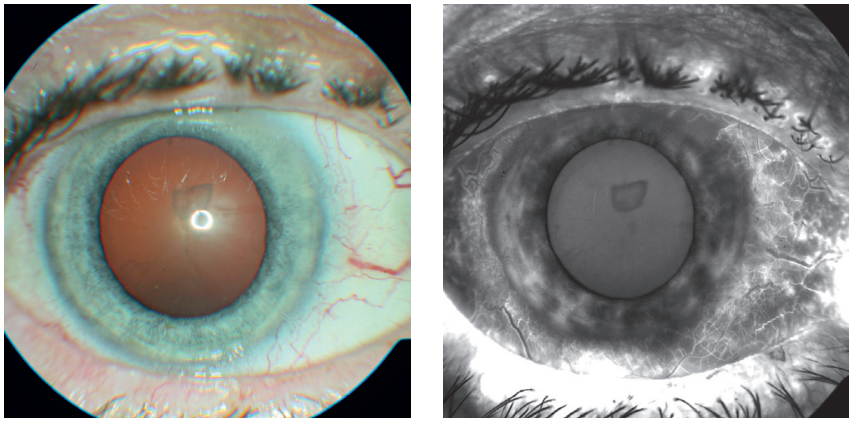


Figure 16. Iris neovascularization. The colour photograph shows a fine network of vessels on the surface of the iris. The angiographic image reveals intense leakage from these vessels.

This allows to image far peripheral regions of the retina (Fig. 18), the origin of vascular pathology in DR. It is possible to locate areas of hypoperfusion, arterio-venous anomalies or NVE that are not visible in classical angiography. DR diagnostics using wide-field angiography makes it possible to determine the stage of DR more accurately, and usually reveals changes indicative of more advanced DR[24, 25, 26]. In the case of examination with the use of classic fundus-camera within the seven retinal ETDRS fields, patients are more often classified as having more benign retinopathy.

Silva et al. have shown that the predominance of peripheral changes, demonstrated in an examination with a wide-field fundus camera, suggests a higher risk of DR progression[27]. In contrast, Wessel et al. found a correlation between the extent of peripheral areas of hypoperfusion diagnosed with wide-field fundus camera and the occurrence of diabetic macular edema (DME)[28].

In the future, the wide-field fundus camera may facilitate accurate evaluation of the severity of DR in screening programs for this condition[29, 30]. At present, however,

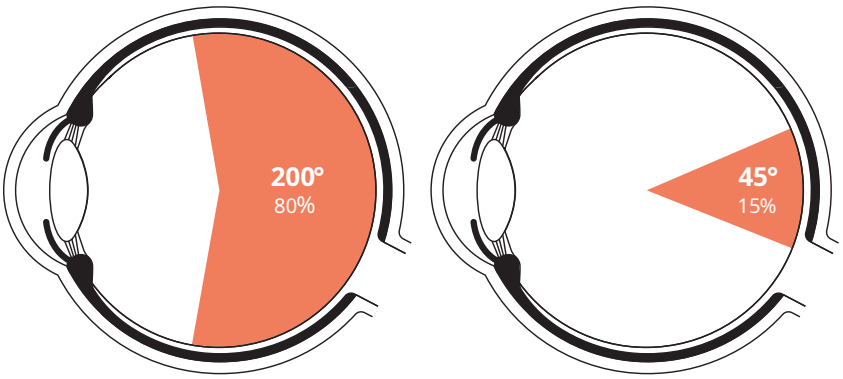


Figure 17. The range of the examination of a wide-field camera and a standard fundus camera.

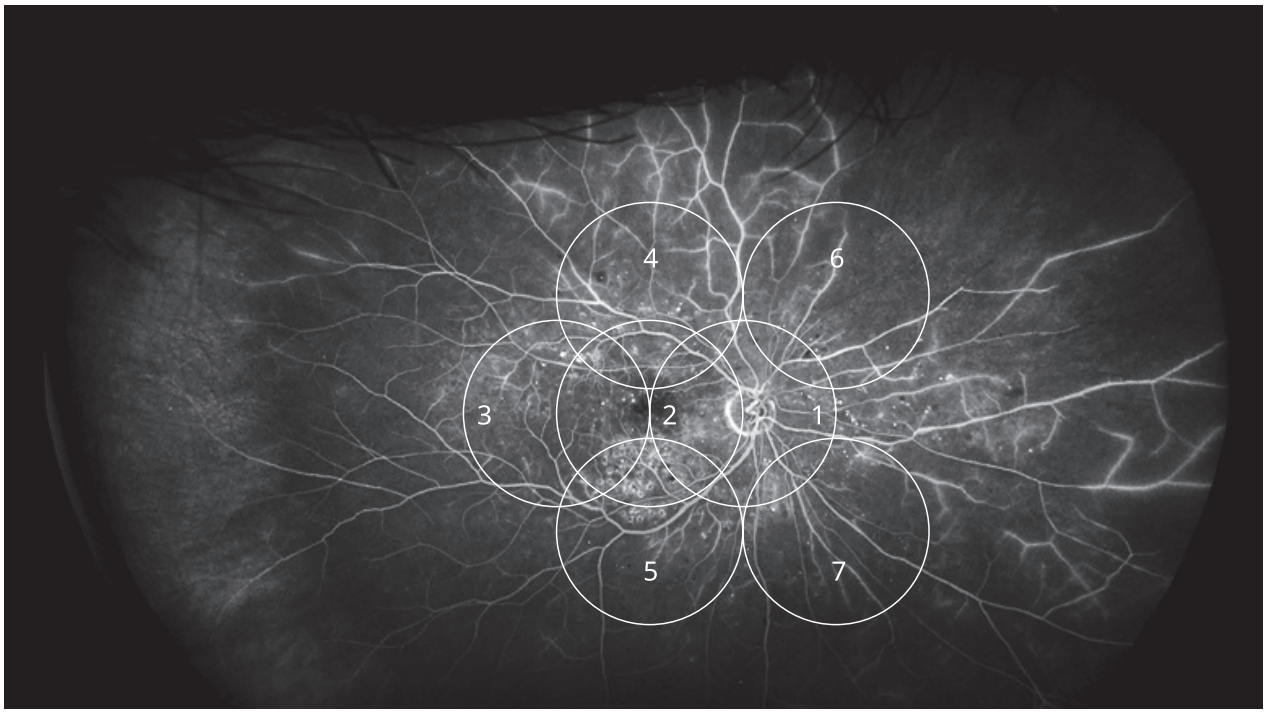


Figure 18. Projection of seven ETDRS fields onto the fundus as seen in the wide-field camera.

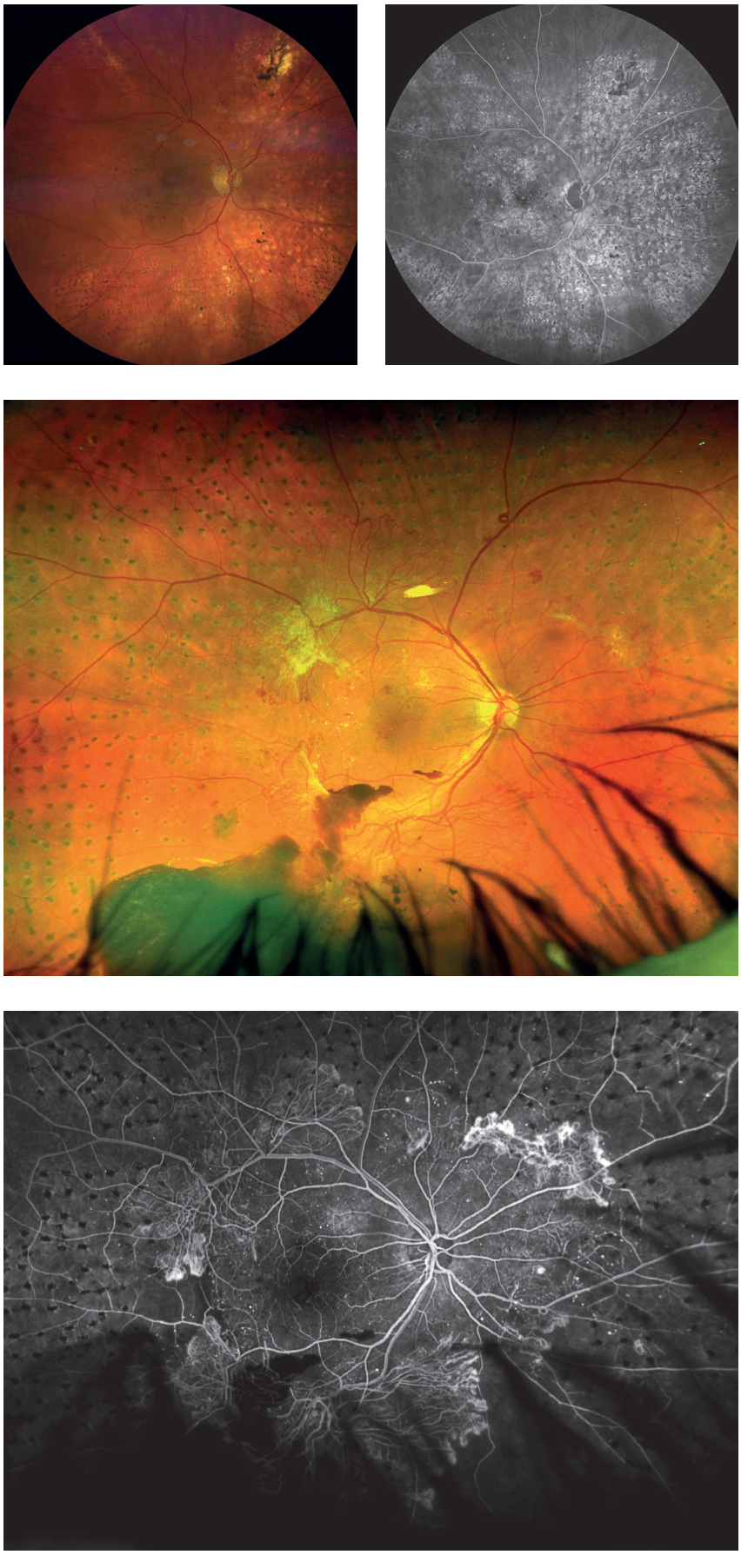


Figure 19. Examples of the use of wide-field imaging systems in the diagnosis of diabetic retinopathy (Clarus by Zeiss and California by Optos).

wide-field systems imaging (Fig. 19) is expensive, and it is hard to imagine their widespread use in ophthalmic clinics.

Optical coherence tomography

General remarks

Optical coherence tomography (OCT) of the retina resembles ultrasonography, with the difference that the scanning wave is electromagnetic[31]. OCT uses the principles of optical reflectometry and interferometry, where measurements are made of wave reflected from the biological tissues being imaged[32]. The measurements concern the time delay and amplitude of this wave.

The light emitted from the source (a superluminescent diode) has a wavelength of 820–860 nm (median 840 nm). It is divided into two beams: sample and reference. The portion of the examination beam that is reflected from the tissue at different depths is analysed in relation to the reference beam, using interferometry. This results in a simple A-scan. By moving the examination beam along the tissue, multiple A-scans are obtained, which can then be assembled into a B-scan image.

Today, two types of retinal tomography are most commonly used:

1. SD-OCT (spectral domain optical coherence tomography),
2. SS-OCT (swept-source optical coherence tomography using tunable lasers).

The first optical tomographs, based on time domain, analysed the interference of the broad light spectrum and scanned at rates as low as 400 cross sections per second. Nowadays, spectral retinal optical tomography (Fig. 20) is commonly used – the scanning speed is tens of thousands per second, or more[33]. These devices use a split beam of light (spectrum) for analysis, which is based on the use of the Fourier transform. The images obtained have high resolution and may be three-dimensional[34]. SD-OCT is therefore a much more accurate technique than older time-domain OCT[35].

In the case of SS-OCT, the wave frequency changes over time. Scanning is extremely fast, up to 100,000 scans per second[36, 37]. A longer wavelength spectrum (median 1050 nm) allows for scanning the tissues at a greater

Figure 20. Retinal Spectral Optical Tomograph using Optopol's Revo system.

Table 2. Retinal layer reflectivity table. The reflectivity of each layer is given sequentially, from the pigment epithelium to inside the eyeball.

Abbreviation	Layer	Reflectivity
RPE	retinal pigment epithelium	hyperreflective
IZ/COST	interdigitation zone/cone outer segment tips	hyperreflective
OS	photoreceptor outer segments	hyporeflective
EZ	ellipsoid zone	hyperreflective
MZ	myoid zone	hyporeflective
ELM	outer limiting membrane	hyperreflective
ONL	outer nuclear layer	hyporeflective
OPL	outer plexiform layer	hyperreflective
INL	inner nuclear layer	hyporeflective
IPL	inner plexiform layer	hyperreflective
GCL	ganglion cell layer	hyporeflective
NFL	nerve fiber layer	hyperreflective
ILM	internal limiting membrane	hyperreflective

depth. Consequently, high-resolution images of not only the retina but also the choroid can be obtained[38].

All OCT devices use artificial colouring of individual retinal layers. A normal image of retinal reflectivity with a description of individual layers is presented in Table 2 (see also Fig. 21–22).

A description of reflectivity of pathological alterations observed in the retina

Hyperreflective lesions:

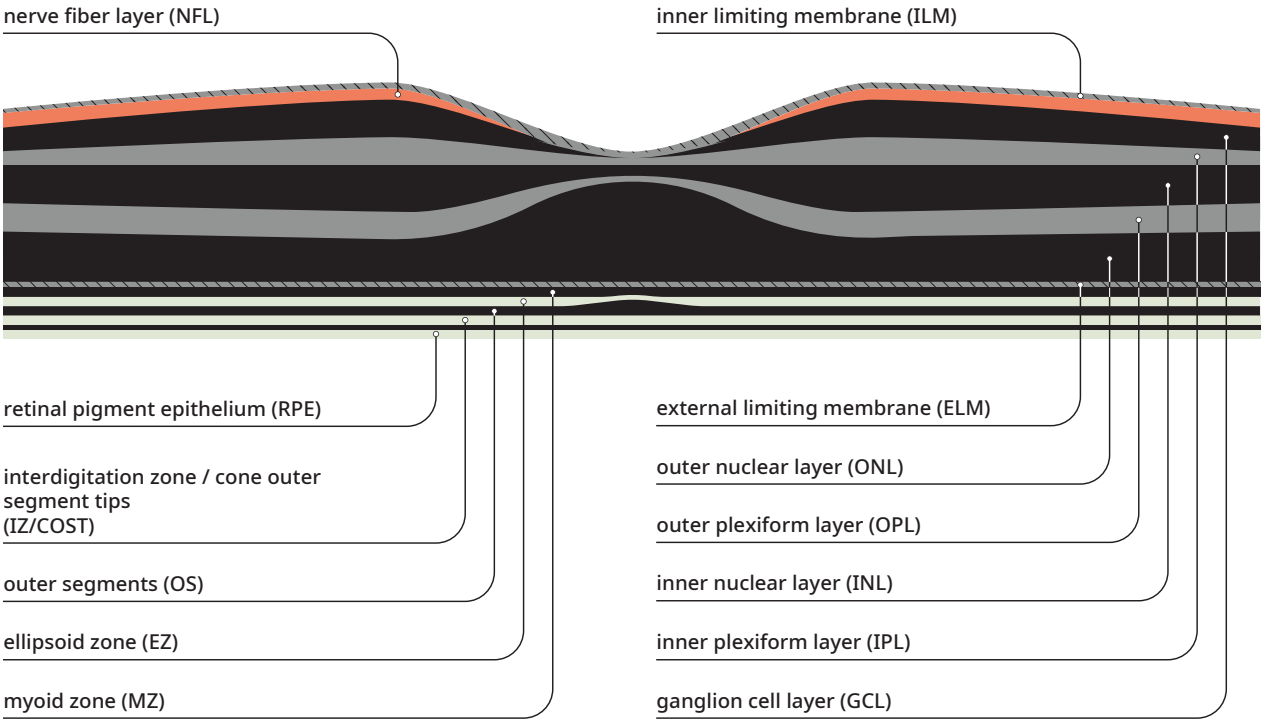
- deposits: drusen, lipofuscin, pigment, pigment clusters, naevi
- fibrous/glial structures: fibrosis, epiretinal membranes, disciform scars,
- vascular structures: microaneurysms, blood, vessels, neovascular membranes.

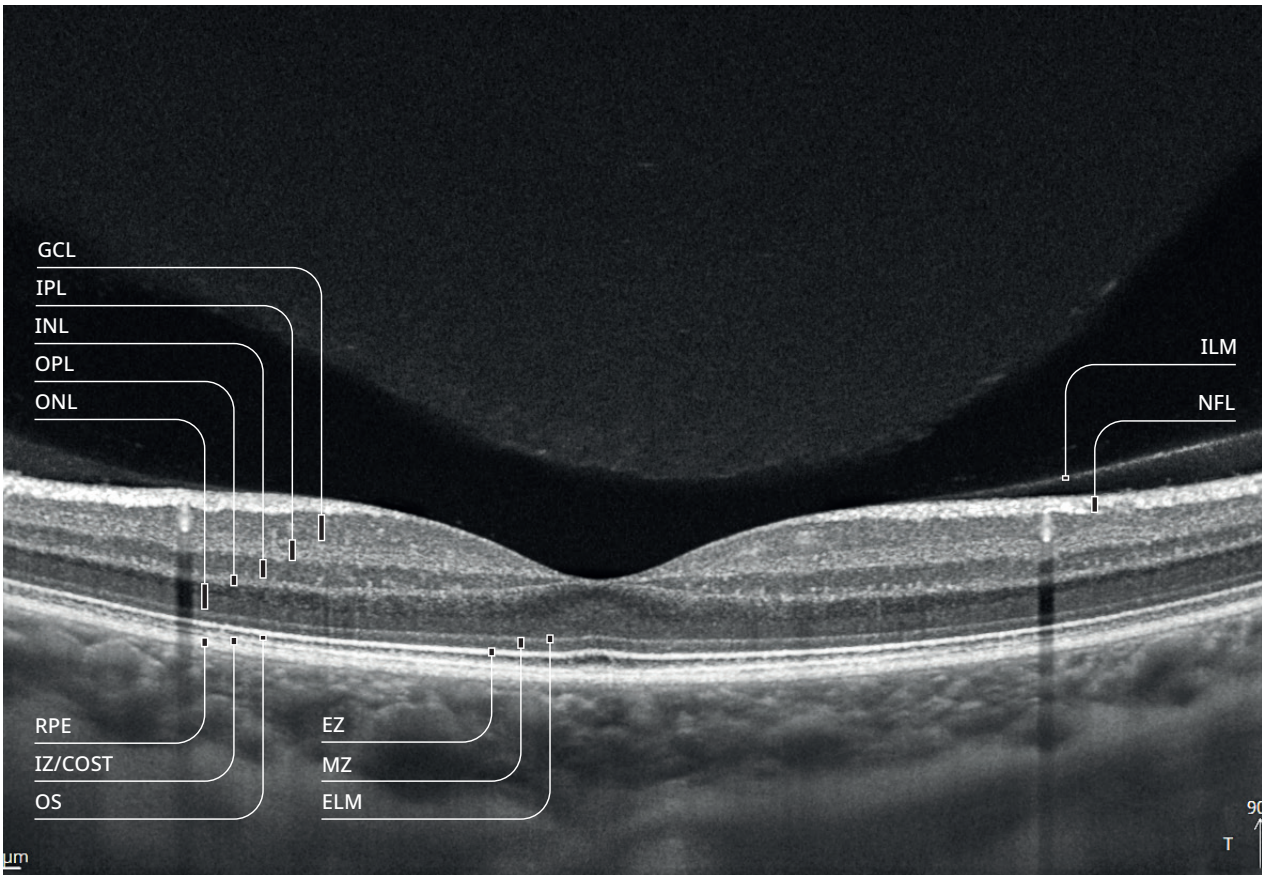
Hyporeflective lesions:

- fluid under RPE – RPE detachment, cysts, pseudocysts, edema.

The following terms are used to describe the SD-OCT scan:

1. hyperreflectivity – hyperreflective structures reflect more light than normal for a given area (examples: hard exudates, epiretinal membranes, pigment);
2. hyporeflectivity – hyporeflective structures reflect less light than normal for a given area (examples: cysts, pseudocysts, subretinal fluid);
3. optical shadow – caused by structures that absorb light more than surrounding tissues (pigment clusters, large vessels, hard exudates, opacities in vitreous body); these structures hinder visualization of the objects located beyond them;





Figures 21–22. A diagram of retinal layers and an image of a normal retina obtained by SD-OCT[39].

4. reverse shadowing – occurs when the transfer of light to deeper layers is facilitated; this applies to atrophy of tissue containing pigment (example: RPE atrophy and increased light penetration into the choroid).

The diagnostic features of OCT

1. Macular cube scan – scanning takes place in a specific area, usually 6×6 mm in the center of the macula. In this case, the scans are of lower resolution to enable faster scanning.
2. Line scans (cross line scans, raster scans) – groups of individual scans of a specific area of the retina. They have higher resolution due to their composition from a much larger number of A-scans than in the case of macular cube scan, and due to oversampling.
3. Retinal maps – it is possible to refer the actual retinal thickness to the normative database. Results are not always reliable, especially with certain conditions, such as myopia. Comparative analysis and tracking changes in retinal thickness over time are most reliable in such situations[40].
4. Retinal topographic maps – 2D maps derived from 3D analysis. They show changes in retinal thickness and areas of edema in a communicative way.

The use of OCT in the diagnosis of diabetic macular edema[41]

In the case of DME, OCT examination not only facilitates the diagnosis of the disease, but also makes it possible to make a qualitative and quantitative assessment of the edema, considering morphology and thickness, respectively, and to monitor the effectiveness of treatment (e.g. laser therapy or intravitreal therapy).

Morphological changes observed in DME on the SD-OCT exam[42]

- diffuse retinal thickening (sponge-like swelling without presence of cystoid spaces, loss of foveal depression),
- cystoid lesions, including classic cystoid macular edema,
- subretinal fluid (serous macular detachment),
- vitreoretinal tractions.

Figures 23–30 show the different types of morphological alterations characteristic of DME on SD-OCT scans.

Angio-OCT

General remarks

The technology used in angio-OCT (OCTA) utilizes the potential of spectral tomography scanning in the plane parallel to the RPE (en face). In addition to the advantages of classical spectral domain optical coherence tomography, the main advantage of such devices is capturing images of the retinal vessels without administering contrast[43]. The SSADA (split spectrum amplitude decorrelation angiography) technology used here identifies the vessels by detecting the movement of blood cells[44]. Multiple scans at the same location allow for the detection of changes in the received signal corresponding to the presence of vascular flow. OCTA actually assesses vascular flow, although the image obtained is a static recording of the flow at a given moment.

OCTA technology is still developing, especially in terms of quantitative assessment. Currently, two measurable OCTA parameters are most commonly reported: vessel density and the vascular flow coefficient or vascular flow area[45]. The vascular density parameter specifies the percentage of tissue volume occupied by vessels, and the flow coefficient indicates the average strength of the flow signal in a given volume[46]. The former index better reflects the pathology of the vessels themselves, whereas the latter reflects changes in tissue physiology and metabolism due to changes in vascular perfusion. Modern devices can also measure the flow area thus enabling the assessment of neovascular membrane size and monitor changes as the treatment progresses.

OCTA can be used to produce images of retinal capillary plexuses (Fig. 31) and assess the perfusion of

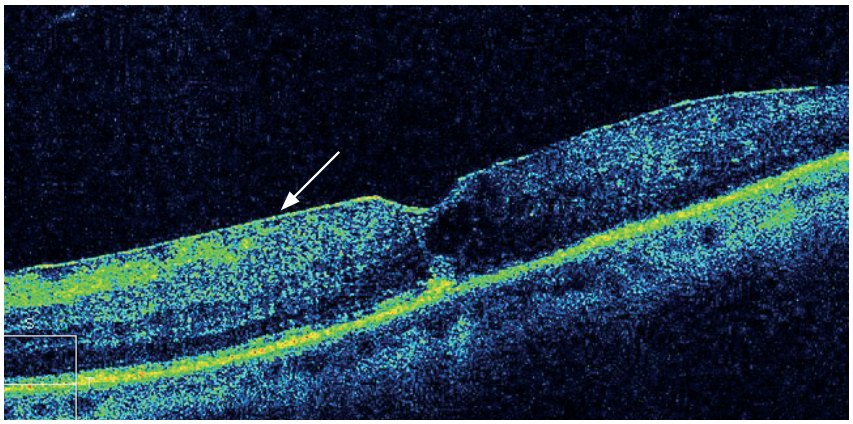


Figure 23. Diffuse retinal thickening with the epiretinal membrane present (indicated by the arrow). Visible sponginess of the sensory retina.

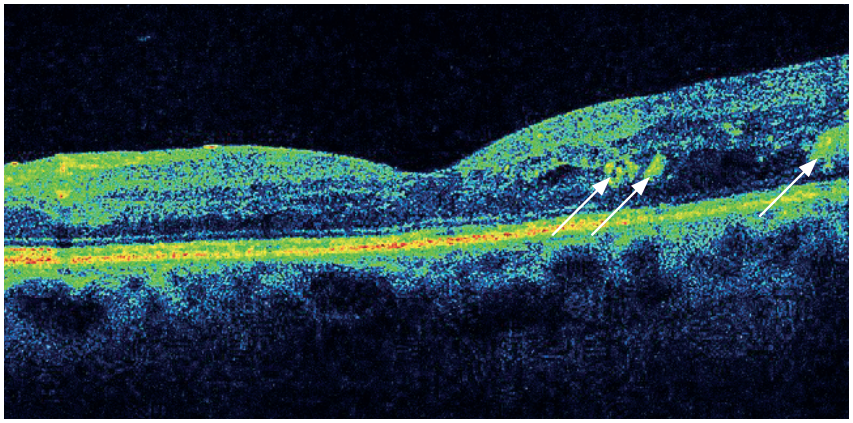


Figure 24. Diffuse retinal thickening and hard exudates – hyperreflective foci in the sensory retina (indicated by arrows).

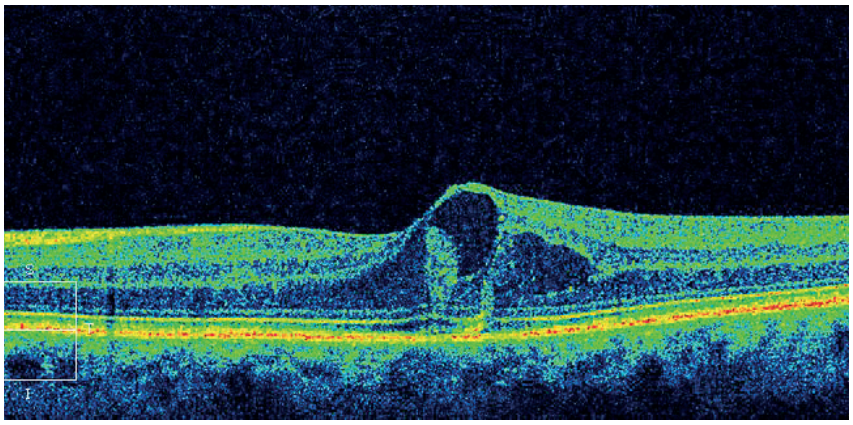


Figure 25. Cystoid macular edema. Numerous pseudocysts are visible in the sensory retina, including in the foveal area. Increase in the thickness of the central retina. Interestingly, despite significant swelling, the continuity of individual layers of the retina is maintained, which explains the relatively good BCVA.

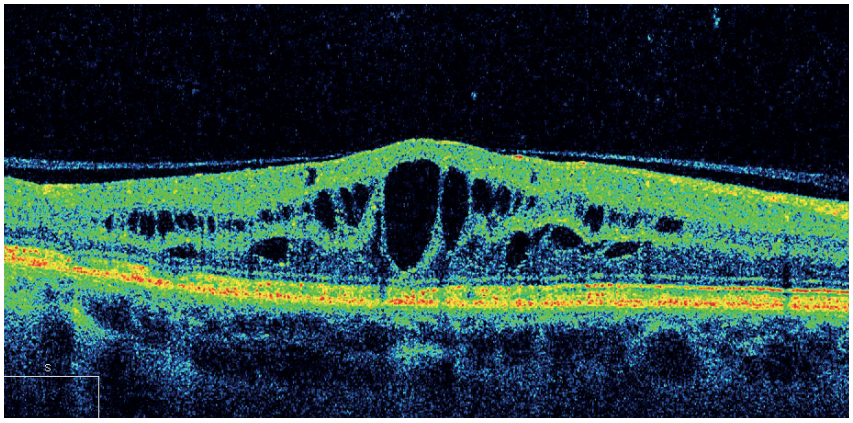


Figure 26. Classic central cystoid macular edema. Numerous cystoid spaces in the sensory retina are visible in the center of the macula. Disturbances in retinal architecture are more significant as compared to Figure 25.

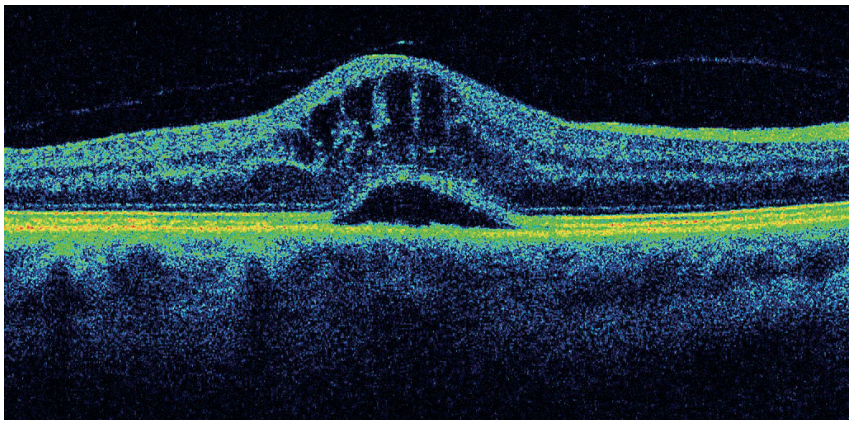


Figure 27. Cystoid macular edema with subretinal fluid present. Numerous cystic changes are visible in the sensory retina, and at the same time, there is fluid present between the retinal pigment epithelium layer and the sensory retina.

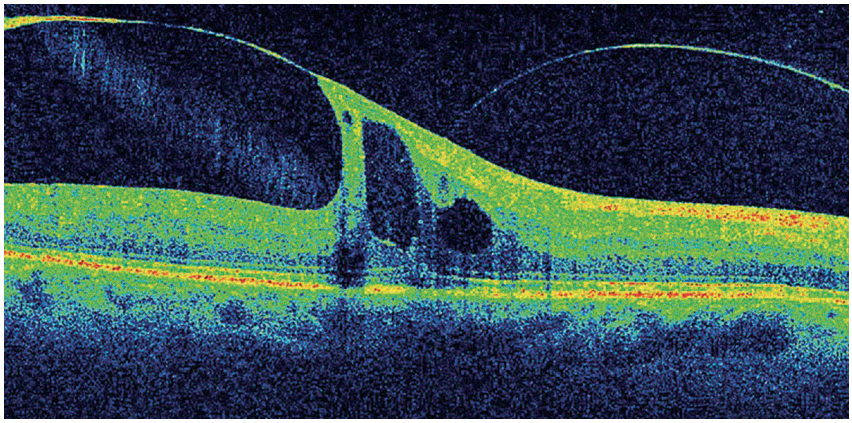


Figure 28. Cystoid lesions in diabetic macular edema with traction of the posterior vitreous surface due to the presence of the epiretinal membrane. There are large cysts in the sensory retina and defects in the photoreceptor layer.

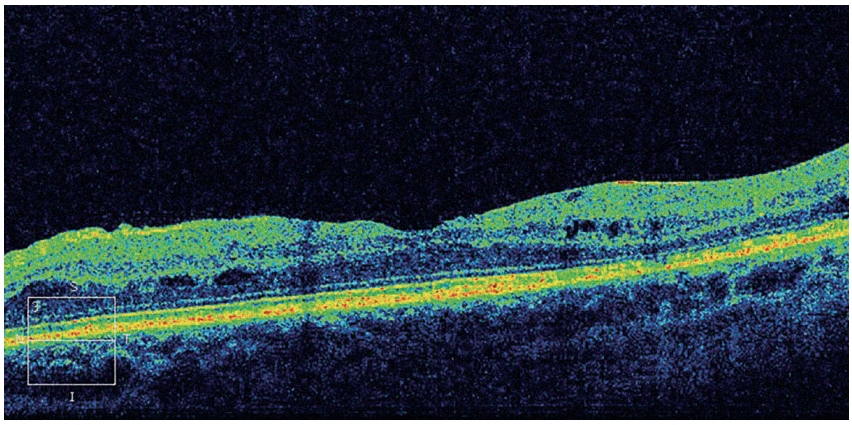


Figure 29. Post-edema retinal thinning. SD-OCT shows reduced thickness of all retinal layers. Pseudocysts are still visible in the sensory retina.

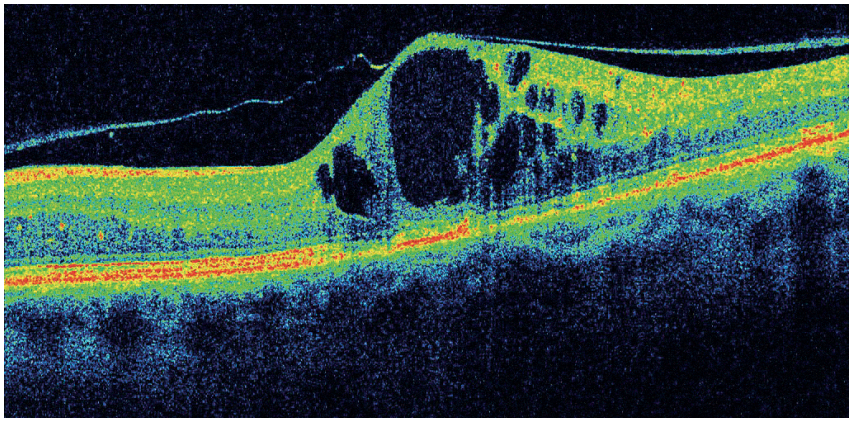


Figure 30. Long-term cystoid macular edema. Very large cysts are visible in the sensory retina, as are distinct defects in the photoreceptor layer – explaining the low visual acuity.

individual sectors of the posterior pole (Figs. 32–33). This applies especially to the diagnosis of capillary drop-out[48, 49] (Fig. 34–35). Grading retinopathy severity requires monitoring the effects of treatment and assessing disease progression. Researchers found a correlation between the size of FAZ area and the severity of DR itself[50, 51] (Fig. 36).

OCTA is also very helpful in the diagnosis of choroidal abnormalities, e.g. neovascular membranes, tumors, perfusion abnormalities in the choroid[52, 53]. Moreover, like classic OCT, it is non-invasive and therefore does not burden the patient with contrast administration.

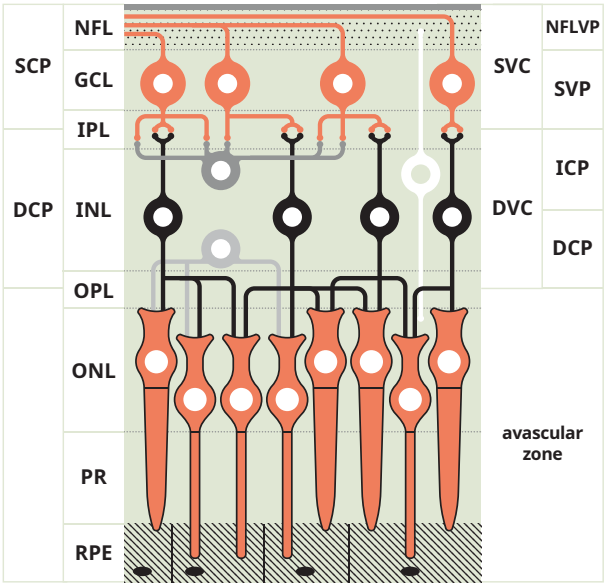


Figure 31. Diagram of the location of individual capillary plexuses in the retina and the extent of vascularization. On the right, proposed new terminology for retinal vascular plexuses[47]. | The following terms are used: SCP – superficial capillary plexus, DCP – deep capillary plexus; NFL – nerve fiber layer, GCL – ganglion cell layer, IPL – inner plexiform layer, INL – inner plexiform layer, OPL – outer plexiform layer, ONL – outer nuclear layer, PR – photoreceptors, RPE – retinal pigment epithelium; SVC – superficial vascular complex, DVC – deep vascular complex, NFLVP – nerve fiber layer vascular plexus, SVP – superficial vascular plexus, ICP – intermediate capillary plexus

Vasculature imaged with OCTA (new terminology)

Superficial vascular complex (SVC):

- nerve fiber layer vascular plexus (NFLVP),
- superficial vascular plexus (SVP) in the ganglion cell layer (GCL) and in the inner plexiform layer (IPL).

Deep vascular complex (DVC):

- intermediate capillary plexus (ICP) in the inner part of the inner nuclear layer (INL) and in the inner plexiform layer (IPL),
- deep capillary plexus (DCP) mostly within the INL at the border with the outer plexiform layer (OPL).

Choroid: large vessels.

Choriocapillaries.

Use of OCTA in diagnosing diabetic retinopathy

OCTA examination allows:

1. the detection of vascular changes in patients with diabetes even before the onset of DR,
2. the precise visualization of ischemic areas (vascular anomalies, loops, capillary drop-out) and FAZ enlargement[54, 55],
3. monitoring FAZ surface area changes during intravitreal therapies,
4. the imaging of retinal neovascularization and intraretinal microvascular abnormalities (IRMA)[56].

The enlarged FAZ surface area and the size of non-perfusion areas observed in OCTA correlate with the severity of DR and the decrease in visual acuity[57, 58, 59]. Comparative studies of healthy subjects and patients with DR indicate a significantly larger FAZ area in DR patients. In addition, DR patients are reported to have a significantly lower density of retinal capillaries in its central part[58, 59].

The technology used in OCTA examinations, as well as its interpretation, is constantly changing and developing. Therefore, the assessment and interpretation of the obtained images is not always unambiguous. Currently, the main advantage of OCTA in DR is the imaging of ischemic areas, which is especially important in the macular region. At the moment, however,

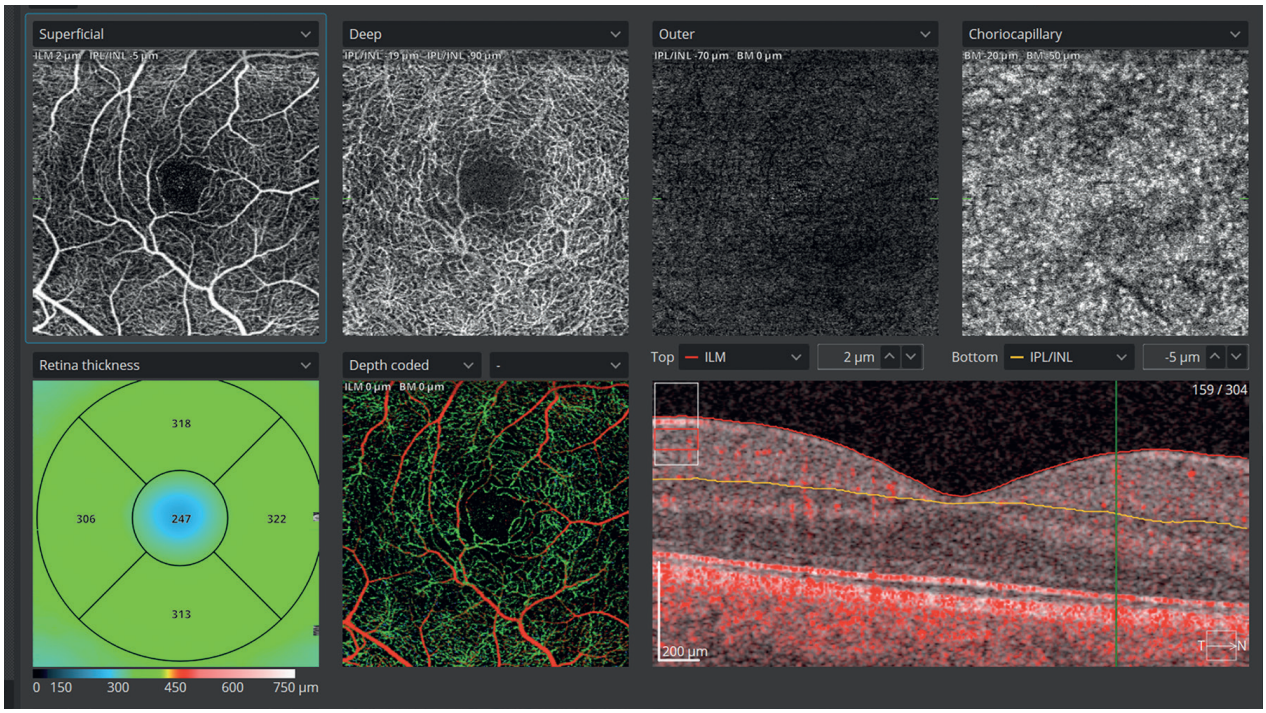


Figure 32. An image from a normal OCTA examination using Optopol's Revo device. The consecutive images in the top row show the vascular signal from each layer of segmentation: superficial plexus, deep plexus, outer retina, and choriocapillaries. The bottom row includes a central retinal thickness map, a depth-encoded map, and a classic SD-OCT cross-sectional scan.

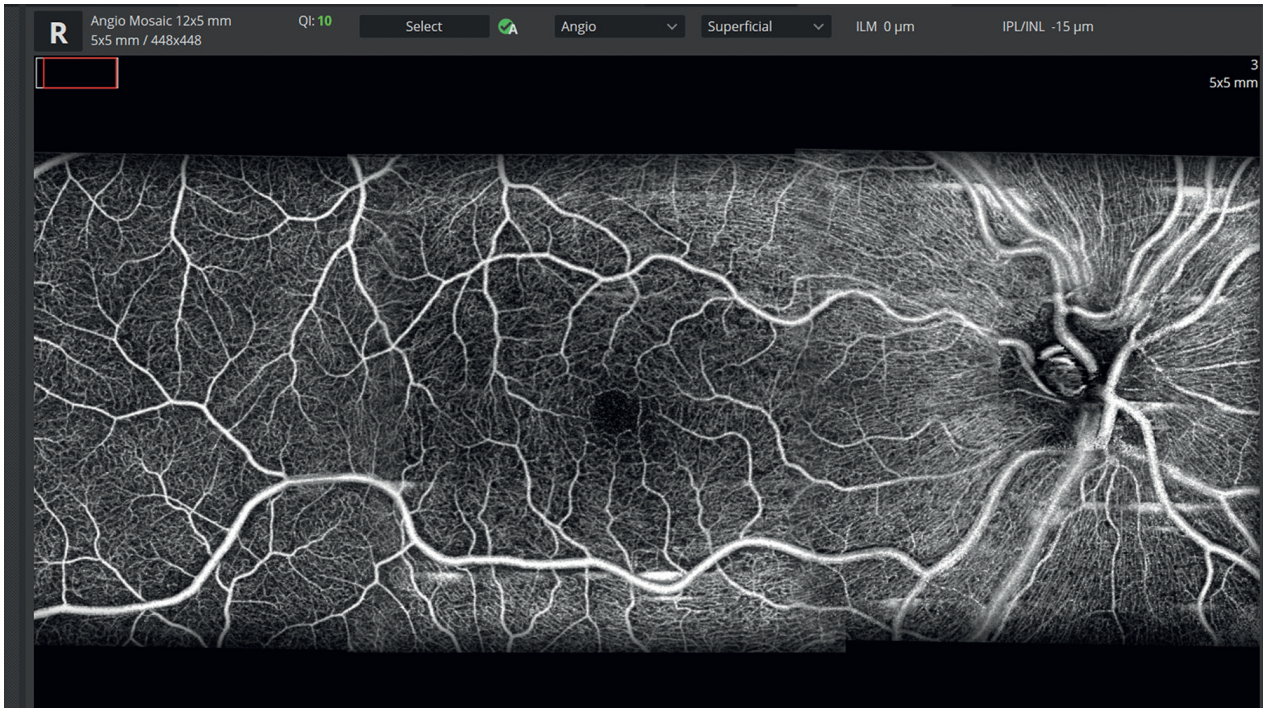


Figure 33. OCTA examination (Revo, Optopol) at the superficial capillary plexus level, mosaic mode.

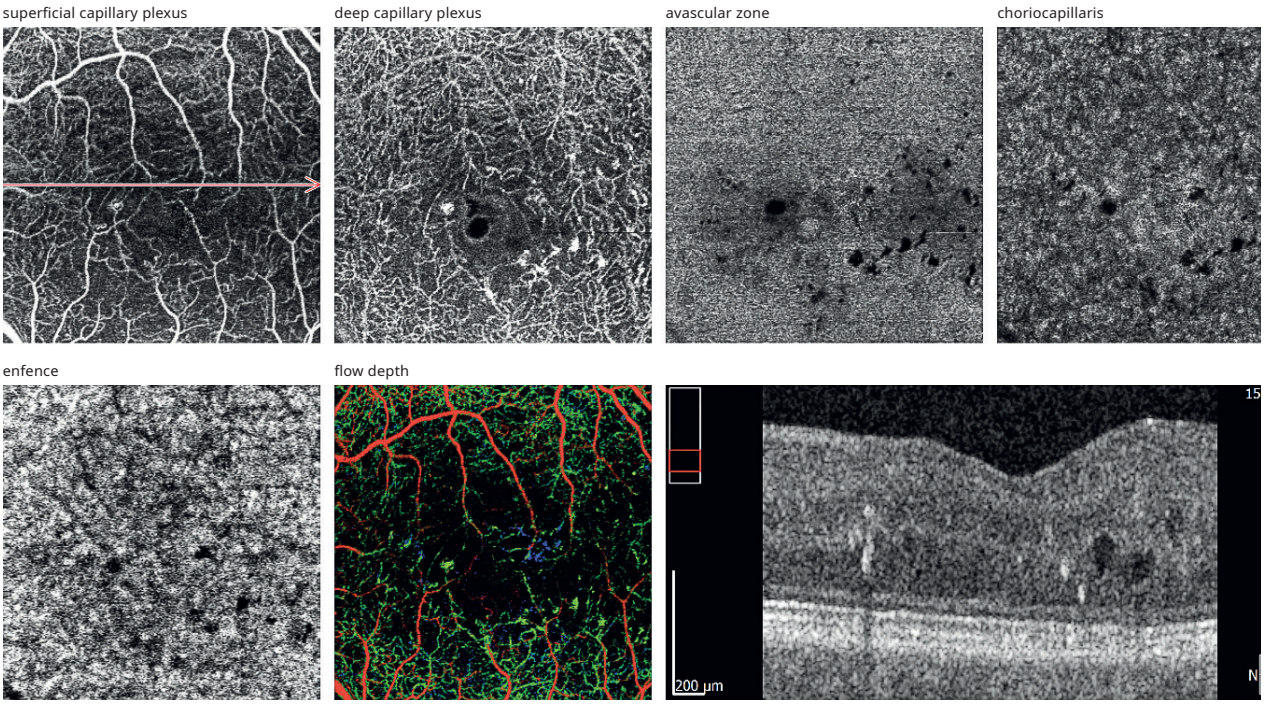


Figure 34. Diabetic macular edema in an OCTA examination (Revo, Optopol). The lesions are visible in the superficial and deep capillary plexuses – impaired perfusion, enlargement of the foveal avascular zone and numerous micro-aneurysms.

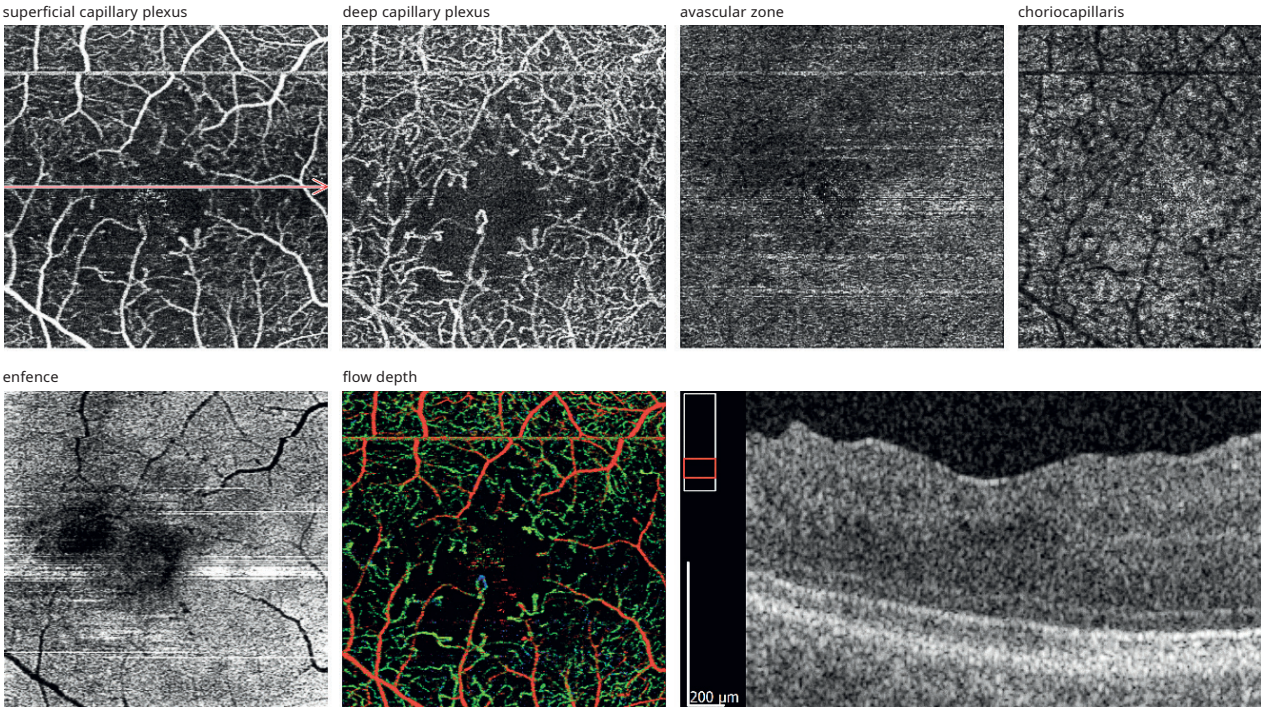


Figure 35. Significant macular ischemia in diabetic macular edema (Revo, Optopol). Superficial and deep capillary plexus images show a marked loss of capillary vessels and consequent widening of the foveal avascular zone.

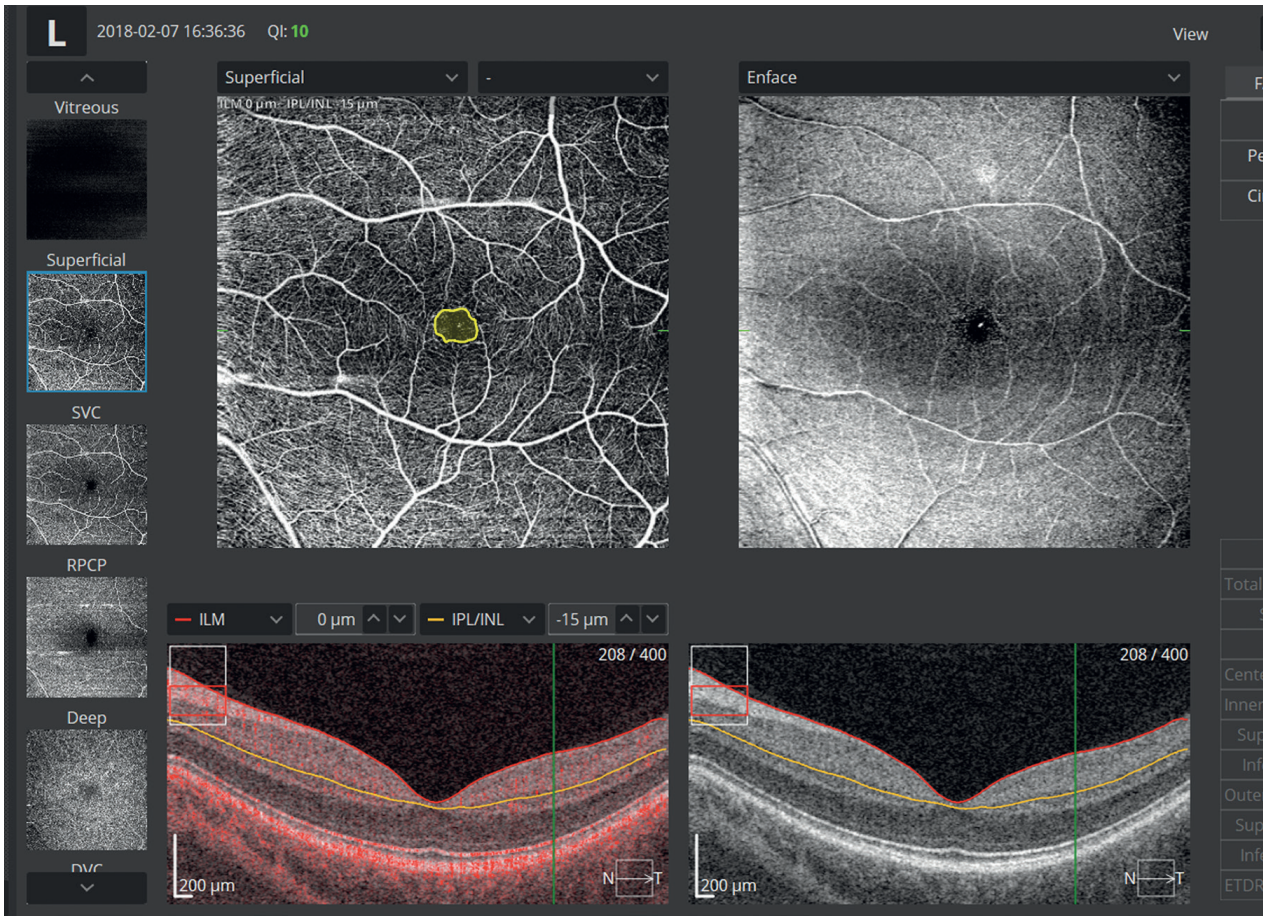


Figure 36. OCTA examination (Revo, Optopol) with automatic marking of the foveal avascular zone at the level of the superficial capillary plexus.

Table 3. Comparison of fluorescein angiography and angio-OCT capabilities.

Fluorescein angiography	Angio-OCT
dye and potential complications	no dye or complications
rather long examination	rapid examination
sign of leakage essential for interpretation	sign of leakage not present, evaluation of vascular structure, capillary drop-out
difficulty in evaluating the choroid	better assessment of the choroid
few artifacts	• numerous artifacts • difficulty in visualizing large vessels and deeper plexuses • small scanning area (work on wide-field SD-OCT systems is in progress) • complicated software

OCTA cannot completely replace fluorescein angiography, since the latter provides a more accurate assessment of retinal periphery, the extent of peripheral hypoperfusion, and the extent of peripheral neovascularization (Table 3).

Ultrasonography

General remarks

Ultrasonography (USG) involves using a beam of ultrasound for tissue assessment and measurement. The ultrasound beam, generated by a transducer, reflects off the tissue and is registered by the same transducer. Once the sound signal is converted into electrical impulses, the obtained data can be represented in a chart or a photographic image[60].

In ophthalmology, the eyeball is evaluated with the use of ultrasound probes of moderate and high frequency: 8–10 MHz, 20 MHz, 30 MHz or 50–100 MHz. High transducer frequency is necessary to obtain images with relatively good resolution. High frequencies are used, for example, in ultrasound biomicroscopy (UBM).

The examination is simple and non-invasive. It is performed by applying a probe to the eyelid with the coupling jelly for better acoustic transmission (Fig. 37).

Terms used in ultrasonography

Echogenicity (sometimes reflectivity):

- high: sclera, foreign bodies, bone, blood, lens opacity, detached retina, fibrous proliferations, optic disc drusen,
- low: vitreous body, transparent lens.

Two types of scans are obtained in ultrasound examination:

1. A-scans are obtained with a single ultrasound source. A one-dimensional plot of amplitude versus time shows the echogenicity of structures in the path of the transducer beam – the height of the individual amplitudes is proportional to the strength of the echo. It allows precise measurements within the eyeball, e.g. the length of the eyeball, anterior chamber depth, size of intraocular lesions (tumors).
2. B-scans are obtained with a vector transducer (one sound source makes oscillating movements) or a linear transducer (multiple sound sources covering a specific area). The examination is performed in the vertical and horizontal planes, at different probe positions. As a result of the overlapping of the reflected waves, a two-dimensional image of a single cross-section of the eyeball is created; with a greater number of reflected waves the image is brighter – the tissue is highly echogenic. B-mode presentation enables the topographic localization of lesions within the eyeball.

The use of ultrasound in diagnosing diabetic retinopathy

In the diagnosis of diabetic retinopathy and its complications, ultrasound is used primarily in patients with opacity in the optical media[61]. It is used for the examination of the retina and vitreous body in the case of vitreous hemorrhage, the examination of fibrovascular proliferation (traction), and the diagnosis of tractional retinal detachment.

Figure 37. Ultrasound examination of the eyeball.

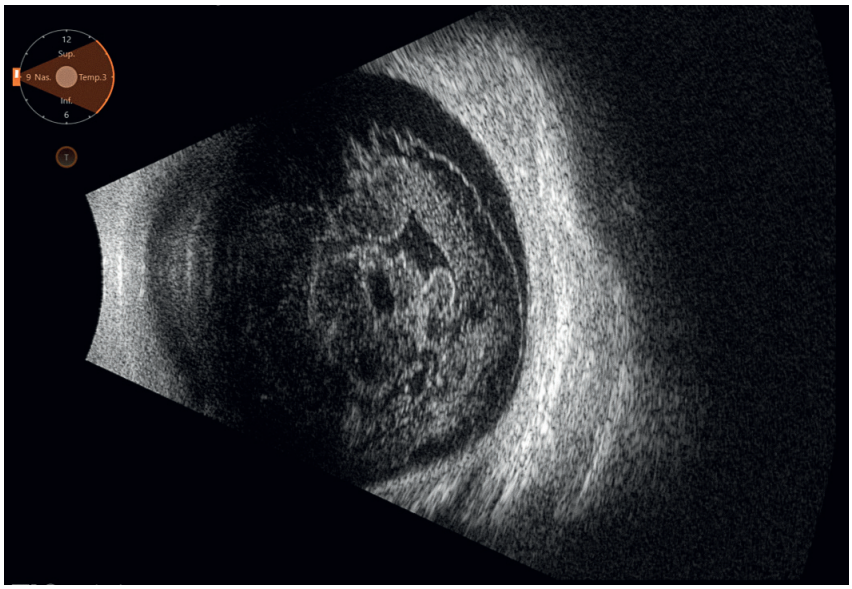


Figure 38. Vitreous hemorrhage with visible lacunas in the ultrasound examination of the eyeball.

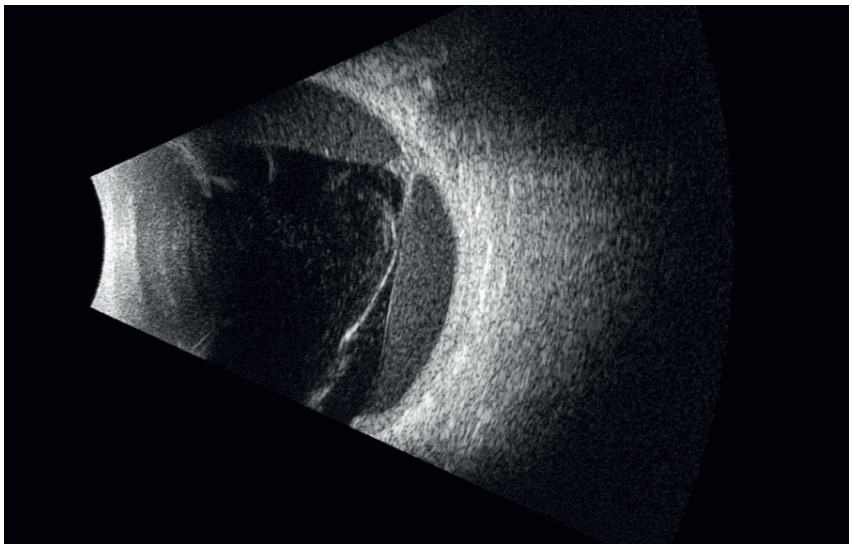


Figure 39. Vitreoretinal traction with pre-retinal hemorrhage visible in the ultrasound examination of the eyeball.

1. Examination of the vitreous body[62]:
   a. A normal vitreous body is hypoechoic, dark in B-scan presentation.
   b. Floaters in the vitreous body – visible as hyperechogenic foci in the vitreous chamber – which move with the movement of the eyeball. Regardless of their origin (age-related, hemorrhagic, inflammatory), they have a similar appearance, hence medical history is crucial. When examining floaters, the following are performed:
      - examination of the amount of floaters – important in monitoring the progression of intraocular inflammation, for instance,
      - dynamic examination – to ascertain whether the floaters are mobile during eye movements,
      - examination of posterior vitreous detachment.
2. Vitreous/preretinal hemorrhage (Figs. 38–39)[63]:
   a. Vitreous hemorrhage in B-scan presentation is visible as numerous small hyperechoic foci in the vitreous that move with eyeball movements.
   b. In A-scan presentation, the hemorrhage projection shows numerous small, low amplitude peaks corresponding to blood cells.

c. In the case of hemorrhage with vitreous detachment, the posterior vitreous border is visible; it should be distinguished from retinal detachment.
d. In preretinal (subhyaloidal) hemorrhage, blood is present between the retina and the posterior border of the vitreous body. The examination in B-scan presentation shows the clear vitreous chamber and the hyperreflective posterior vitreous border.

3. Fibrous/fibrovascular proliferation:
   a. These are characterized by a wide variety of signs. The preretinal membranes are hyperechoic and usually show little or no mobility on dynamic examination. In the scans in A presentation, very thin and high peaks are visible in the projection of the membranes.
   b. In the case of fibrovascular proliferation occurring in proliferative diabetic retinopathy, attention is paid to its localization and the traction exerted on the retina. It is common that vitreous hemorrhage prevents accurate examination of the fundus. The presence of fibrovascular proliferation and vitreous hemorrhage suggests a prompt posterior vitrectomy should be performed, without waiting for spontaneous resorption of the hemorrhage. Fibrovascular membranes are most often associated with the optic nerve disc, have high echogenicity and poor mobility; attention should also be paid to the condition of the retina and its traction by the proliferations[64].
4. Retinal detachment[65]:
   a. In the ultrasound examination, the retina is thick and has high echogenicity, clearly evident in A-scans (very high signal).
   b. In simple rhegmatogenous detachment, the retina is thick, hyperechoic, wrinkled, mobile, and undulates with eyeball movement.
   c. Diabetic retinopathy is more frequently associated with tractional retinal detachment caused by traction of the fibrovascular membranes.

Other examinations

Two more examinations should be mentioned, which are mainly used in scientific practice:

1. Examination of the central part of the visual field (microperimetry) – it can provide additional information about the function of the retina, especially in the case of diabetic macular edema[66]. The changes in the field of vision then include scotomas and sensitivity impairment[67, 68]. Microperimetry uses laser scanning ophthalmoscopy, hence the examination is accurate. However, it is not used in everyday practice, and is thus limited to being a valuable supplement to clinical trials on DME[69].
2. Multifocal electroretinogram (mERG) – similarly as microperimetry, it is an examination used in scientific studies. The test involves analysing the electrical response from specific regions of the retina. Besides demonstrating obvious damage in the case of developed retinopathy, mERG can also be used to estimate the risk of its development. A prolonged response time from the observed areas of the retina with the simultaneous lack of retinopathy may indicate an increased risk of its development in a given area[70]. mERG can be used as a tool to help predict the functional effect after surgery and is sometimes performed before pars plana vitrectomy in advanced retinopathy[71, 72].

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Chapter 5: Types of lesions in diabetic retinopathy

Introduction

The following section briefly summarizes the lesions observed in the retina in diabetic retinopathy (DR). The changes are divided into three categories[1, 2]:

1. the consequences of microvascular leakage: intraretinal hemorrhages, hard exudates, retinal edema,
2. consequences of structural damage to the vessel walls: microaneurysms, venous abnormalities, arterial vessel abnormalities,
3. the consequences of hypoxia: venous beading, cotton wool spots, intraretinal microvascular abnormalities (IRMA), fibrovascular proliferation, preretinal and intravitreal hemorrhages[3].

As shown in Figure 1, larger flame hemorrhages occur in the nerve fiber layer (NFL). In contrast, small round hemorrhages are typically located in the outer plexiform layer (OPL) or the inner nuclear layer (INL). Cystoid lesions and hard exudates are similarly located. In contrast, microaneurysms are characteristic of the INL, although they can also occur in the NFL. Retinal edema is usually located primarily in OPL, sometimes involving INL as well.

Microaneurysms[4, 5, 6]

1. Pathomechanism:
   a. punctate dilation of arterial vessels, formed in areas devoid of pericytes, located in the nerve fiber layer (smaller) or in deeper retinal layers (larger),
   b. cellular microaneurysms, newly formed as

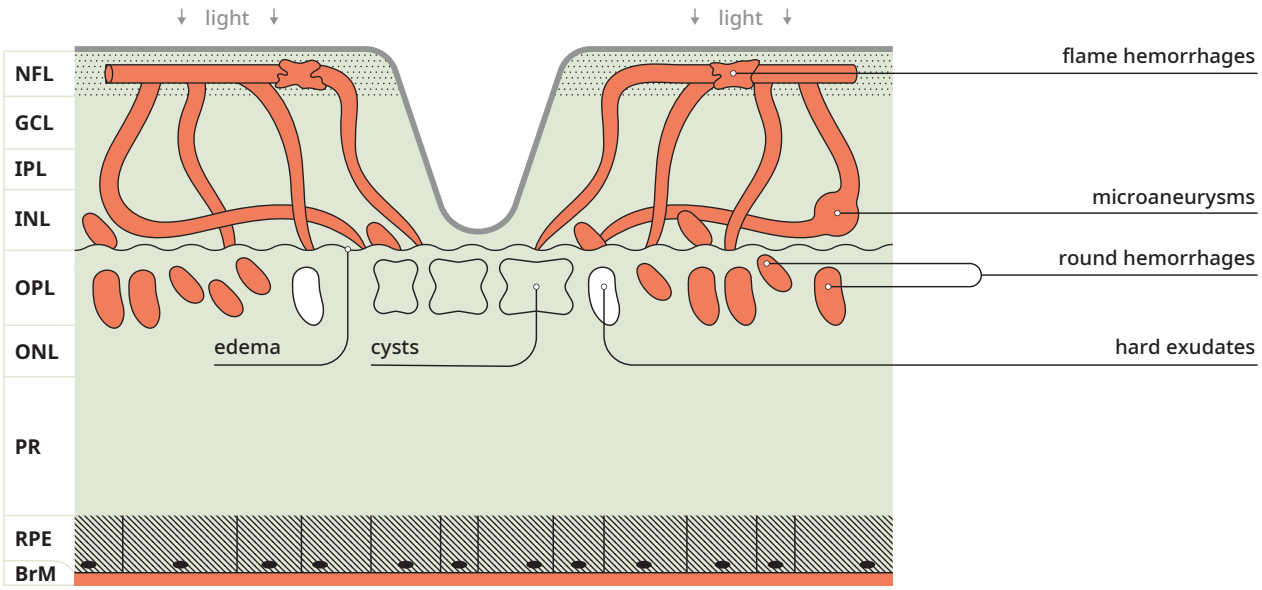
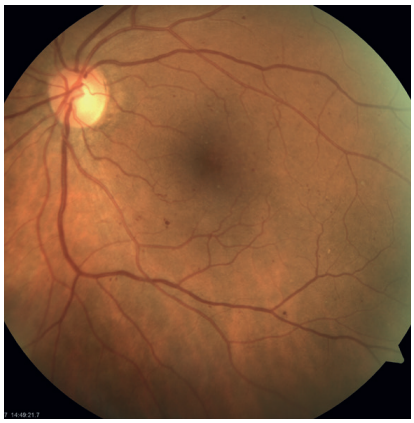


Figure 1. Diagram of the location of lesions typical of non-proliferative diabetic retinopathy in the retinal layers. | NFL – nerve fiber layer, GCL – ganglion cell layer, IPL – inner plexiform layer, INL – inner nuclear layer, OPL – outer plexiform layer, ONL – outer nuclear layer, PR – photoreceptors, RPE – retinal pivgment epithelium, BrM – Bruch's membrane



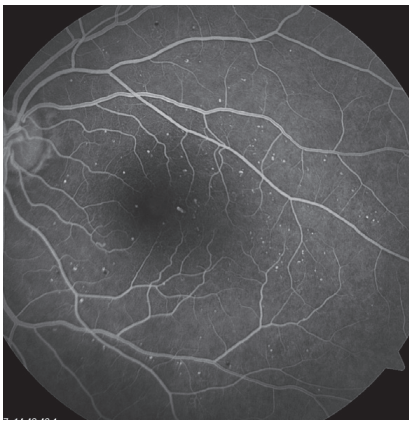
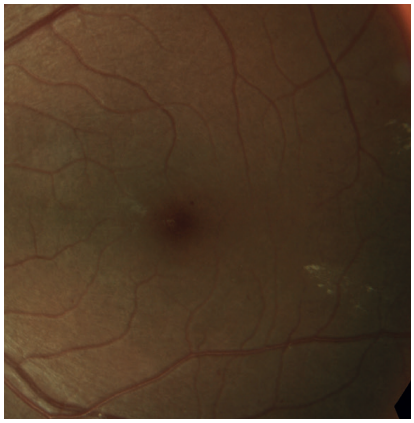


Figure 2. Mild non-proliferative diabetic retinopathy. The colour image shows few punctate foci corresponding to microaneurysms. Microaneurysms present more clearly on the angiographic image.



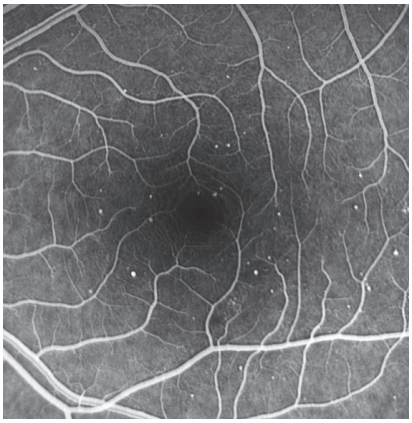
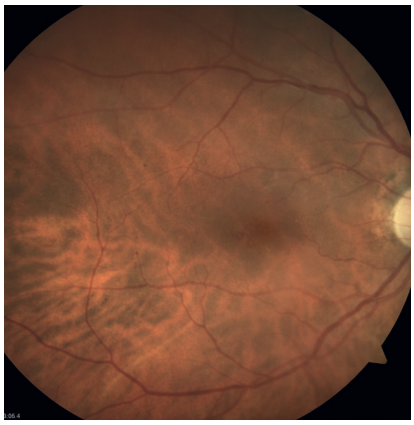


Figure 3. Numerous microaneurysms on magnified colour and angiographic images. Note that the number of revealed microaneurysms is significantly higher on the angiographic image than on the colour image.



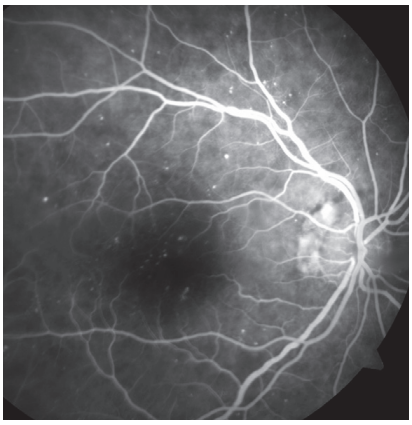
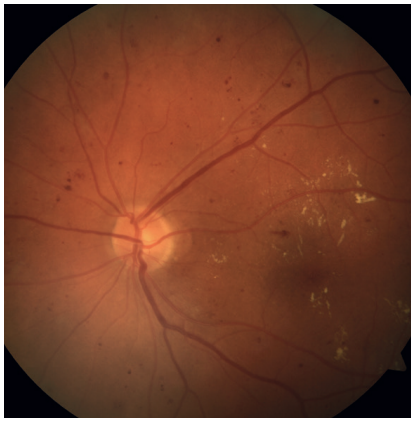


Figure 4. Mild non-proliferative diabetic retinopathy. Ophthalmoscopy shows only microaneurysms. Angiography reveals single small foci of hyperfluorescence corresponding to microaneurysms. There is no significant leakage from microaneurysms.



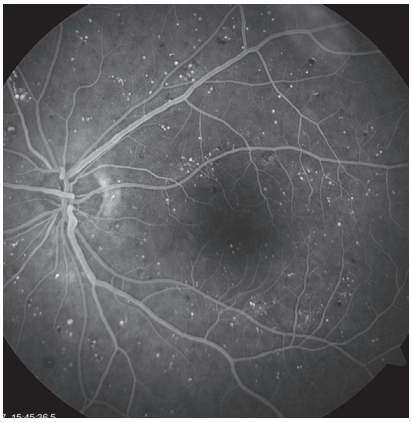


Figure 5. Moderate non-proliferative diabetic retinopathy. The colour image shows multiple microaneurysms, less numerous hemorrhages, and small hard exudates. Angiography reveals foci of hyperfluorescence consistent with microaneurysms and good vascular perfusion. Foveal edema and neovascularization are absent.

a result of endothelial cell proliferation at the site of pericyte loss,

c. often located near the area of hypoperfusion,
d. causing leakage of fluid from the vessel lumen into the retinal tissue (edema),
e. ruptured microaneurysms are the source of extravasation of blood visible as hemorrhages on the fundus.

2. Ophthalmoscopic and angiographic image (Figs. 2–5):
   a. tiny red dots in the NFL or in the deeper layers of the retina, sometimes difficult to distinguish from punctate hemorrhages located in the deeper layers of the retina,
   b. fluorescein angiography (FA) shows small punctate foci of hyperfluorescence (usually the number of microaneurysms visualized in FA is higher than in ophthalmoscopic examination); in late-stage FA, due to leakage, they may be surrounded by retinal edema – staining of retinal tissue.

Retinal hemorrhages[7, 8]

1. Pathomechanism:
   a. ruptured microaneurysms/vascular hemorrhages, mainly in the NFL,
   b. damage to – and thrombosis of – vessels of the deep capillary plexus, affecting deeper layers of the retina (mainly the INL).
2. Ophthalmoscopic image (Figs. 6–7, 9):
   a. flame-shaped hemorrhages, located in the NFL (their shape follows the course of the fibers),
   b. dot-blot hemorrhages, located in deeper retinal layers, most often in the INL and the OPL.

Hard exudates[9, 10, 11]

1. Pathomechanism:
   a. damage to the blood-retinal barrier, resulting in leakage from the compromised vessels,

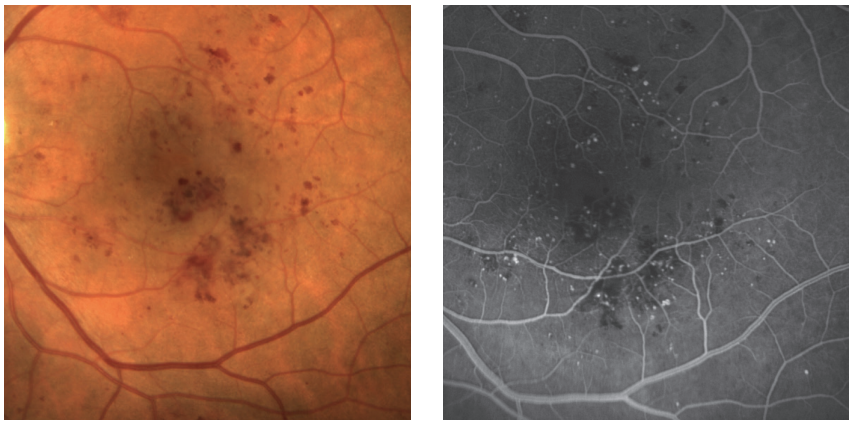


Figure 6. Dot-blot hemorrhages located in the deeper layers of the retina. They block fluorescence on the angiographic image. Above some hemorrhages, microaneurysms are visible, which indicates their deep position in the retina.

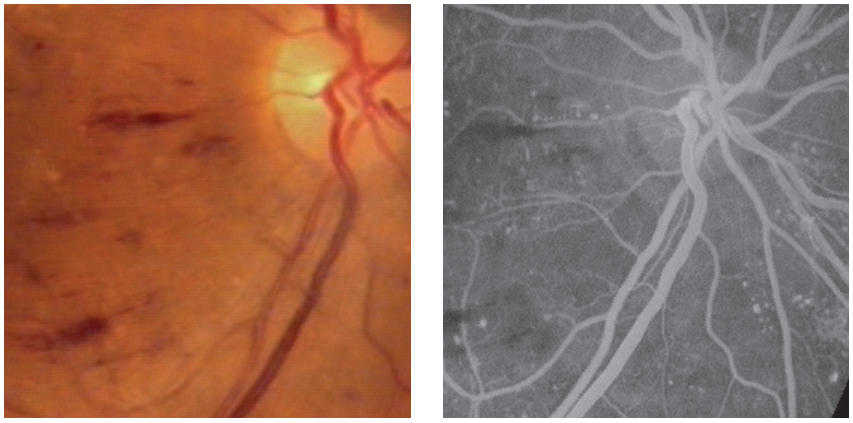
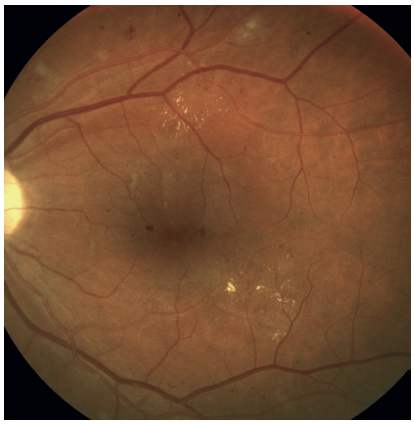


Figure 7. Flame-shaped hemorrhages located in the nerve fiber layer. Visible blockage of fluorescence by blood. Microaneurysms are located below the level of the hemorrhages.



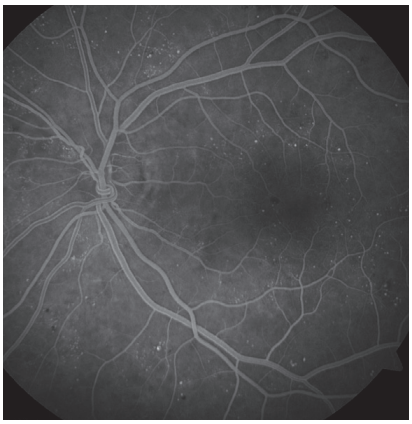
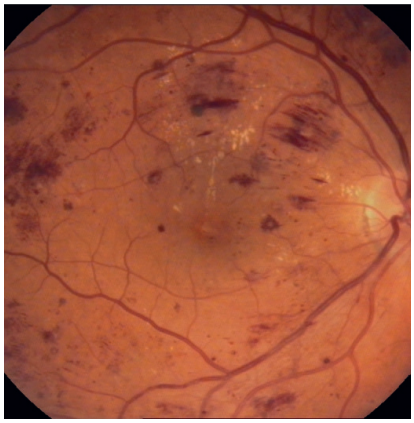


Figure 8. Moderate non-proliferative diabetic retinopathy. Microaneursms, hemorrhages and small hard and soft exudates visible on colour fundus photo. Fluorescein angiography reveals small hyperfluorescent foci corresponding to microaneurysms, and small areas of hypoperfusion at the location of cotton wool spots.



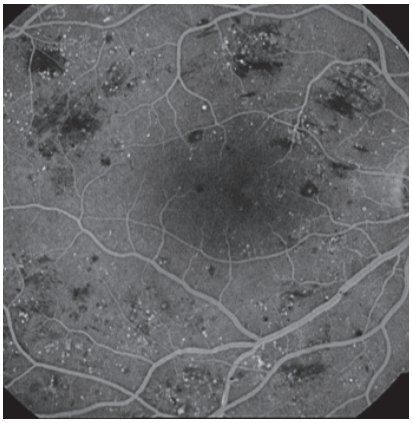


Figure 9. Severe non-proliferative diabetic retinopathy. The color photo shows microaneurysms, flame-shaped and dot-blot hemorrhages, small hard-exudates. The angiographic image shows blockage of fluorescence by hemorrhages, as well as numerous micoroaneurysms and areas of impaired perfusion.

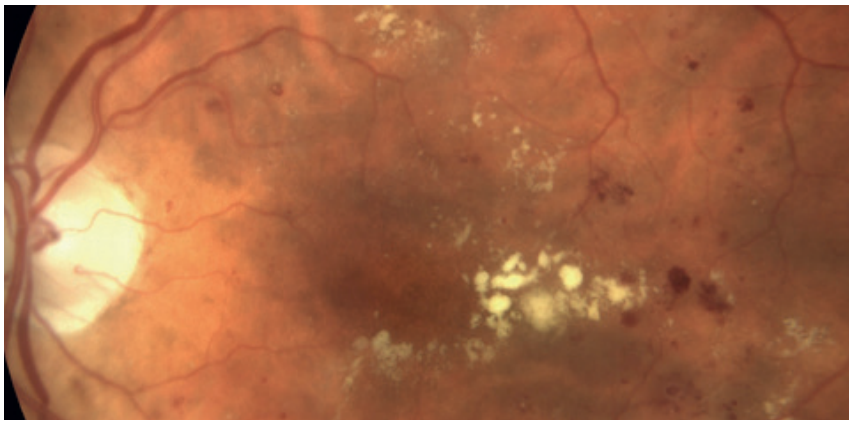
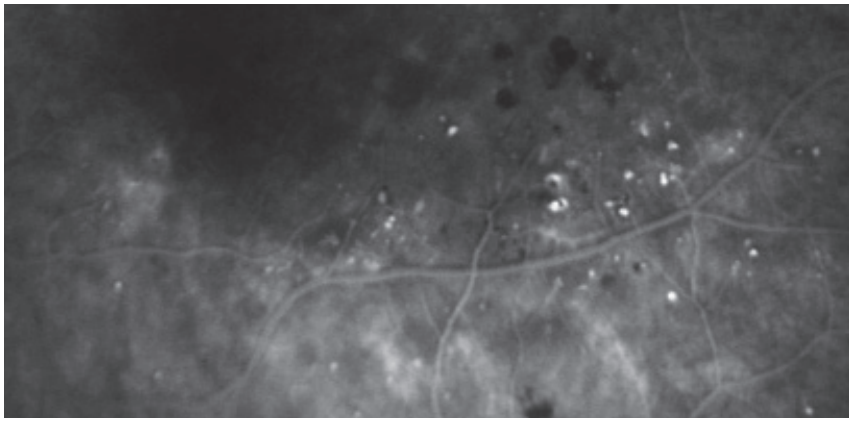


Figure 10. The colour photo shows clusters of hard exudates temporal and inferior to the fovea of the left eye. The angiographic image shows microaneurysms that are the source of these lesions, located inside the arch of exudates. In this situation, the angiographic images allow for effective focal laser therapy.



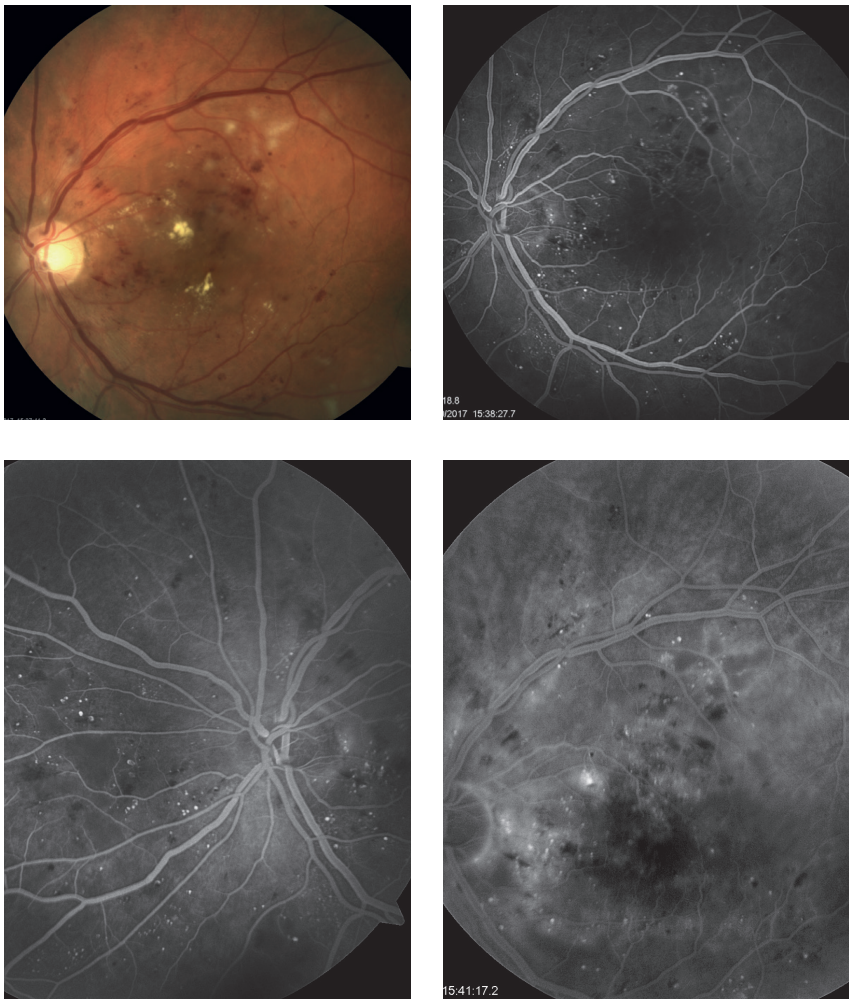
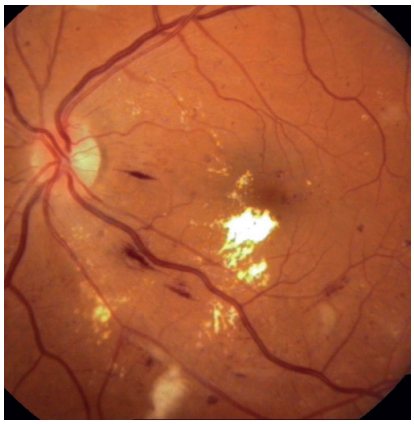


Figure 11. Severe non-proliferative diabetic retinopathy with macular edema. The colour photograph shows numerous hemorrhages in all quadrants as well as cotton wool spots and hard exudates in the macular area. Angiographic images reveal numerous microaneurysms as small foci of hyperfluorescence and areas of impaired perfusion in the projection of cotton wool spots. Hypoperfusion is also visible in the nasal sectors of the retina.

   b. accumulation of lipids and proteins,
   c. lesions are mainly located within the outer plexus layer, on the border of the normal and edemetous retina,
   d. in chronic form there may be a progression of exudates towards the fovea,
   e. the absorption of hard exudates may take months or even years.
2. Ophthalmoscopic image (Figs. 8–11):
   a. yellow waxy areas with geographical shapes; often in the center of hard exudates, a visible cluster of leaking microaneurysms,
   b. in their active form they are accompanied by retinal edema,
   c. during remission, for example after successful laser therapy, hard exudates are not accompanied by retinal thickening (no edema).

Retinal edema, including macular edema[12, 13]

1. Pathomechanism:
   a. leakage from damaged capillaries (diffuse edema),
   b. leakage from microaneurysms (focal edema),
   c. fluid accumulates initially between the inner nuclear layer and outer plexiform layer, then the edema progresses towards the inner retinal layers,
   d. progression of edema results in the formation of cysts located mainly in the outer plexiform layer (cystoid macular edema (CME)).
2. Ophthalmoscopic image (Figs. 11–13):
   a. retinal edema presents as retinal thickening (best detectable on examination in stereoscopic image),



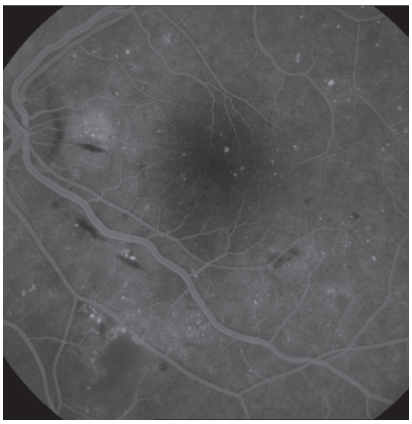
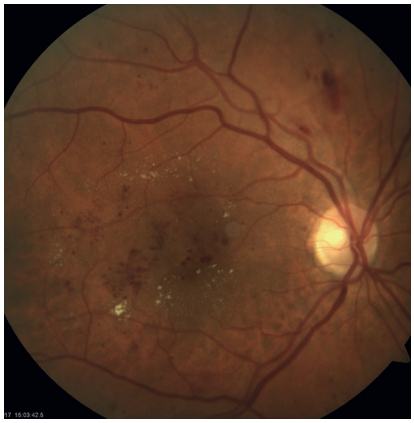


Figure 12. Moderate non-proliferative diabetic retinopathy with macular edema. The ophthalmoscopic image shows dot-blot and flame hemorrhages in all quadrants, hard exudates covering the fovea, and cotton wool spots. The angiographic image shows the blockage of fluorescence by conglomerates of hard exudates and microaneurysms, which are the source of the edema.



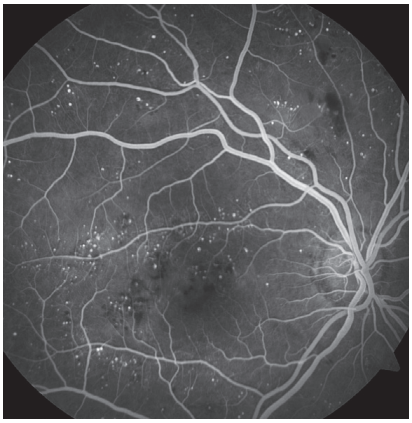
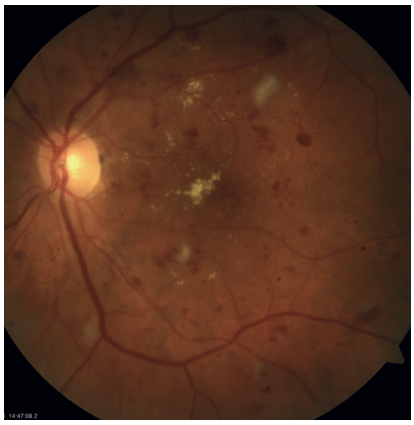


Figure 13. Macular edema in moderate non-proliferative diabetic retinopathy. The colour photograph shows numerous hemorrhages, microaneurysms and small hard exudates at the macula. The fluorescein angiography reveals a large number of microaneurysms.



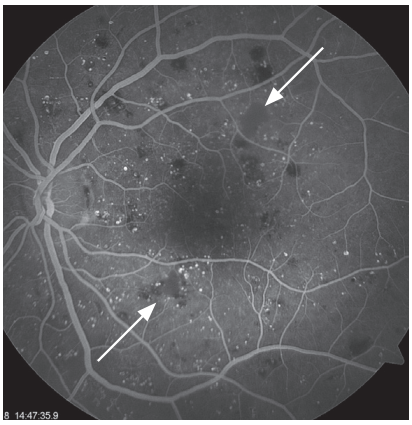
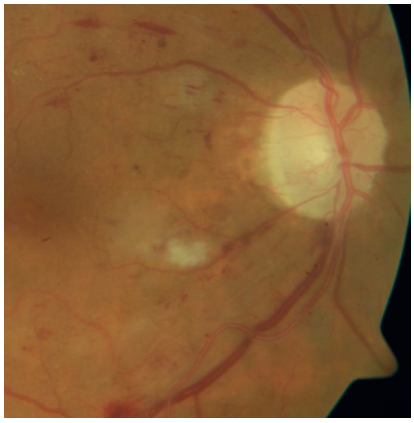


Figure 14. The colour image shows small cotton wool spots located outside the center of the fovea. A cluster of hard exudates is visible in the macular center. In the angiographic image, small foci of hypoperfusion (indicated by the arrows) are visible in the area of cotton wool spots.



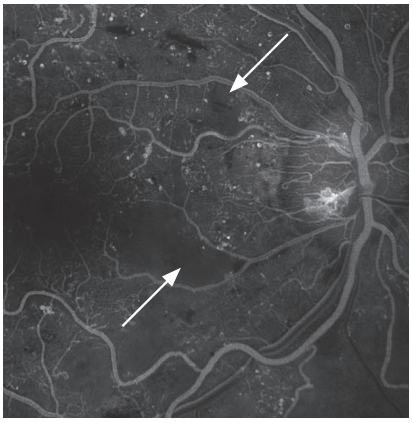


Figure 15. Cotton wool spots. In the colour photograph, they are visible in the superior and inferior areas of the papillomacular bundle. In the angiographic image, they correspond to areas of impaired capillary perfusion, visible as uniformly grey areas devoid of background fluorescence (indicated by the arrows).

b. optical coherence tomography (OCT) is a reliable method of quantative evaluation of the edema.

Cotton-wool spots[14, 15, 16]

1. Pathomechanism:
   a. closure of the precapillary arterioles in the nerve fiber layer and the formation of an area of impaired perfusion,
   b. accumulation of waste products from the neuronal system outside the fibres.
2. Ophthalmoscopic and angiographic images (Figs. 14–15):
   a. white, fluffy areas with indistinct borders, located in the nerve fiber layer; a large number of cotton wool spots characterizes severe nonproliferative diabetic retinopathy (NPDR) and indicates the risk of transformation into proliferative retinopathy.
   b. visible in FA as areas devoid of capillary perfusion.

Venous abnormalities[17, 18]

1. Pathomechanism:
   a. retinal hypoperfusion,
   b. their presence is a marker of the risk of progression to proliferative retinopathy,
   c. change from beaded to normal vessels is a marker of PRP efficacy.
2. Ophthalmoscopic image (Fig. 16):

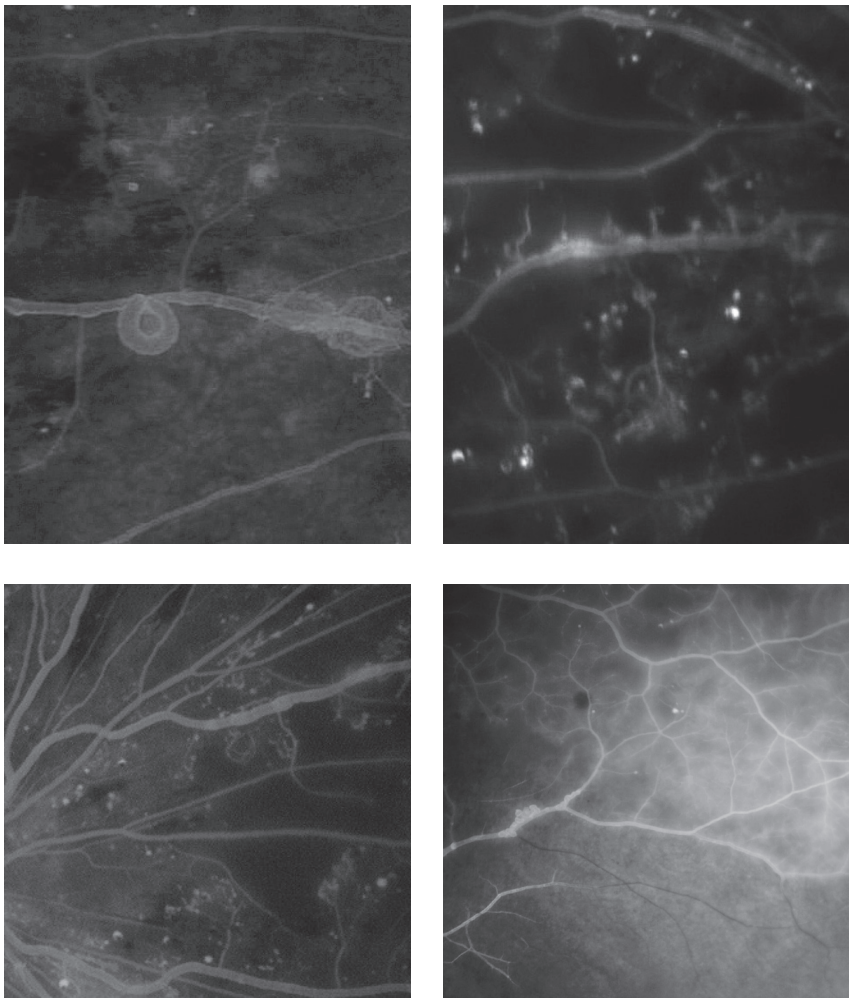
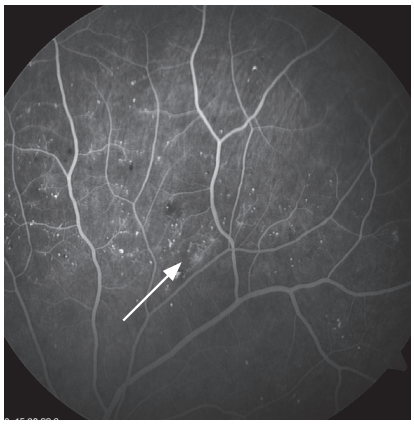


Figure 16. Angiographic images show both venous and arterial abnormalities. There is visible venous constriction (venous beading), narrowing of the small arterial vessels, marked areas of capillary hypoperfusion and intraretinal microvascular abnormalities.



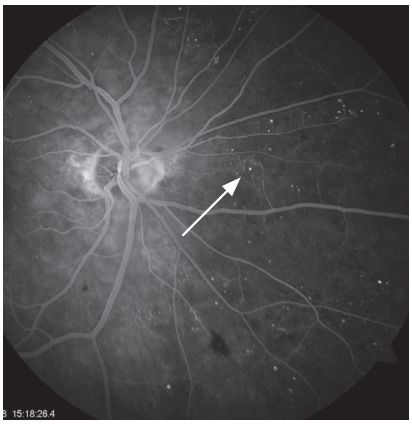
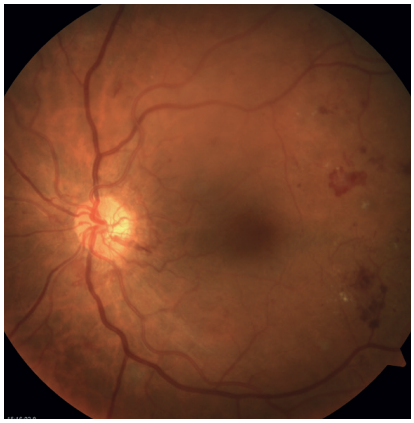


Figure 17. Intraretinal microvascular abnormalities (IRMA). Visible signs of IRMA: twisting vessels revealing additional divisions and anastomoses of already existing small vessels at the end of a small artery (indicated by the arrows). No leakage present.



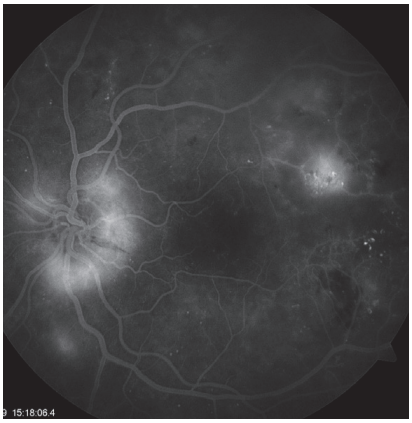
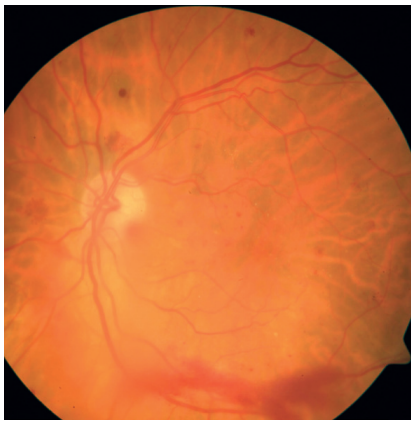


Figure 18. Neovascularization at the disc (NVD) and neovascularization elsewhere (NVE) in high-risk proliferative diabetic retinopathy. The colour photograph shows distinct NVD and an area of NVE temporally to the fovea. The late-phase angiographic image shows intense leakage from pathological vessels.



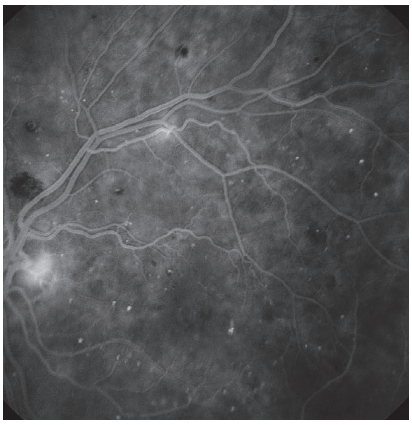
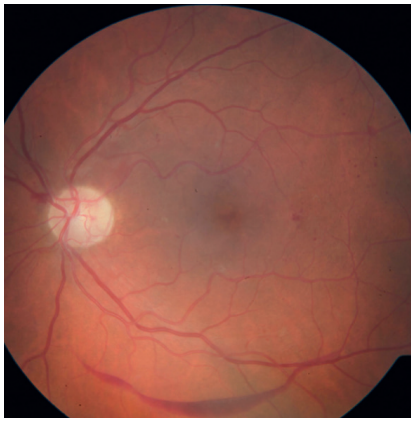


Figure 19. High-risk proliferative diabetic retinopathy. The colour photograph shows preretinal hemorrhage and numerous dot-blot hemorrhages. The angiography reveals a modest leakage from neovascularization on and off the disc. In such cases, neovascularization is difficult to detect by ophthalmoscopy alone.



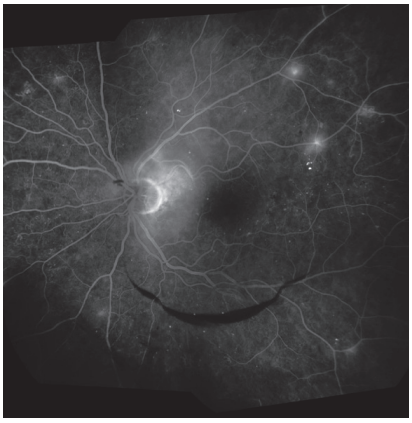


Figure 20. High-risk proliferative diabetic retinopathy. Ophthalmoscopically, there are vaguely visible pathological vessels on the optic disc. There is also a small boat-shaped preretinal hemorrhage in the inferior temporal sector. Angiography reveals marked leakage from neovascularization on and off the optic disc. Macular edema is absent.

a. irregular shape of the veins with dilatations and beading,
b. venous loops and reduplication,
c. they usually occur at the border of or within the ischemic retina.

Intraretinal microvascular abnormalities (IRMA)[19, 20]

1. Pathomechanism:
   a. the formation of connections between arterioles and venules with bypassing of capillaries,
   b. the cause is retinal hypoperfusion.
2. Ophthalmoscopic and angiographic images (Fig. 17):
   a. small, spider-shaped vessels resembling flat neovascularization,
   b. horizontal course in the retina (they do not cross the internal limiting membrane),
   c. location outside of large vessels,
   d. they usually occur on the border of hypoperfusion areas,
   e. no leakage in the FA.

Neovascularization[21, 22, 23, 24]

1. Definitions:
   a. neovascularization at the disc (NVD) – means the presence of pathological vessels on the optic disc and/or within a distance of 1 DD from the optic disc,
   b. neovascularization elsewhere (NVE) – means the presence of pathological retinal vessels at a distance greater than 1 DD from the optic nerve disc.
2. Pathomechanism:
   a. retinal hypoxia,
   b. production of vascular growth factors, primarily vascular endothelial growth factor (VEGF), by the ischemic retina,
   c. growth of pathological vessels as the retinal defense against hypoxia.
3. Ophthalmoscopic and angiographic image (Figs. 18–20):
   a. NVD – pathological vessels, usually fan-shaped, sometimes resembling fern leaves, are visible on or near the optic nerve disc,
   b. NVE – pathological vessels usually develop at the border of ischemic and normal retina; they tend to be quite flat in the early stage; in severe and prolonged ischemia, they are located clearly above the level of the ocular fundus,
   c. neovascularizations cross the border of the internal limiting membrane,
   d. in FA, both NVD and NVE show intense leakage throughout the examination (usually FA is not necessary for diagnosis).

Preretinal hemorrhages and vitreous hemorrhages[25]

1. Pathomechanism: hemorrhages from pathological vessels – NVD and/or NVE.
2. Ophthalmoscopic image (Figs. 19–20):
   a. preretinal hemorrhages are located between the retina and the posterior vitreous limiting membrane and have a characteristic boat shape,
   b. vitreous hemorrhages vary in severity and duration:
      • dispersed blood in the vitreous body,
      • thick hemorrhage (no view of the fundus),
      • blood clots located mainly in the lower sections of the vitreous.

Fibrovascular proliferation[26, 27]

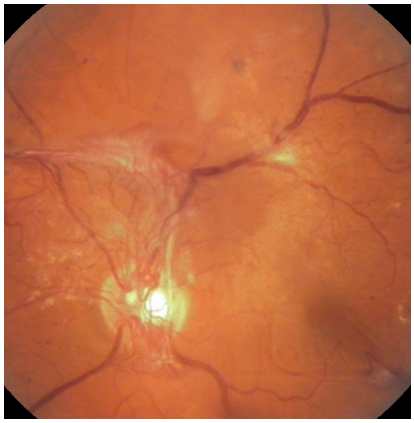
1. Pathomechanism:
   a. proliferation of glial tissue as a scaffold for neovascularization,
   b. may occur without vessels after their regression.
2. Ophthalmoscopic image (Figs. 21–23):
   a. white bands of connective tissue, usually ac-

companying the vessels, extending from the optic disc or from the larger peripheral vessels,

b. in an advanced stage, traction of the retina by fibrous vascular tissue,

c. in extreme situations, tractional retinal detachment.

Typical PDR signs: neovascularization, preretinal and intravitreal hemorrhages, fibrovascular proliferation, may be accompanied by other signs, which are also typical for NPDR, i.e. hard and soft exudates, intraretinal haemorrhages, microaneurysms, and arteriovenous abnormalities.



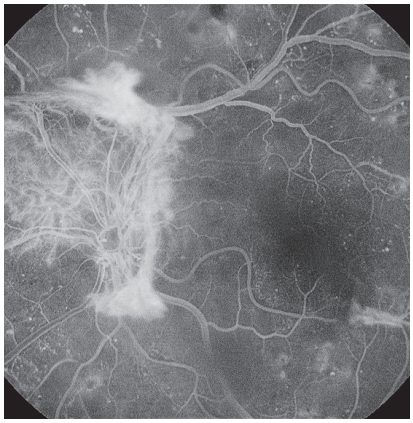
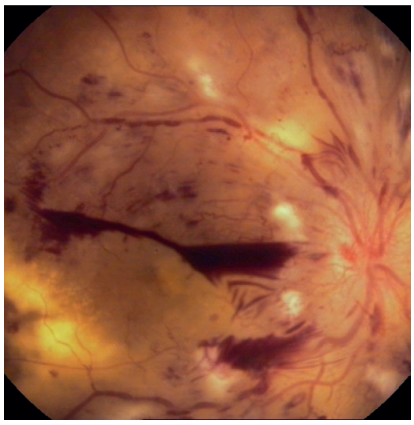


Figure 21. High-risk proliferative diabetic retinopathy. Ophthalmoscopically visible fibrovascular proliferation on the optic disc. Angiography reveals a leak from neovascularization at the disc and beyond the optic nerve, and areas devoid of capillary perfusion in the nasal sector. Multiple arteriovenous anastomoses. Fovea without significant edema.



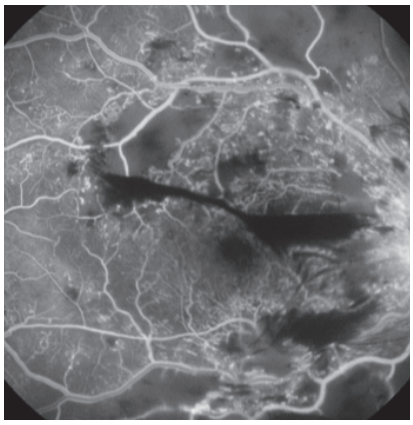
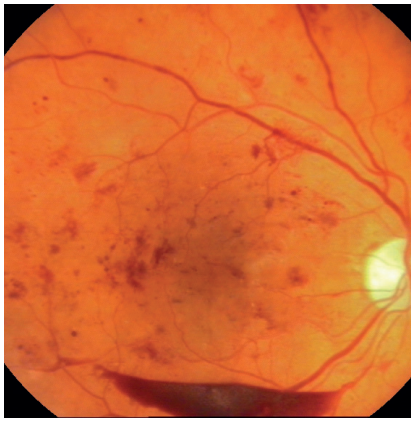


Figure 22. High-risk proliferative diabetic retinopathy with macular edema. Ophthalmoscopy reveals neovascularization at the disc (NVD), preretinal hemorrhages, cotton wool spots, hard exudates, and retinal edema throughout the posterior pole. Angiography shows NVD leakage and extensive areas devoid of capillary perfusion.



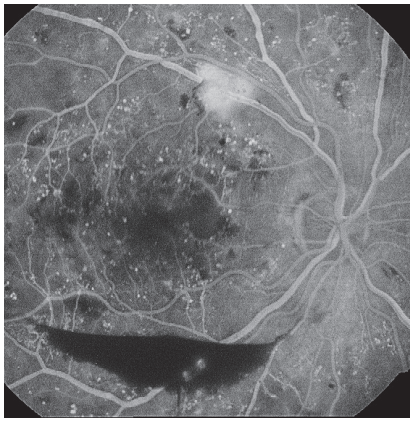


Figure 23. High-risk proliferative diabetic retinopathy. The colour photograph shows a boat-shaped preretinal hemorrhage and numerous microaneurysms and hemorrhages in the entire fundus. The angiographic image reveals the spot of neovascularization beyond the optic nerve, most likely the source of the hemorrhage. Diffuse macular edema is present.

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Chapter 6: Classifications of diabetic retinopathy

General information

Classifications of the severity or stage of a clinical entity are created to improve communication between physicians, and to facilitate therapeutic decision making. In this regard, the classification of diabetic retinopathy (DR) is no exception.

To be more precise, such classifications aim to:

1. facilitate communication between physicians (and/or researchers) who need to describe the disease,
2. set out the principles for medical interventions,
3. improve the effectiveness of the therapeutic process by assigning the appropriate therapeutic pathway to a particular stage of the disease.

An important aspect in creating any classification of a disease entity is the choice of criteria according to which such distinctions are made. Since DR involves a multitude of morphological changes observed on the fundus (cf. Chapter 5: *Types of lesions in diabetic retinopathy*, pp. 83–92), associated with different pathophysiological processes occurring in tissues due to increased blood glucose, it is these changes that form the basis for the classification of this entity. Additional diagnostic tests are not always necessary to determine the type of retinopathy.

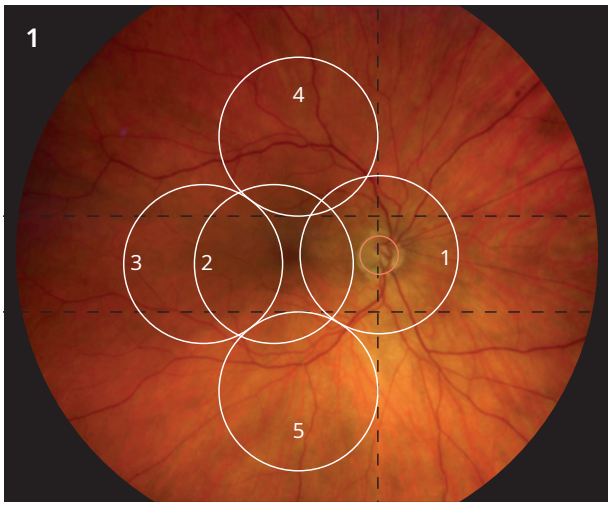
The evolution of the DR classification system has led to the creation of an increasing number of subgroups. This, in turn, has been made possible by the classification of an increasing number of fundus-related signs. At a certain point, the complexity of DR classification (the full version of the Early Treatment Diabetic Retinopathy Study (ETDRS) classification) made it impractical for use in everyday clinical practice[1]. Hence, simplified versions have been developed for diabetologists and ophthalmologists to use in their day-to-day work.

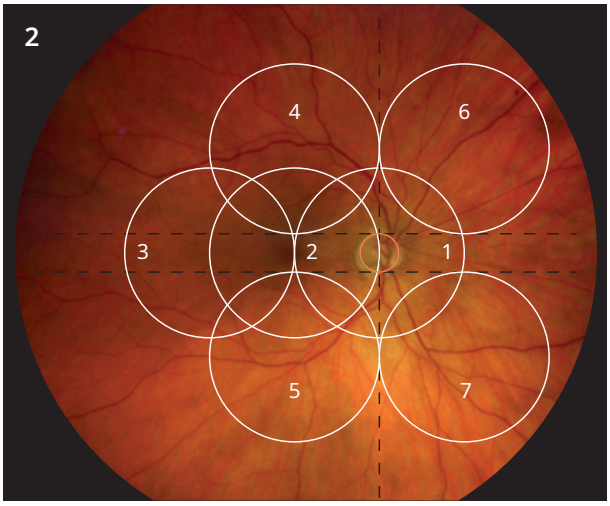
A history of the classification of diabetic retinopathy

The classification of diabetic retinopathy dates back to the 1960s and is closely linked to large clinical trials exploring treatment options of this condition. After several decades, the recommendations for the management of different types of retinopathy needed organizing, all the more so as retinal laser photocoagulation was intensively used for the treatment of DR. This form of therapy had been used for years, purely on the basis of medical practice, without the support of large randomized clinical trials. It was, therefore, necessary to clearly define the group of patients eligible for laser treatment.

The first DR classification system was developed in the USA in 1968, at a symposium organized by the US Public Health Service at Airlie House in Warrenton[2, 3]. The assessment of retinopathy was based on five standard photographic fields: Field 2 in the centre of the fovea, Fields 4 and 5 above and below the fovea, and Fields 1 and 3 nasally and temporally to the fovea (Fig. 1).

The Airlie House classification considered the following lesions observed on the fundus: microaneurysms, hemorrhages, soft exudates, venous constrictions, intraretinal microvascular abnormalities (IRMA), and vascular proliferations. The fundus lesions were classified into three categories: absent, mild to moderate, or severe. This historic classification system was too simple and did not take into account an appropriate





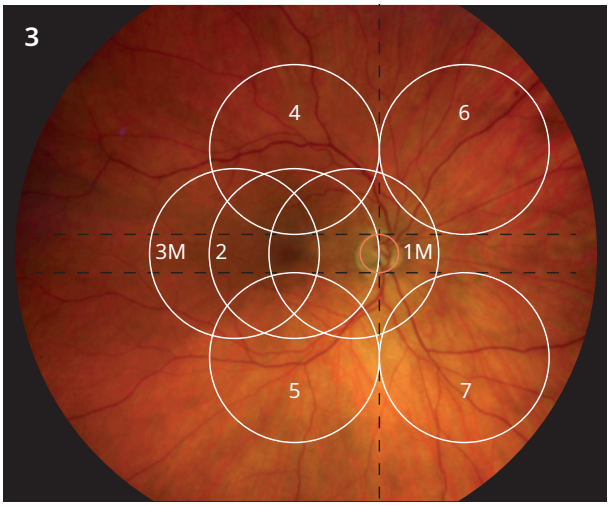


Figure 1. Five standard fundus photographic fields according to Airlie House. Figure 2. Seven standard fields of retinal evaluation according to DRS recommendations. Figure 3. Fields for evaluating the fundus according to the ETDRS modification.

number of subgroups, therefore the research was extended. The first large clinical trials were undertaken by the Diabetic Retinopathy Study (DRS) group from 1971 to 1979[4]. Following DRS recommendations, the fundus assessment was performed in seven fields (Fig. 2). Two additional fields covered the upper and lower nasal sectors from the optic disc. Later, the ETDRS group introduced further modifications to this scheme, placing more emphasis on the fovea assessment (Fields 1 and 3 also included the fovea, Fig. 3), but the classic seven-field DRS grading system is still in use.

In addition, the DRS introduced the modified Airlie House classification, which had more subcategories. The main question posed by the research group was whether immediate panretinal laser photocoagulation (PRP) in patients with severe non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR) prevents severe vision loss (SVL), defined as BCVA < 5/200. The results of the research are presented in Table 1. The study resulted in the creation of the definition of high-risk proliferative diabetic retinopathy (HR PDR, sometimes abbreviated to HRC PDR – high risk characteristics diabetic retinopathy) – see Table 2.

With retinopathy defined in this way, PRP reduced SVL by almost a half over four years[5]. Therefore, with this type of retinopathy, the DRS group recommended immediate panretinal laser photocoagulation (PRP). The recommendations for the remaining analysed types of retinopathy were ambiguous. The study did not provide a clear answer to the question of whether immediate panretinal photocoagulation in mild PDR and severe NPDR is better than delayed, until high risk characteristics develops. The decision had to be made after analysing all risk factors. Currently, the definition and recommendations regarding HR PDR developed by the DRS group are still in place.

Research focusing on the classification and treatment recommendations for diabetic retinopathy continued

Table 1. Diabetic Retinopathy Study 1972–1979[6].

Baseline severity of retinopathy	Follow-up time (years)	Control patients (% with SVL)	Patients treated with PRP (% with SVL)
Severe non-proliferative	2 4	3 13	3 4
Mild proliferative	2 4	7 21	3 7
High risk proliferative	2 4	26 44	11 20

BCVA < 5/200 on two consecutive examinations at four-month intervals | SVL – severe visual loss, defined as BCVA < 5/200 on two consecutive examinations at four-month intervals, BCVA – best corrected visual acuity, PRP – panretinal photocoagulation

with the ETDRS group. In subsequent studies, the group attempted to answer the question of whether early PRP was effective in preventing severe vision loss in patients with diabetic retinopathy who had not yet reached the stage of HR PDR, namely in moderate and severe non-proliferative retinopathy and in early proliferative retinopathy. The results were inconclusive. After five years, SVL occurred in only 2.6% of patients who underwent early panretinal laser photocoagulation and in 3.7% of patients who received deferred laser therapy. The need for vitrectomy within five years was 2.2% in the early PRP group and 3.9% in the deferred laser therapy group[7]. Thus, although the rate of serious complications was significantly lower in the early photocoagulation group than in the patients with deferred treatment, it remained very low in both groups. Due to potential complications associated with intensive panretinal photocoagulation, the ETDRS did not recommend early PRP in the group of patients with mild to moderate non-proliferative retinopathy. In more advanced retinopathy, PRP may be considered, but potential complications must be taken into account.

Table 2. Definition of high-risk proliferative diabetic retinopathy (HR PDR)[8].

1.	NVD with a surface area of ¼ to ⅓ DA on or within one disc diameter of the optic disc
2.	NVD with pre-retinal or vitreous hemorrhage
3.	NVE with > ½ DA and with pre-retinal or vitreous hemorrhage

DA – area of the optic nerve disc
NVD – neovascularization at the disc
NVE – neovascularization elsewhere

ETDRS developed a complete classification system for diabetic retinopathy, which is still the basis of clinical trials today. It took into account many more lesions visible on the fundus than the Airlie House classification when evaluating the severity of retinopathy. The system was widely used in scientific research, but it turned out to be too complicated and ineffective in everyday medical practice. Therefore a simplified version of this classification is used in day-to-day practice – Table 3.

A milestone in the development of the DR classification was the introduction of a definition of severe non-proliferative retinopathy, the DR stage when

Table 3. Simplified classification of diabetic retinopathy, according to Wilkinson[9].

Severity level	Findings observed upon dilated ophthalmoscopy
No apparent retinopathy	no abnormalities
Mild NPDR	microaneurysms only
Moderate NPDR	more lesions than just microaneurysms but less than severe NPDR
Severe NPDR	US definition: any of the following and no signs of PDR (4:2:1 rule) • severe intraretinal hemorrhages and microaneurysms in each of four quadrants • definite venous beading in two or more quadrants • moderate IRMA in one or more quadrants International definition: any of the following and no signs of PDR • more than 20 intraretinal hemorrhages in each of the four quadrants • definite venous beading in two or more quadrants • prominent IRMA in one or more quadrants
PDR	one or both of the following • neovascularization • vitreous/preretinal hemorrhage

NPDR – nonproliferative diabetic retinopathy, PDR – proliferative diabetic retinopathy, IRMA – intraretinal microvascular abnormalities

Table 4. The UK classification system for diabetic retinopathy (National Screening Comitee UK)[10].

Type	Ophthalmoscopic changes	Recommendations
R0	none	annual follow-up
R1	simple retinopathy (background): microaneurysms, retinal hemorrhages +/- any exudate	annual follow-up
R2	preproliferative retinopathy: R1 plus venous beading, venous loops or reduplication, IRMA, multiple deep round or blot hemorrhages	ophthalmic consultation
R3	proliferative retinopathy: NVD, NVE, pre-retinal or vitreous hemorrhage, pre-retinal fibrosis +/- tractional retinal detachment	urgent ophthalmic consultation

IRMA – intraretinal microvascular abnormalities, NVD – neovascularization at the disc, NVE – neovascularization elsewhere

PRP can be considered. A simplified definition of this retinopathy, i.e. the 4:2:1 rule, is still the basis for defining the so-called threshold disease – in other words, non-proliferative retinopathy with the highest risk of progression to proliferative retinopathy.

It should be kept in mind that the simplified definition of severe NPDR is not the same as the definition of severe NPDR in the original ETDRS classification. For example, it does not take into account such signs as soft exudations and areas of hypoperfusion, and falls roughly between the ETDRS definitions of moderate and severe non-proliferative retinopathy.

Therefore, it is important to bear in mind that defining severe non-proliferative retinopathy according to the 4:2:1 rule is a compromise. However, it transpired that the diagnostic efficacy of this form of classification is high, and it allows for appropriate and quick patient referral for further therapy.

In Europe, there are also other DR grading systems. Table 4 provides an example of the British classification system.

Stages of diabetic retinopathy in the international classification

No retinopathy

In the absence of retinopathy, the fundus image appears normal. Sometimes pathologies associated with the presence of concomitant diseases can be found, for example arterial hypertension, but no changes typical for diabetic retinopathy are observed (Fig. 4).

Mild non-proliferative diabetic retinopathy

This is a retinopathy associated with structural damage to the arterial wall, often referred to as background diabetic retinopathy (Fig. 5–6). Only microaneurysms, usually few in number, are observed on the fundus. Although the number of detected microaneurysms typically is greater in fluorescein angiography (FA), it is not necessary to perform this test in the event of mild retinopathy. In such cases, patients should be examined annually, or sometimes twice a year (the recommendations of ophthalmological societies differ from country to country – see Chapter 13: *Principles of diabetic retinopathy screening and monitoring*, pp. 231–238).

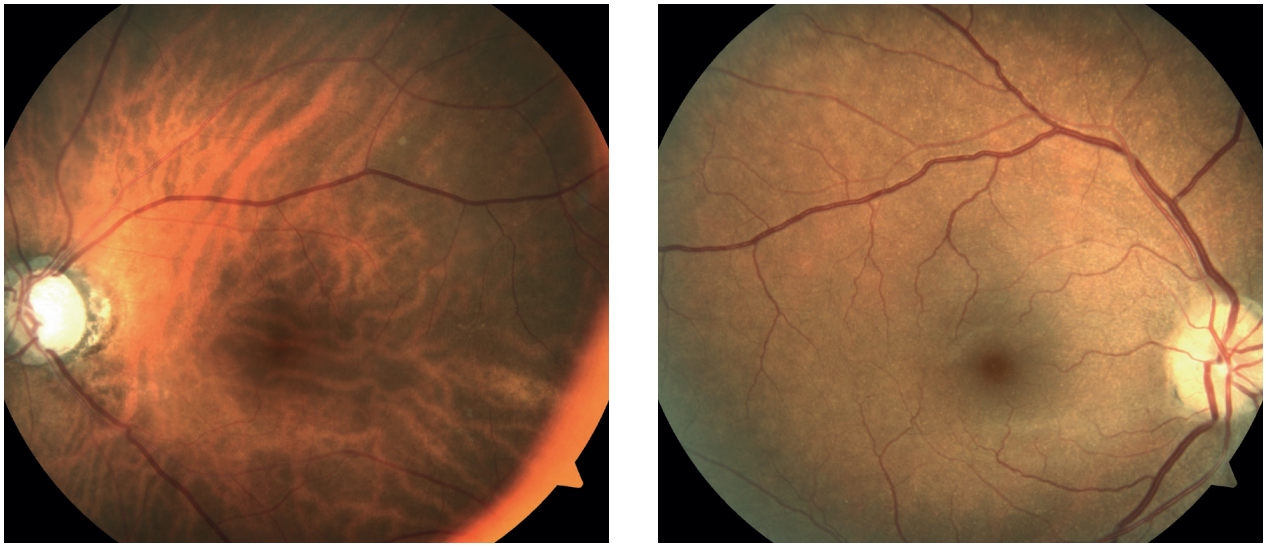


Figure 4. Mild arterial hypertensive angiopathy: arterial narrowing and arterio-venous crossing signs. No evidence of retinopathy. The image of the fundus is normal. There are no microaneurysms and hemorrhages, which are the first symptoms of diabetic retinopathy.

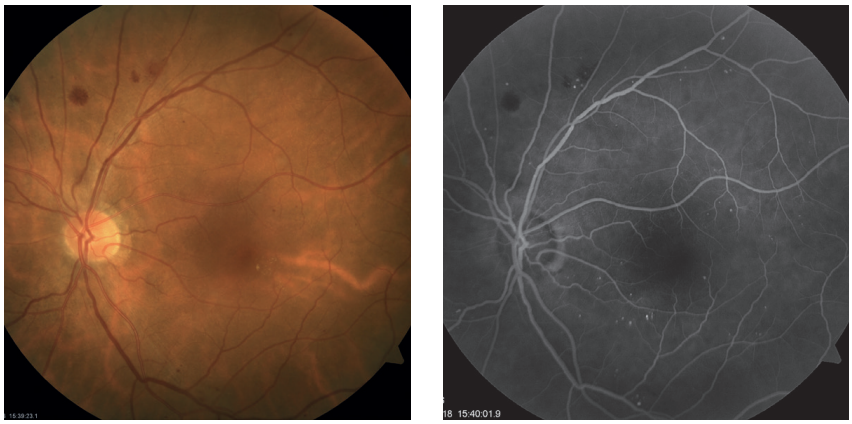


Figure 5. Mild non-proliferative diabetic retinopathy. The colour photograph shows a few microaneurysms, which can be more clearly identified on the angiographic image. There are also dot-blot hemorrhages. No macular edema or neovascularization.

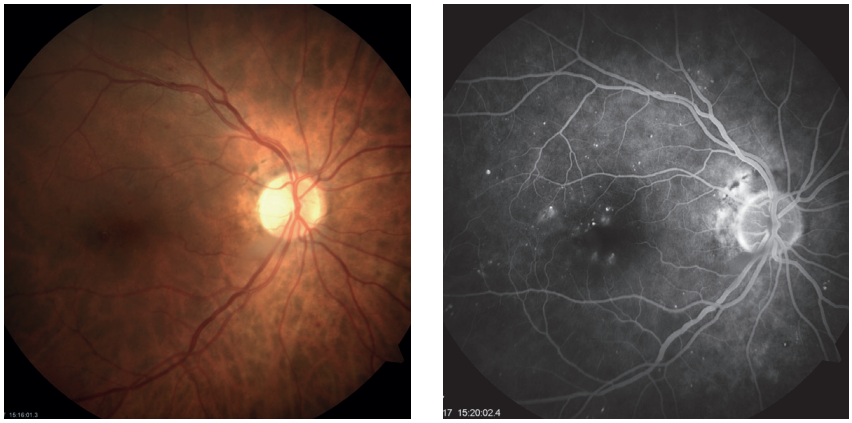
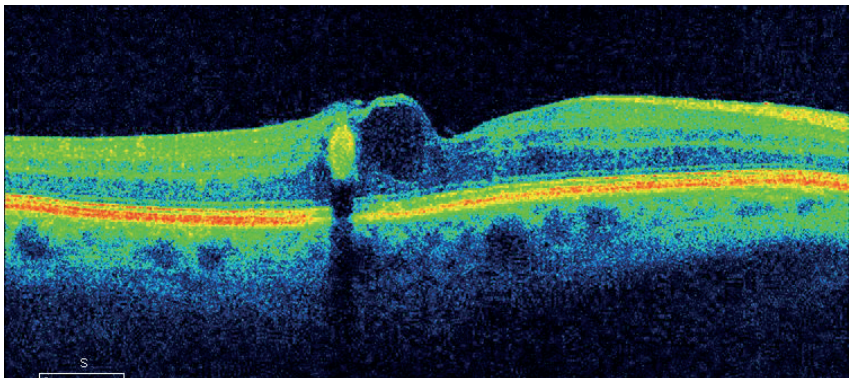


Figure 6. Mild non-proliferative diabetic retinopathy with macular edema. The colour photograph shows several microaneurysms located around the fovea. The angiographic image reveals a leak from these microaneurysms, causing foveal edema. Clinically significant macular edema was confirmed in SD-OCT scans.



Moderate non-proliferative diabetic retinopathy

According to Wilkinson's definition, based on the simplified ETDRS classification rules, that expression describes a retinopathy that is more advanced than mild non-proliferative retinopathy, but less severe than severe non-proliferative retinopathy (Figs. 7–8). In practice, this is a retinopathy with multiple microaneurysms and hemorrhages, although the hemorrhages are not very numerous, and are not very severe. Hard exudates may be present. Cotton wool spots are less common in this type of retinopathy and they usually are neither extensive nor numerous. There are no venous anomalies, IRMA, or large areas of hypoperfusion. Patients with this type of retinopathy without macular edema (DME), should be monitored every 6–12 months (according to the American Academy of Ophthalmology (AAO) and the Royal College of Ophthalmologists (RCO) guidelines)[11, 12].

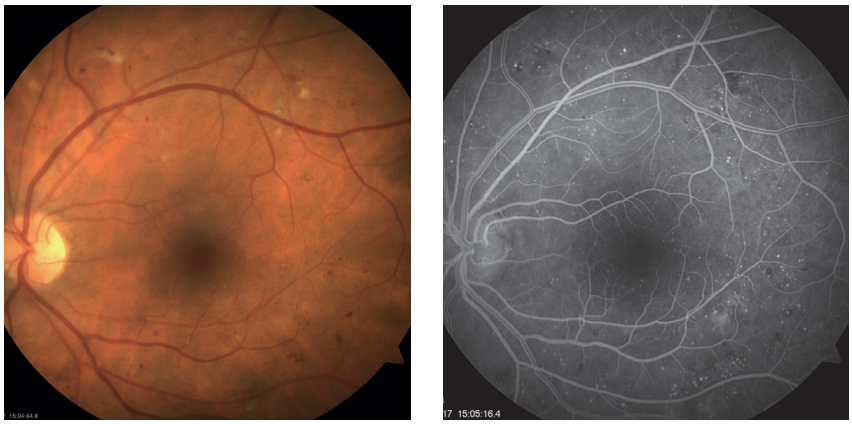


Figure 7. Moderate non-proliferative diabetic retinopathy. The colour photograph shows moderately numerous microaneurysms and hemorrhages as well as a few cotton wool spots. In the angiographic image, the microaneurysms are clearer. No clinically significant macular edema or neovascularization is detected.

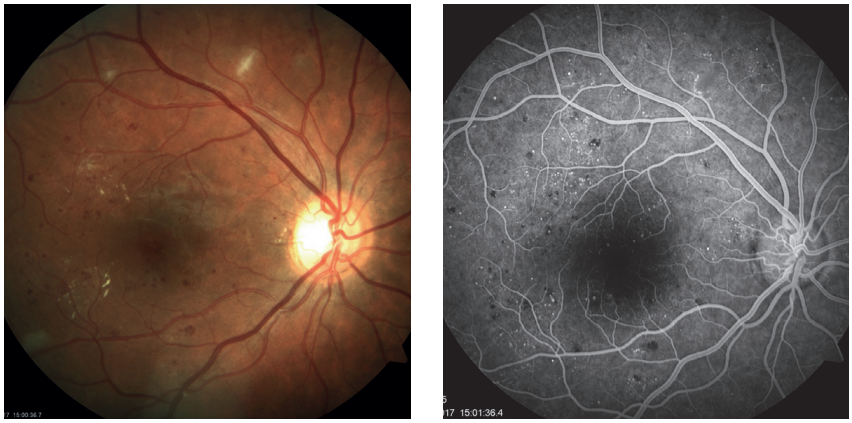
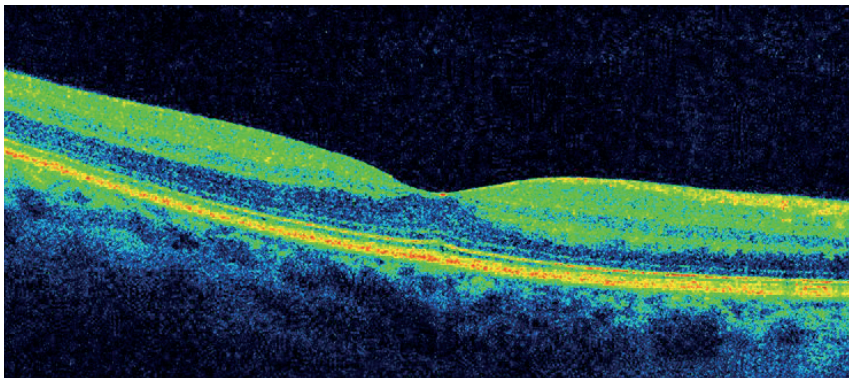


Figure 8. Moderate non-proliferative diabetic retinopathy, more advanced than in Figure 7. The colour photograph shows multiple microaneurysms as well as hard and soft exudates. The angiographic images show numerous microaneurysms and isolated areas of hypoperfusion in the area of cotton wool spots. The SD-OCT shows no sign of clinically significant macular edema.



Severe non-proliferative diabetic retinopathy

According to the Wilkinson classification, this type of retinopathy corresponds to pre-proliferative retinopathy in the British classification (R2). As a result of progressive changes in the vessels, perfusion of a large portion of the retina is impaired (Fig. 9). Hence, the presence of signs characteristic of ischemia: venous anomalies, IRMA, cotton wool spots. Dot-blot hemorrhages are numerous and located in the deeper layers of the retina. Vascular perfusion is easier to assess in FA. Patients with this type of retinopathy should be monitored more frequently, at least every 4–6 months.

Proliferative diabetic retinopathy

Proliferative diabetic retinopathy is characterized by the presence of neovascularization at the optic nerve disc (NVD) and neovascularization elsewhere (NVE). Usually, pathological vessels can be identified by ophthalmoscopy, but in case of doubt, FA is helpful

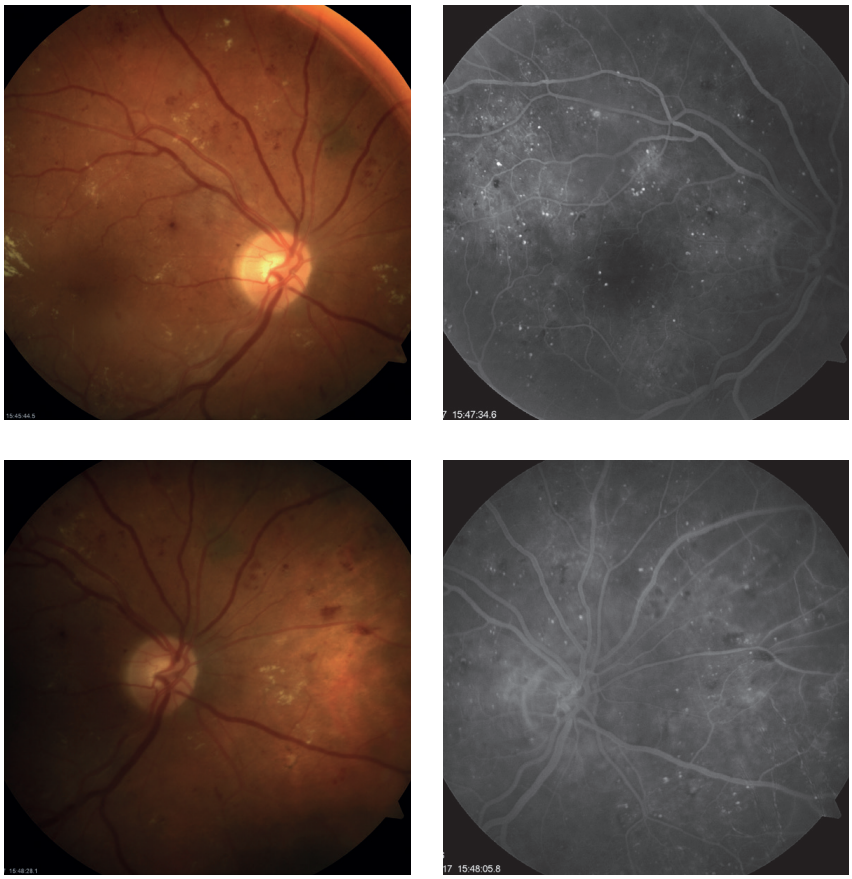
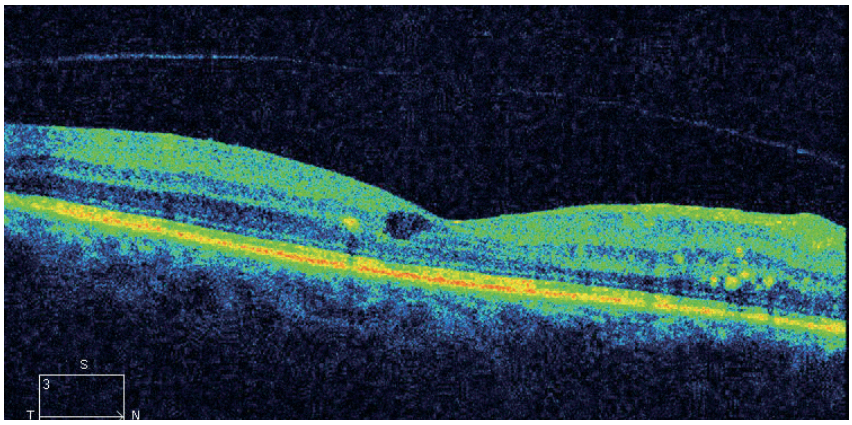


Figure 9. Severe non-proliferative diabetic retinopathy. The colour photographs show numerous dot-blot hemorrhages, microaneurysms, and hard and soft exudates. Additionally, the angiographic images show areas of hypoperfusion and venous vessel anomalies, located mainly in the nasal sector. SD-OCT reveals the features of moderate macular edema in the form of retinal thickening and cystic lesions in the sensory retina.



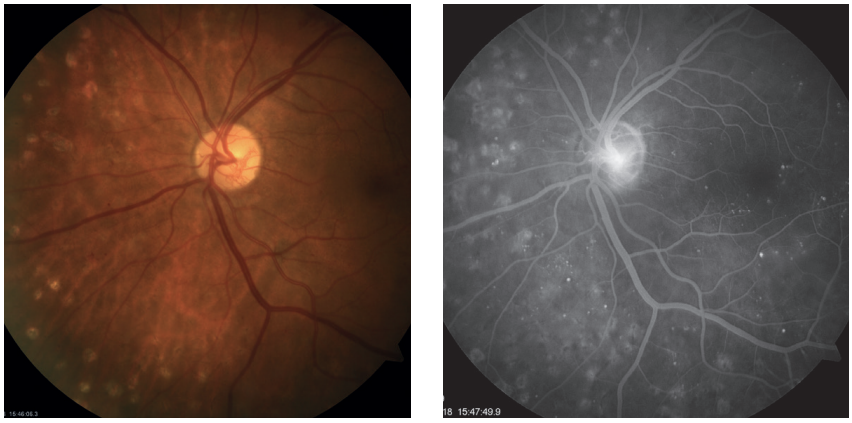


Figure 10. Initial proliferative diabetic retinopathy. The ophthalmoscopic image shows small vascular proliferation on the optic nerve disc. Late-phase angiography reveals leakage from pathologic vessels on the optic disc and no significant macular edema.

(Figs. 10–15). This is the case when we suspect initial NVD or small, difficult to locate neovascularization areas in the peripheral part of the retina. Leakage from pathological vessels is usually clearly visible in FA. Pathological vessels may be accompanied by pre-retinal or vitreous hemorrhages. The mere presence of such a hemorrhage in the process of diagnosing DR indicates its proliferative nature, even if the source of neovascularization turns out to be difficult to detect at the fundus. Any PDR indicates that prompt intervention is required: laser therapy, intravitreal therapy or surgical treatment (see Chapter 9: *Diabetic retinopathy management*, pp. 177–193).

Diabetic macular edema

See Chapter 8: *Diabetic maculopathy (diabetic macular edema) – diagnosis and treatment*, pp. 113–176 for details on DME classification.

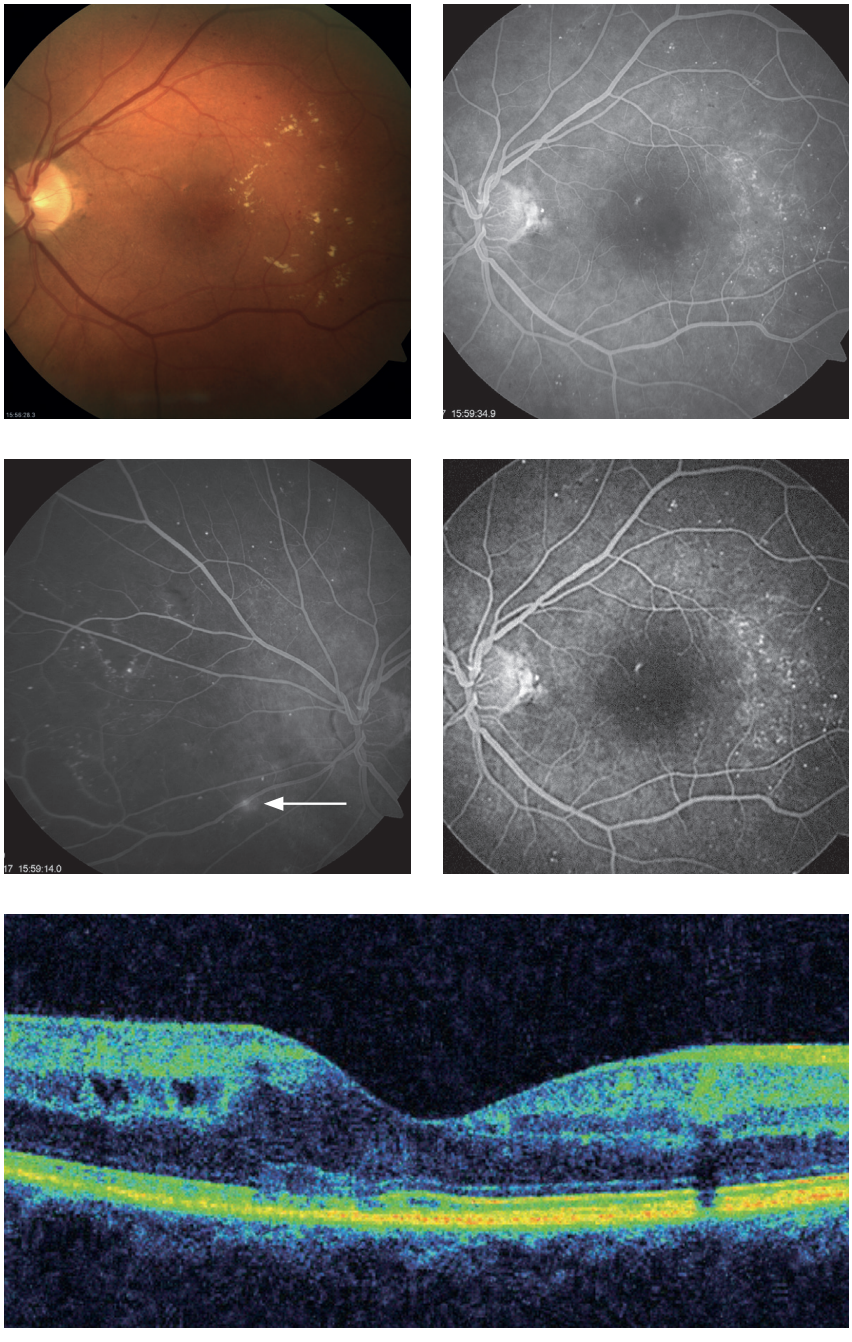


Figure 11. Initial proliferative diabetic retinopathy with macular edema. Ophthalmoscopy shows edema in the temporal part of the macula. Angiography presents small neovascularization in the nasal sector (indicated by the arrow). SD-OCT reveals macular edema in the form of diffuse retinal thickening and cysts present in the sensory retina.

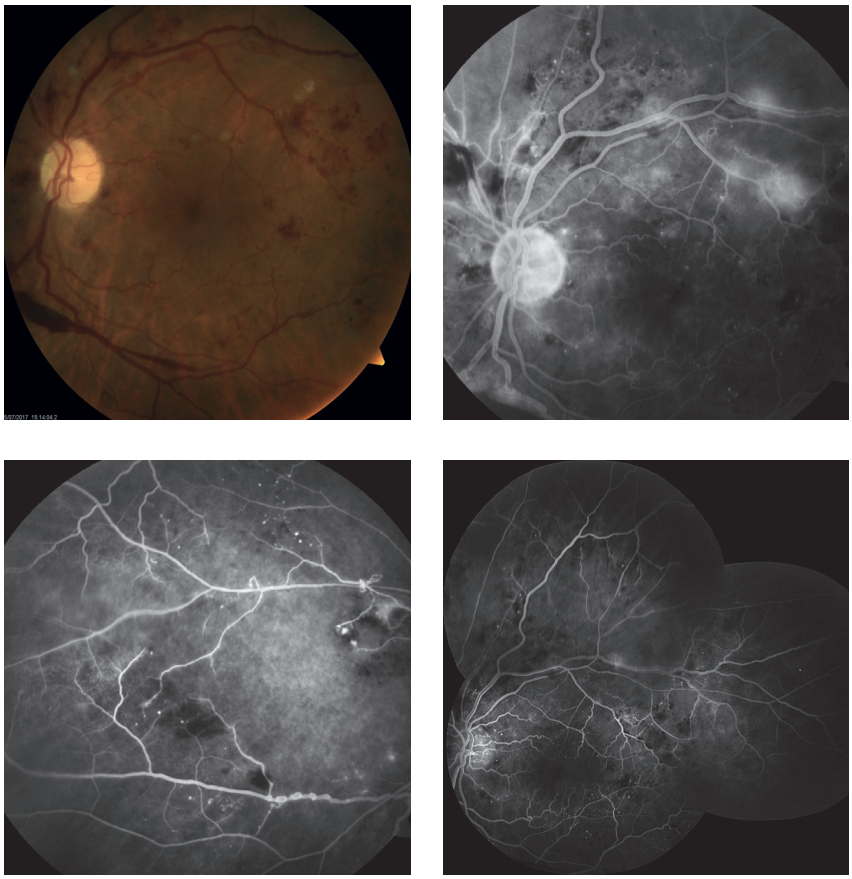


Figure 12. High-risk proliferative diabetic retinopathy. The ophthalmoscopic image shows preretinal hemorrhage, indicating the presence of neovascularization. The angiographic images reveal leakage from numerous vascular proliferations beyond the optic disc. In the nasal sector, there are extensive areas of hypoperfusion as well as venous beading, constrictions at venous vessels. No foveal edema.

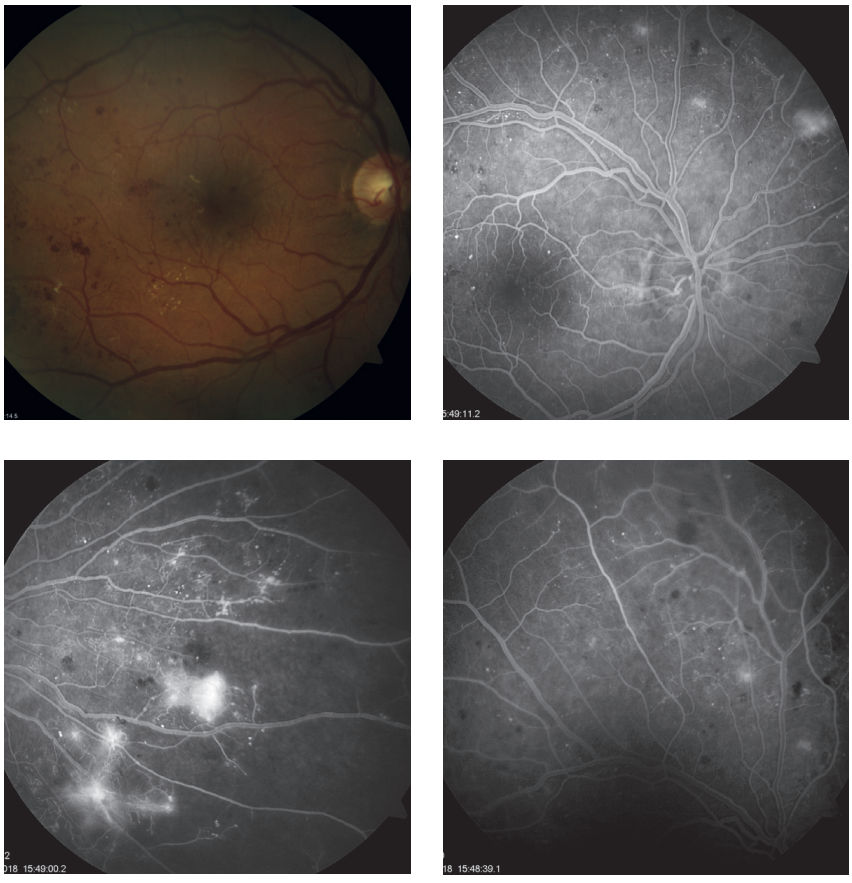


Figure 13. High-risk proliferative diabetic retinopathy. Extensive vascular proliferation beyond the optic nerve disc (leaks) and areas of hypoperfusion are visible in the nasal quadrants.

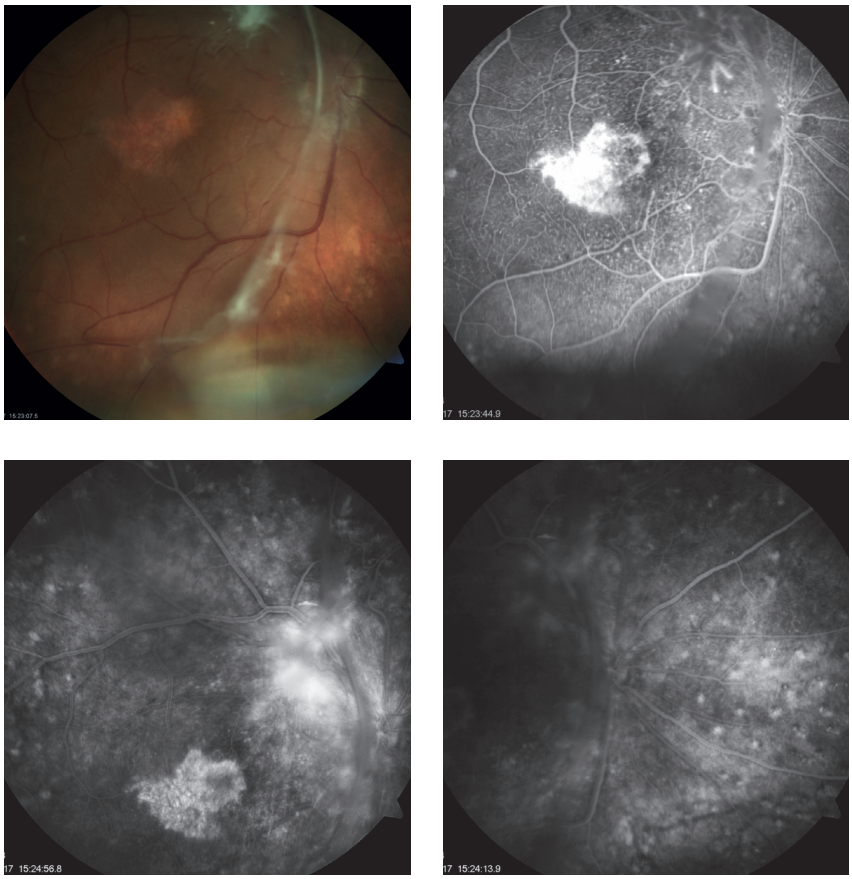


Figure 14. Advanced proliferative diabetic retinopathy after laser therapy. The optic nerve disc shows multiple fibrous proliferations. Angiography reveals trace vasculature of the membranes on the optic disc, but fibrous tissue staining predominates. Extensive post-edematous atrophy of retinal pigment epithelium is visible in the macula. In the nasal sectors, there are few visible spots after laser photocoagulation – it is necessary to supplement the laser treatment.

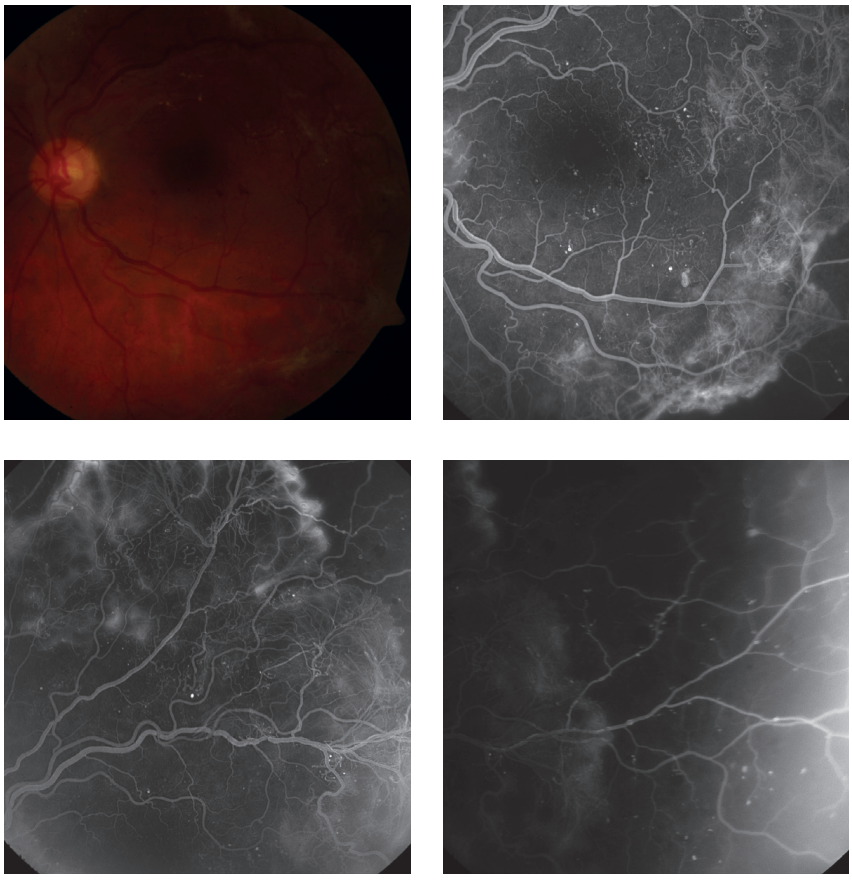


Figure 15. Previously untreated advanced proliferative diabetic retinopathy with preretinal hemorrhage. Peripheral areas are devoid of capillary perfusion and there is neovascular proliferation beyond the optic nerve disc.

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Chapter 7: Systemic treatment of diabetic retinopathy and diabetic macular edema

Monika Łukaszewicz

General remarks

Diabetic retinopathy (DR) develops in uncontrolled diabetes mellitus (DM). When diabetes is managed well, the risk of retinopathy decreases. The neglect of diabetes presents a serious obstacle to the effective treatment of retinopathy by an ophthalmologist. Glycemic control and the normalization of blood pressure and lipid profile are the basis of systemic treatment and preventing the progression of diabetic retinopathy[1].

Treatment is carried out on three levels:

1. Primary prevention is designed to prevent DR in diabetes. It consists of systemic lifestyle modifications, such as increased physical activity and nutrition, pharmacological treatment of hyperglycemia and hypertension, and regular screening tests.

2. Secondary prevention is designed to prevent the progression of DR once it has been diagnosed, through further risk factor control, regular screening for the severity of fundus lesions, and the development and implementation of evidence-based recommendations. The key to effective screening in primary and secondary prevention is access to a specialized ophthalmologist and fundus examination. On a population scale, a possible future solution would be provided by telemedicine methods involving artificial intelligence.

3. The prevention of blindness in the course of DR, i.e. tertiary prevention, is based on laser and surgical procedures (including pars plana vitrectomy), combined with a growing reliance on anti-VEGF agents.

Clinical trial results

Epidemiological studies in highly developed countries, such as the USA and the United Kingdom, show a decreasing incidence of blindness in the course of DR, which is the result of educational effort coordinated by public health units, increasing patient awareness, early detection of eye fundus lesions during screening tests, careful monitoring of risk factors, and the availability of effective tertiary treatment[2].

Large randomized clinical trials conducted with diabetic patients – the Diabetes Control and Complication Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) – have shown that improving glycemic control and blood pressure reduces the risk of retinopathy developing and progressing in patients with type 1 and 2 diabetes (DM1 and DM2).

The DCCT study showed that with DM1 intensive glycemic control was the most important factor, and the patients randomized to the intensive treatment group reduced their risk of developing DR by 75% and of DR progressing by 54% over 6.5 years. There was a 35–50% reduction in the need for cataract surgery and vitrectomy in this group[3, 4].

In patients with DM2 who were intensively treated in the UKPDS study, the risk of DR was reduced by 25%[5]. A similar result (20% reduction) was obtained in the meta-analysis by Hemmingsen et al.[6]. However, it is worth remembering that in the event of detecting ophthalmic problems, sudden adjustment of metabolic parameters is not recommended, because in some cases, it leads to retinopathy worsening (especially in pregnant patients), and also increases the risk of

developing hypoglycemia. In such clinical situations, treatment goals are set on an individual basis and modified at each visit to a diabetologist.

For patients with DM2 in the UKPDS study, adequate blood pressure control was shown to be of the greatest importance, since it reduced the risk of DR progression by 34%, and the risk of visual deterioration over nine years by 47%[7, 8].

In the Steno-2 study, a multifactorial intervention for glycemia, hypertension, dyslipidemia and microalbuminuria – using hypoglycemic drugs, converting enzyme inhibitors, and statins – reduced the risk of microvascular and macrovascular complications (including DR) by 50%[9]. This study demonstrated the effectiveness of a proactive, multifactorial approach to risk factors in patients with DM2.

The replicability of the results of epidemiological studies and large population studies was an essential factor in developing a general strategy for managing risk factors in all patients – both with and without retinopathy. In this regard, diabetes and ophthalmological societies around the world recommend adequate glycemic control (with HbA1c < 7%) along with the treatment of arterial hypertension and dyslipidemia[10].

Disease progression

Type 2 diabetes is a chronic, progressive disease. Therefore, it is necessary for informed patients to self-monitor: they should know how to respond to changes in control parameters and when to see a doctor. Patients who are passive in the face of the changes require regular visit at their diabetes clinic. In the vast majority of patients, the inevitable progression of the disease necessitates patient monitoring and careful treatment adjustment.

New technologies come with new benefits. Diabetes helpline services, mobile phone and computer applications, and above all, sensors for continuous blood glucose measurement play an increasingly important role in education, self-monitoring and prevention[11].

Mobile applications make it easy for patients to track and control their physical activity, diet, weight loss, sleep quality and water intake to help them set individual goals. Personalized educational and motivational content via SMS or e-mail, as well as reminders to take medications and test blood pressure and blood glucose levels, lead to behavioural changes and improve glycemic control.

The future lies in automatic retinopathy screening – a fundus scan without pupil dilatation, assessed remotely.

Medicines

The DCCT and UKPDS studies used the classic antidiabetic drugs, namely insulin, metformin, and sulfonylurea derivatives. In groups in which a reduction in the incidence and progression of retinopathy was recommended, these drugs were used intensively, i.e., higher and more frequent doses were recommended to lower HbA1c.

In recent years, new groups of DM2 drugs have been launched: DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 analogues. Despite the proven positive effect on many macrovascular complications arising from diabetes, such as stroke, myocardial infarction, and cardiovascular death, an independent beneficial effect on diabetic retinopathy has not been confirmed for any of those drugs.

GLP-1 analogues

GLP-1 analogues are increasingly more often used in the treatment of DM2. Results from two large studies on cardiovascular events – Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation (LEADER)

and Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) – have led to changes in the recommendations for the treatment of diabetes due to the strong preventative effect of these drugs in relation to the macroangiopathic complications of diabetes.

Both studies confirmed the beneficial effects of GLP-1 analogues in reducing the number of cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes. Results for liraglutide (LEADER) and dulaglutide (REWIND) in respect to retinopathy were neutral, while the use of semaglutide (SUSTAIN-6) was associated with a significant progression of retinopathy[12]. These results were very surprising and incomprehensible because experimental studies confirmed the beneficial effects of this group of drugs[13, 14], and their use so far has not been associated with side effects on the visual system[15].

Unfortunately, a well-known phenomenon that accompanies abrupt diabetes control is the worsening of diabetic retinopathy. Therefore, when starting therapy in people with very high glucose levels, caution is required, and treatment goals should not be too ambitious at the beginning. The progression of retinopathy probably results from the rapid reduction of glucose concentration in patients with pre-existing retinopathy, rather than from the use of a specific drug[16].

Fenofibrate

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials[17] have demonstrated a beneficial effect of fenofibrate on retinal vascularization in patients with DM2[18] and an improvement in the course of mild retinopathy, both in the mechanism of lowering lipid concentrations and independently of this mechanism. Hence, this drug may have a significant role in the prevention of diabetic retinopathy. This positive effect contrasts with other drugs for which cardiovascular prognostic benefits have been demonstrated – such as empagliflozin, liraglutide, perindopril in combination with indapamide, and ramipril – but which have not shown positive effects in the treatment of diabetic retinopathy.

Fenofibrate has also been shown to reduce uric acid levels[19], which may reduce metabolic disturbances in diabetes.

Aspirin

Aspirin is used in diabetes as an anticoagulant to prevent microangiopathy[20]. In the ETDRS study[21], at a dose of 650 mg, aspirin did not prevent the progression of proliferative retinopathy, nor did it reduce the risk of blindness. At the same time, it did not increase the risk of vitreous bleeding. Furthermore, aspirin does not affect laser therapy efficacy[22].

The use of aspirin does not significantly increase the risk of bleeding during and after vitrectomy[23]. It is worth emphasizing that it is the severity of diabetic complications that predisposes the patient to bleeding, not the use of antiplatelet or anticoagulant drugs[24].

The presence of diabetic retinopathy does not preclude the use of aspirin to reduce the risk of cardiovascular events[25].

Evidence for the effects of drugs on the endothelium

Due to the complexity of the mechanism that leads to microangiopathic complications in diabetes, including retinopathy, drugs that improve the condition of the vascular endothelium may have a beneficial effect in systemic treatment.

The endothelium regulates blood pressure, distributes nutrients and hormones because the processes of coagulation, fibrinolysis and inflammation take place and interact on its smooth surface. Endothelial dysfunction in diabetes leads to the development and

progression of macroangiopathic complications and is also associated with microangiopathic complications: retinopathy, nephropathy and neuropathy.

The most important factors that influence its functioning are hyperglycemia, insulin resistance, hyperinsulinemia and dyslipidemia. Among many anti-diabetic drugs, metformin, gliclazide, pioglitazone, exenatide and dapagliflozin undoubtedly have a beneficial effect on the endothelium. Other drugs, such as sulfonylurea derivatives, DPP-4 inhibitors, and liraglutide, have neutral effects, whereas the effects of insulin analogs, such as empagliflozin and canagliflozin, require further study.

In addition to hypoglycemic drugs, statins and fenofibrate also improve endothelial function. Ezetimibe awaits trials in a diabetic patient population. The effect of aspirin is dose-dependent – low doses (up to 81 mg) improve endothelial function, while high doses (325 mg) do not. Clopidogrel still requires further study. Some hypotensive drugs – angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers – have beneficial effects on the endothelium[26].

Benfotiamine[27] and alpha-lipoic acid[28] improve endothelial function in patients with DM2, and vitamin D3, which is beneficial for the endothelium, may have a positive effect on the metabolic syndrome but requires further research in terms of diabetes[29, 30], especially as it promotes endothelial regeneration[31]. Benfotiamine, a drug used in the treatment of diabetic neuropathy, acts on several pathomechanisms of retinopathy[32]. Its protective effect in this disease has been confirmed in experimental models[33, 34].

Complex supplements

In the era of evidence-based medicine (EBM), all reports on the impact of supplements on health should be treated anecdotally, which does not mean that an individual patient cannot benefit from the use of such substances.

The number and quality of works on this topic are limited. The DiVFuSS study[35] used xanthophyll pigments, antioxidants, and selected botanical extracts: the supplement contained vitamins C, D3 and E (d-α tocopherol), zinc oxide, eicosapentaenoic acid, docosahexaenoic acid, α-lipoic acid (racemic mixture), coenzyme Q10, mixed tocotrienols/tocopherols, zeaxanthin, lutein, benfotiamine, N-acetylcysteine, grape seed extract, resveratrol, turmeric root and green tea leaf extract, and Pycnogenol – a patented sea pine bark extract, *Sp Pinus pinaster*.

Multifactorial treatment

Multifactorial effective treatment of diabetes includes the remediation of all comorbidities, deficiencies and metabolic disorders[36], including:

- chronic inflammation, such as chronic tonsillitis or gastritis, allergies, tooth decay,
- recurrent inflammation, for example, urinary tract infections caused by urolithiasis,
- vitamin deficiencies, including vitamin D3, vitamin B12,
- hyperlipidemia, hyperuricemia, hypokalemia,
- disorders of the thyroid gland and other endocrine glands,
- any other medical condition that affects the course of diabetes.

Diabetic diet

The diabetic diet is now defined as part of a healthy lifestyle, which also includes regular recreational physical activity. The diet should involve calorie restriction, which is necessary in the case of obesity and overweight. It should exclude mammalian proteins and necessarily include carbohydrate products with a low glycemic index, i.e. groats and nonleafy vegetables rich in polyphenols, as the diet basis. High-protein or high-fat diets are not recommended. If no progress

is made with a dietary regimen, the patient should seek a dietician's assistance.

Stress

Stress, both acute and chronic, is an major factor that affects diabetes management. Fatigue, chronic sleep deprivation, and hypercortisolemia are some elements of stress that should be discussed with patients so that they can consider practising self-care.

Detailed recommendations on systemic treatment can be found in the annually updated Recommendations of the Polish Diabetes Society (Polskie Towarzystwo Diabetologiczne)[37].

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Chapter 8: Diabetic maculopathy (diabetic macular edema) – diagnosis and treatment

Introductory remarks

Diabetic macular edema (DME) is the leading cause of legal blindness in patients with diabetic retinopathy (DR)[1, 2]. In 24% of patients, untreated DME causes the loss of three lines on the ETDRS chart within three years from its onset[3].

The prevalence of DME in the entire population of people with diabetes mellitus (DM) ranges from 1 to 10% (data vary considerably in the published studies)[4, 5, 6, 7, 8] and depends on the type of diabetes and its duration[9, 10, 11] (see Chapter 1: *Epidemiology of diabetes, diabetic retinopathy and diabetic macular edema*, pp. 23–26).

Risk factors for the development of DME are still debated[12, 13, 14, 15, 16]. The most commonly mentioned ones are listed below:

- longer duration of diabetes,
- high levels of HbA1c,
- proteinuria (patients with insulin-dependent diabetes),
- high levels of plasma lipids (patients with type 1 diabetes (DM1)),
- the severity of the retinopathy,
- increased posterior vitreomacular adhesion (VMA).

The incidence of DME clearly increases with the duration of the diabetes, and it values are higher in individuals taking insulin (Table 1). In the WESDR study presented in the table, the vast majority of the group with younger onset diabetes used insulin (87%). The peak incidence of DME occurred after 12 years in younger onset diabetes and after 10 years in older onset diabetes[9, 11].

Anatomy of the fovea and foveal avascular zone

The anatomy of the fovea differs from other parts of the retina (see Chapter 3: *Anatomical aspects of diabetic retinopathy*, pp. 47–49). Being aware of these differences allows us to understand the mechanism of DME development and to rationalize the therapeutic management of this disease.

Let us recall that in the area of the fovea itself, there is a reduced number of retinal layers. Practically, there

Table 1. Incidence of diabetic macular edema in relation to the duration of the diabetes (according to the Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR))[11].

Type of diabetes	4-year incidence rate (%)	10-year incidence rate (%)
Younger onset	8.2	20.1
Older onset, taking insulin	8.4	25.4
Older onset, not taking insulin	2.9	13.9

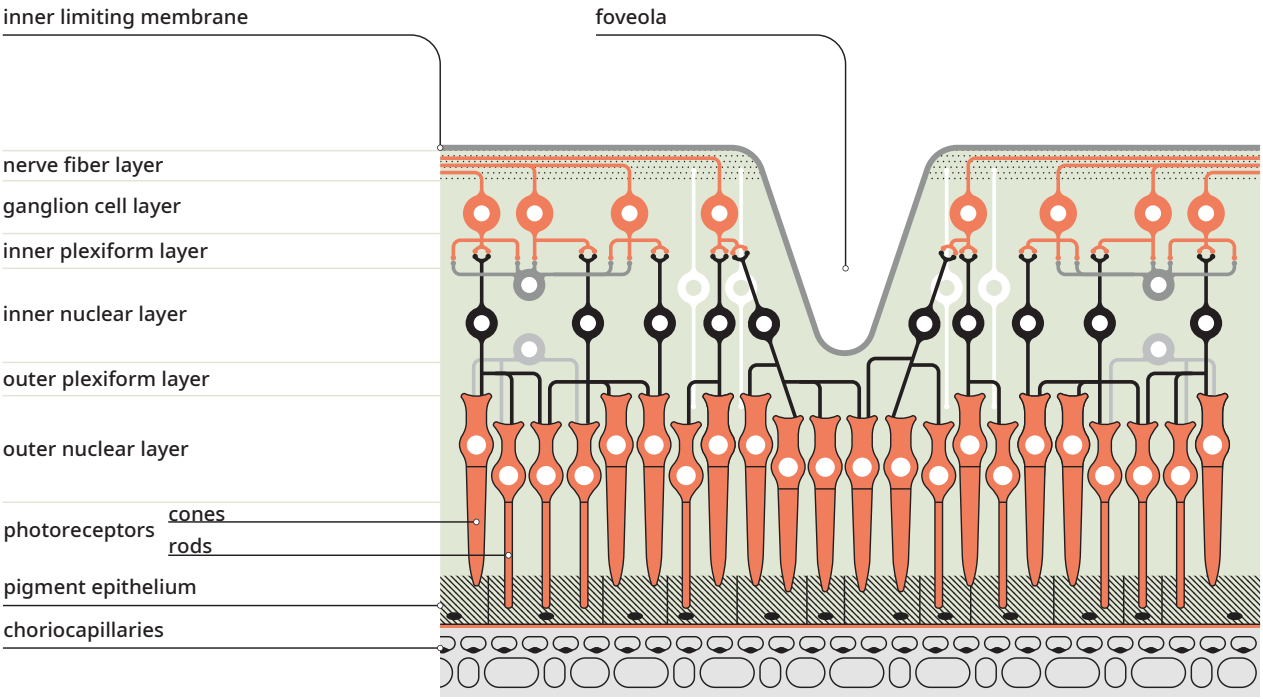


Figure 1. Diagram of the fovea structure (cross-section).

are only cones and the inner limiting membrane (ILM). The remaining layers are moved to the sides, forming a foveal depression (Fig. 1). A characteristic feature of the fovea is the thick outer plexiform layer (OPL), the so-called Henle's fiber layer, corresponding to obliquely running axons of the cones. Henle's fiber layer is the main location of central retinal edema.

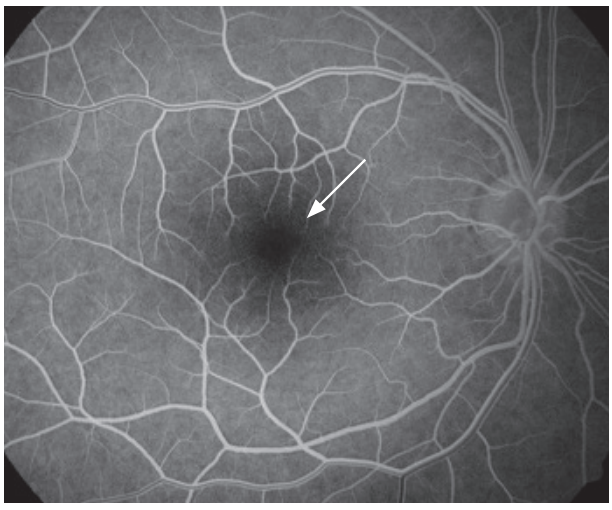


Figure 2. Foveal avascular zone (indicated by the arrow) visible in fluorescein angiography.

The central part of the fovea is occupied by the foveal avascular zone (FAZ), which is approximately 350–500 µm wide (Fig. 2). Outside this central zone, blood is distributed through two capillary plexuses: superficial (in the nerve fiber layer (NFL)) and deep (primarily in the inner nucleated layer (INL)), which nourish the inner layers of the retina (Fig. 3). One level of capillaries is present only at the border of the avascular zone and is located in the ganglion cell layer (GCL). The external retina, on the other hand, is avascular and receives oxygen due to diffusion from the choroid.

Pathomechanism of diabetic macular edema

The pathomechanism of DME formation is somewhat similar to that of the underlying microvascular changes

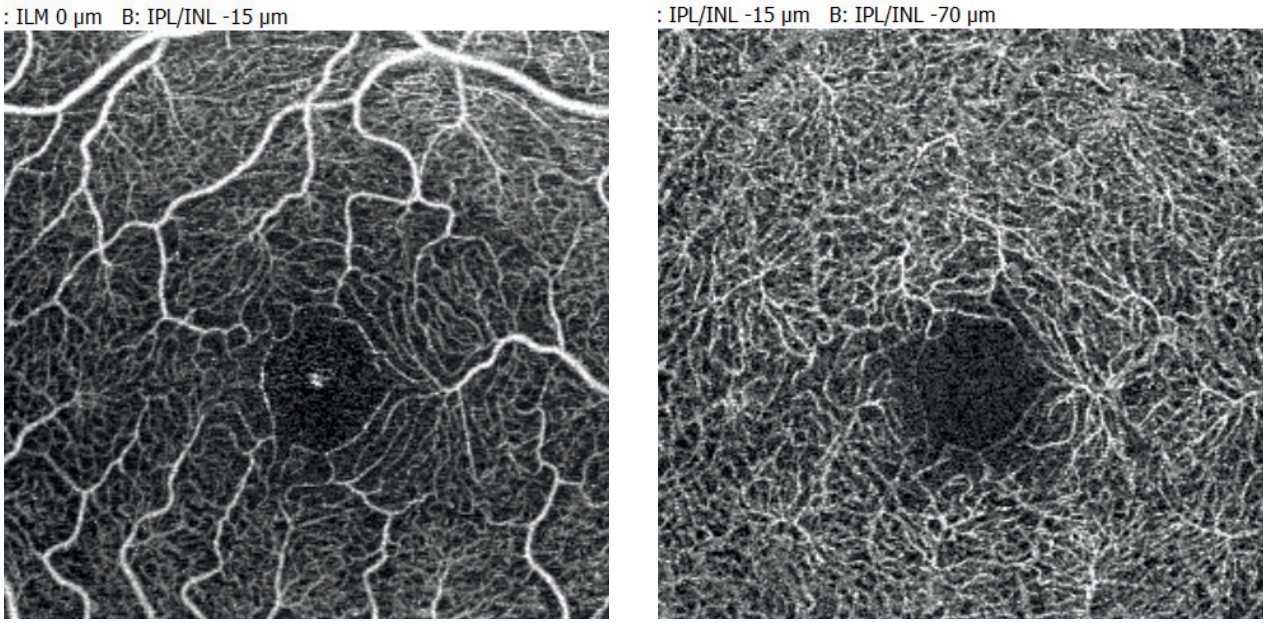


Figure 3. Angio-OCT of a normal fovea. Visible foveal avascular zone in the superficial (left scan) and deep (right scan) capillary plexus.

in all diabetic retinopathy. Changes in capillaries, such as loss of pericytes, increase the permeability of vessels adjacent to the fovea and lead to the formation of leaking microaneurysms[17, 18]. Thus, despite the lack of vessels in the very centre of the fovea, fluid migrates to the centre from the adjacent edematous retina.

One of the consequences of tissue edema is hypoxia, to which the retina reacts in two ways. First, the autoregulatory mechanisms lead to the dilation of arterioles and increased flow, which in turn increases the hydrostatic pressure in the capillaries and veins[19]. This rise in pressure causes further damage to the small vessels and leads to the leakage of fluid beyond their lumen. Secondly, there is an increased production of vascular endothelial growth factor (VEGF)[20]. Its elevated level is believed to be responsible for even greater vascular permeability and edema increase.

Additionally, the course of edema increase is accompanied by inflammatory processes. The level of inflammation mediators – cytokines, is elevated[21]. That adds significantly to increase in vascular permeability and mounting up of the edema.

Other factors which cause the retention of fluid, and are both typical of diabetes, include the impairment of vascular autoregulatory processes and the impairment of choroidal circulation, which is inflammation[22].

Outside the foveal avascular zone, fluid leaking from the vessels and microaneurysms is eliminated from the extracellular space in two directions:

1. to the intravascular space of the veins,
2. into the choroid via the retinal pigment epithelium (RPE) pump.

In the macular center, which is devoid of vessels, the only mechanism for fluid elimination is the activity of the RPE pump. In DME, there is an approximately twelve-fold increase in vascular permeability and only a two-fold increase in the activity of the RPE pump. This disproportion leads to an accumulation of fluid in this area[23, 24].

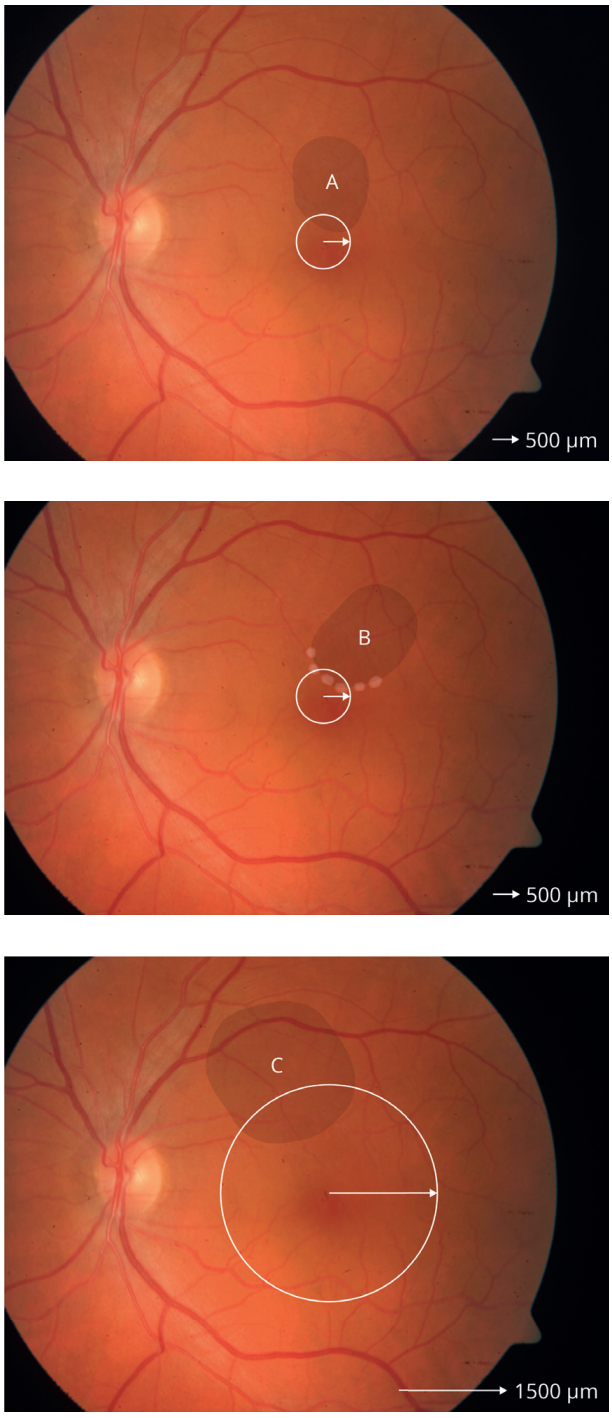


Figure 4. Clinically significant macular edema (definition):
A – retinal thickening within 500 µm from the centre of the fovea,
B – hard exudates within 500 µm from the centre of the fovea with adjacent retinal thickening,
C – retinal thickening of at least the size of the area of the optic nerve disc (1 DA), any part of which is located closer than one disc diameter from the centre of the fovea.

The vitreous body also plays a role in the formation of DME, as it functions differently in diabetic patients than it does in a healthy person. Increased glycation and cross-linking of vitreous collagen fibers in diabetics lead to a greater tendency to develop strong vitreoretinal adhesion or even traction, and secondary macular edema[25, 26].

Pathophysiology of DME (key mechanisms)

- loss of pericytes and an increase in vascular permeability,
- leaking microaneurysms at the border of the ischemic retina,
- increase in the VEGF level,
- increase in cytokine level (inflammatory process),
- disruption of vascular autoregulatory mechanisms,
- impaired choroidal circulation,
- changes in the vitreous.

Understanding the mechanism of DME formation allows us to understand the methods of its treatment. Consequently:

1. Lowering blood pressure reduces the passive flow of fluid through the damaged inner blood-retinal barrier.
2. GRID laser therapy reduces the number of photoreceptors in the posterior pole and thus the oxygen demand of the tissue. In addition, the pathway of oxygen flow from the choroid to the retina is shortened, and as a consequence, oxygenation of the macula improves.
3. Focal laser therapy directly destroys the source of the leak, i.e. microaneurysms, and improves the functioning of the RPE as a pump.
4. Subthreshold micropulse laser treatment (SMPLT) improves RPE metabolism and thus the functioning of the RPE as a pump to eliminate fluid from the retina.
5. VEGF receptor inhibitors reduce the effect of increased vascular permeability.
6. Steroidal and non-steroidal anti-inflammatory drugs inhibit inflammation mediators.

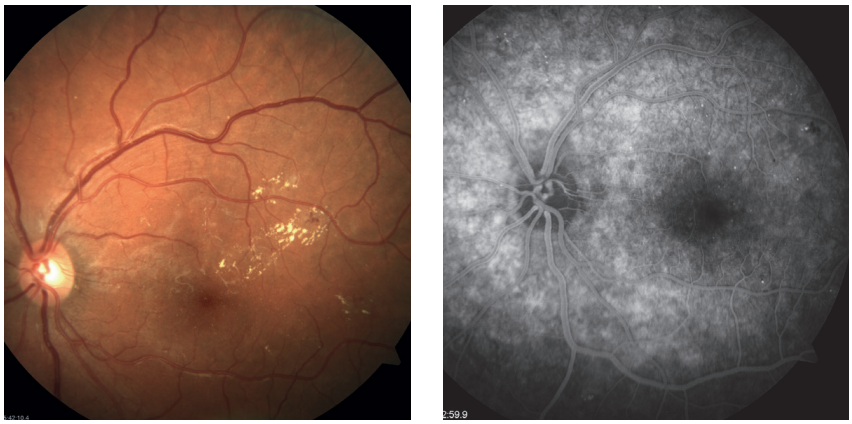


Figure 5. Focal macular edema. The colour image shows a cluster of microaneurysms surrounded by hard exudates. Microaneurysms can be identified and located in angiographic images.

7. Pars plana vitrectomy (PPV) eliminates the traction exerted on the retina by pre-retinal membranes and/or increased vitreous adhesion. In the absence of traction, vitrectomy improves the oxygenation of the retina and reduces the number of pro-inflammatory and pro-edema mediators in the posterior vitreous chamber, and eliminates increased subclinical vitreous adhesion.

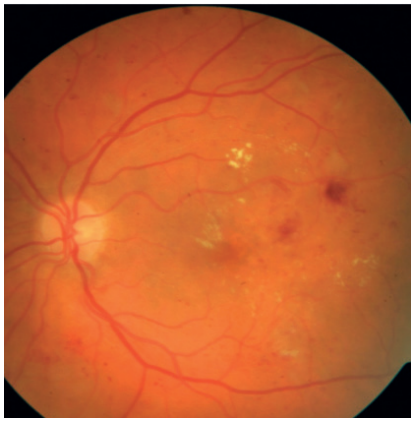
Morphological aspects of diabetic macular edema

Fluid leakage most often accumulates between the inner nuclear layer and outer plexiform layer. In more advanced stages, it takes the form of cystoid edema – in this case, cysts are formed in the outer plexiform layer. In 15–30% of cases, DME takes the form of subretinal fluid (SRF). This form is most likely to occur with a significant impairment of the choroidal circulation and, as a consequence, poorer fluid elimination by the RPE[27].

One of the signs of DME is the formation of a star shape from hard exudates around the fovea. These are deposits of lipoprotein that remain after the pumping of salt and water into the choroidal space. These deposits are gradually eliminated by macrophages. The elimination time may be very long, even up to several years[28, 29]. Thus, it is possible that an examination shows residual hard exudates, but there is no actual edema of the retina.

Definitions related to diabetic macular edema

1. Diabetic macular edema (DME):
   a. retinal thickening within 1 DD from the macular center or definite hard exudates in this area (ETDRS classification)[3],
   b. retinal thickening within 2 DD from the macular center (nowadays, this definition is rarely used)[30].
2. Clinically significant diabetic macular edema (CSME, Fig. 4) was defined as at least one of the following (ETDRS)[3]:
   a. thickening of the retina within 500 µm or less from the macular center,
      or
   b. hard exudates within 500 µm or less from the macular center, if accompanied by retinal thickening,
      or
   c. retinal thickening with an area equal to or greater than the optic disc (≥ 1 DA) any part of which is within one disc diameter from the foveal center.
3. Focal and diffuse edema – the literature lacks precise definitions of these terms, which are often used to describe macular edema in fluorescein angiography (FA)[31].
   a. In the case of focal macular edema (Fig. 5), the following facts are taken into account:
      • its source is microaneurysms,



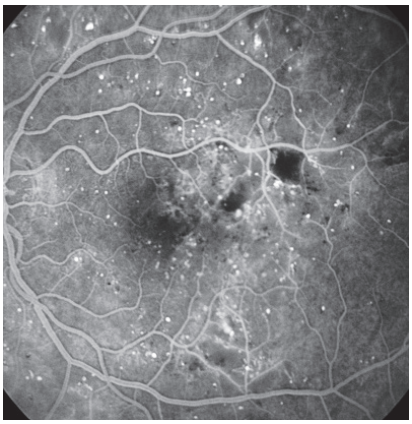


Figure 6. Diffuse macular edema. The colour image shows relatively few hard exudates and hemorrhages (petechiae) in the macular area. An angiographic image reveals diffuse staining of retinal tissue covering the entire posterior pole.

- it is often accompanied by hard ring-shaped exudates surrounding the microaneurysms,
- FA reveals microaneurysms that are the source of edema (local edema is seen in the late FA phase).

b. Diffuse edema (Fig. 6) is characterized by the following features:

- its source is mainly leakage from dilated capillaries (a general increase in vessel permeability),
- hard exudates are not always present and they are relatively small in relation to the extent of the edema,
- extensive retinal staining is evident in the late phase of FA; it covers a large area and has no focal source.

4. Subclinical diabetic macular edema (SCDME)[32]:
   a. clinically diagnosed mild retinal edema, but less than in the CSME definition,
   b. has no clinical features of DME (no stereoscopic retinal edema and no hard exudates) but a mild increase in retinal thickness as shown by retinal optical coherence tomography (OCT).
5. Refractory diabetic macular edema (refractory DME)[33] persists despite different forms of treatment such as photocoagulation, intravitreal therapy etc. It usually causes faster vision loss in older people and is associated with poorer glycemic control. This term is often used in the context of the efficacy of new intravitreal drugs being introduced in DME treatment.

Table 2. Classification of diabetic macular edema (DME) according to Wilkinson[34].

Severity	Signs upon dilated ophthalmoscopy
DME absent	no apparent retinal thickening or hard exudates in the posterior pole
DME present	apparent retinal thickening or hard exudates in the posterior pole
Macular edema categories	
Mild DME	some retinal thickening or hard exudates in the posterior pole, but far from the center of the macula
Moderate DME	retinal thickening or hard exudates approaching the center of the macula but not involving the center
Severe DME	retinal thickening or hard exudates occupying the center of the macula

The classification of diabetic macular edema

Table 2 shows the current classification of diabetic macular edema commonly used in Europe and the

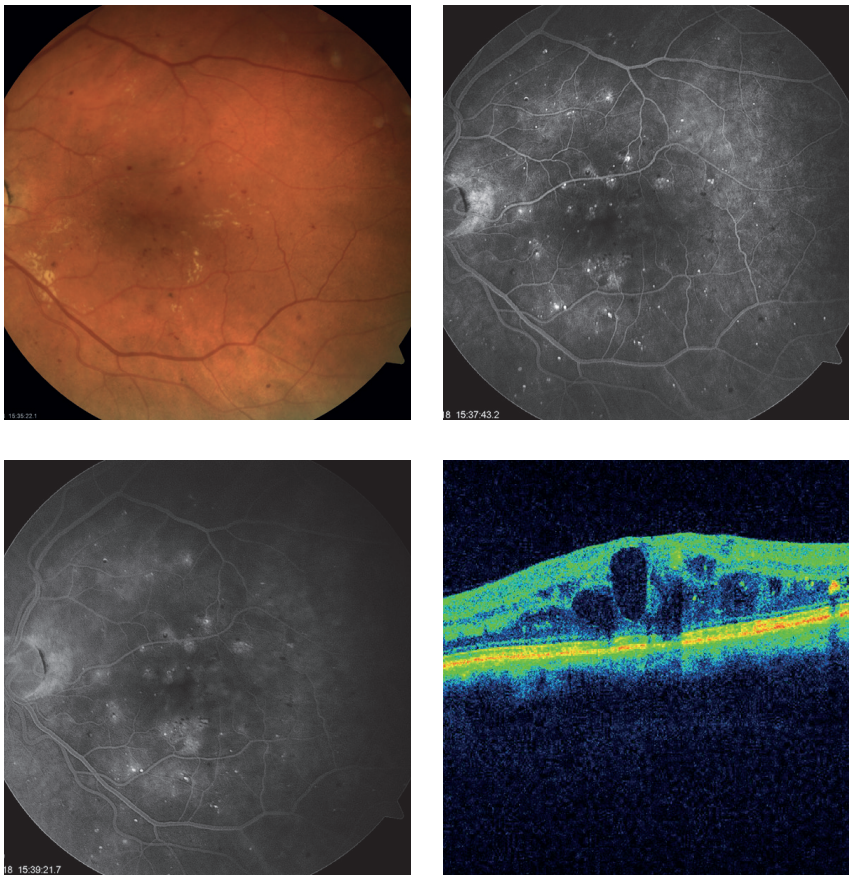


Figure 7. Moderate diabetic macular edema. Hard exudates near the centre are visible in the colour image. The fluorescein angiography reveals microaneurysms that are the source of edema – focal retinal staining. SD-OCT examination shows central cystoid retinal edema of moderate severity.

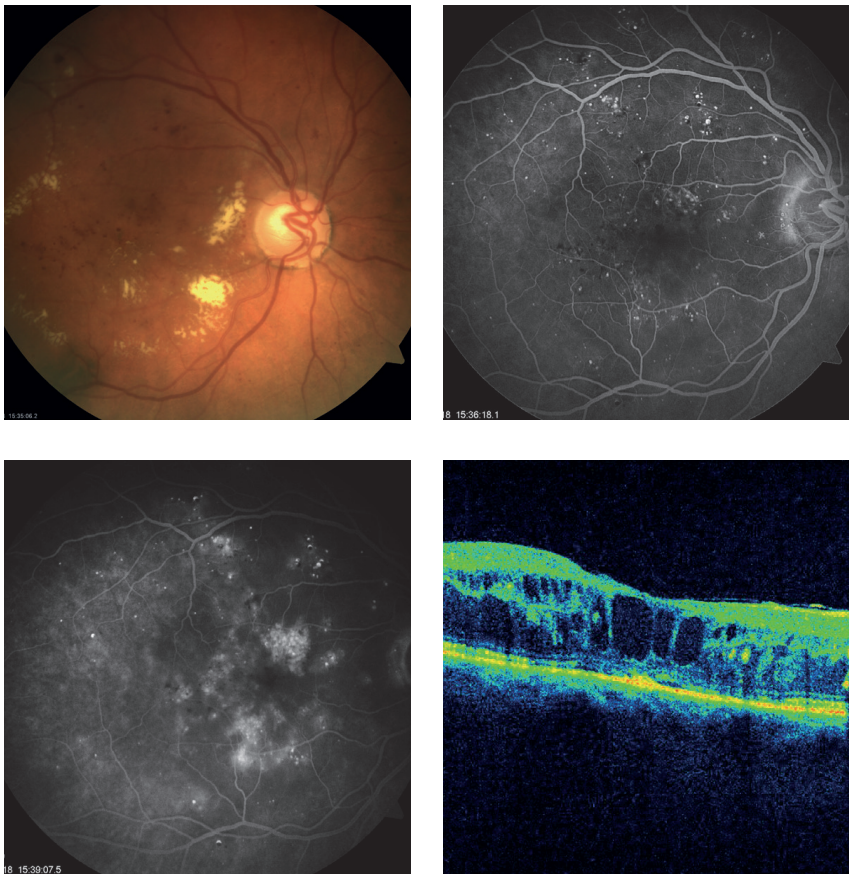


Figure 8. Severe diabetic macular edema. Hard exudates covering the macular center are visible in the colour image. Fluorescein angiography reveals diffuse posterior pole swelling. SD-OCT shows extensive cystoid lesions in the outer plexiform layer. Damage to the photoreceptor layer is also visible.

USA. This division is based on the result of fundus examination in a stereoscopic image.

Diagnostic examples of moderate and severe DME are shown in Figures 7–8. It can be seen that the introduction of spectral domain optical coherence tomography (SD-OCT) to DME diagnostics allows for a more accurate assessment of the extent of damage within the layers of the retina.

It should be emphasized that the simple Wilkinson classification of DME and the CSME definition were proposed many years ago on the basis of ophthalmoscopic images. Additionally, the CSME definition was intended to be used to qualify the patient for macular laser photocoagulation. We now have advanced diagnostic techniques such as SD-OCT and angio-OCT (OCTA) at our disposal, and we avoid application of retinal-damaging laser in the centre of the posterior pole. Therefore, there is a need to create a modern classification that takes into account the current state of knowledge. Parodi et al. proposed a classification of DME based on the pathogenesis of the disease[35].

The pathogenetic classification of diabetic macular edema distinguishes types of DME:

- vasogenic,
- nonvasogenic,
- tractional,
- mixed.

Vasogenic DME is diagnosed in the presence of retinal edema accompanied by visible vascular anomalies, such as microaneurysm clusters and dilated capillaries in the macular area (with the possible presence of hard exudates).

Nonvasogenic DME is defined as retinal edema without visible vascular abnormalities (with the possible presence of hard exudates).

Tractional DME is diagnosed in the case of retinal thickening along with traction in the macular area visible in OCT. The source of traction may be the epiretinal membrane, partial vitreous detachment with local traction, and VMA.

Among patients with DME, the prevalence of vasogenic edema was 65%, nonvasogenic 23%, tractional 5.5%, and mixed 6.5%[35].

Nowadays, the morphological division of DME is sometimes used, based on the OCT image (see pp. 123–125).

Diagnosis of diabetic macular edema

Ophthalmoscopic examination in a stereoscopic image

A simple stereoscopic examination of the fundus is an effective method for the detection of DME[36, 37, 38]. The examination is performed with a slit lamp using focusing lenses: non-contact or contact. In everyday practice, these are most often non-contact lenses with the power of +90D or +78D (commonly known as Volk lenses). In the examination we obtain a magnified and inverted image. Stereoscopy is an essential part of such an examination as it enables the assessment of retinal thickening. Direct ophthalmoscopy with a monocular ophthalmoscope does not provide a spatial image, so its usefulness is very limited. In practical terms, such equipment is only used when examining bedridden patients or during home visits.

In addition to Volk lenses, contact lenses can be used for examination with a slit lamp – the same as those used for retinal laser therapy. However, such a procedure requires anesthesia of the cornea and placing a lens on the eyeball. Lenses used most commonly to assess DME are those that cover the entire posterior pole, such as Area Centralis by Volk or Mainster Focal/Grid by Ocular. There are also contact lenses for assessing the macula itself, such as the Super Macula by Volk or the High Mag Mainster by Ocular.

The use of a contact lens for the examination of the macula (without laser therapy) is justified for patients with severe photophobia, who strongly clench their eyelids. After inserting the lens, we can comfortably assess the posterior pole in a high-quality stereoscopic image.

The main feature of macular edema is retinal thickening, which is visible in a stereoscopic image. Additionally, edema may be accompanied by hard exudates (see the CSME definition, p. 117). However, it should be noted that the mere presence of hard exudates in the macular area alone is not sufficient for diagnosing macular edema. It is possible that after successful DME therapy, the hard exudates are at the stage of resolution without increasing the thickness of the retina. OCT is helpful in such situations.

On the fundus examination alone, it is possible to determine the extent of edema in a stereoscopic image, i.e. diagnose focal or diffuse edema, but more accurate data will be obtained by performing FA and OCT.

Fluorescein angiography

FA remains the most reliable method of diagnosing DME, especially the zones of ischemia. Its role is to assess the extent of edema and its source – that is, the location of leaking microaneurysms. FA should be performed prior to planned laser therapy of the central retina in order to precisely locate the sources of the leakage[39].

FA is the key and most reliable test in the diagnosis of ischemic maculopathy. In a situation where there is a clear deterioration of vision in a patient with DR, without the obvious features of increased DME, it should always be performed. This recommendation is included in the guidelines of the American Academy of Ophthalmology (AAO) regarding the use of diagnostic tools in diabetic retinopathy[40].

In addition, by means of FA, we are able to assess the condition of the peripheral retina and determine the type of retinopathy. Both of these aspects are crucial for the planning of proper treatment. Macular edema cannot be treated in isolation, without attention to peripheral changes in the retina.

It should be emphasized that the role of FA in the diagnosis of DME is evolving, especially with the increasing popularity of non-invasive OCT and OCTA as a diagnostic method[41]. OCT is also an excellent tool for monitoring the effectiveness of DME treatment.

The European Society of Retina Specialists (EURETINA) recommends that FA be performed at the beginning of the diagnostic process. During treatment, OCT is most often performed as a non-invasive form of the follow-up, but angiography is used again if diagnostic doubts arise[42].

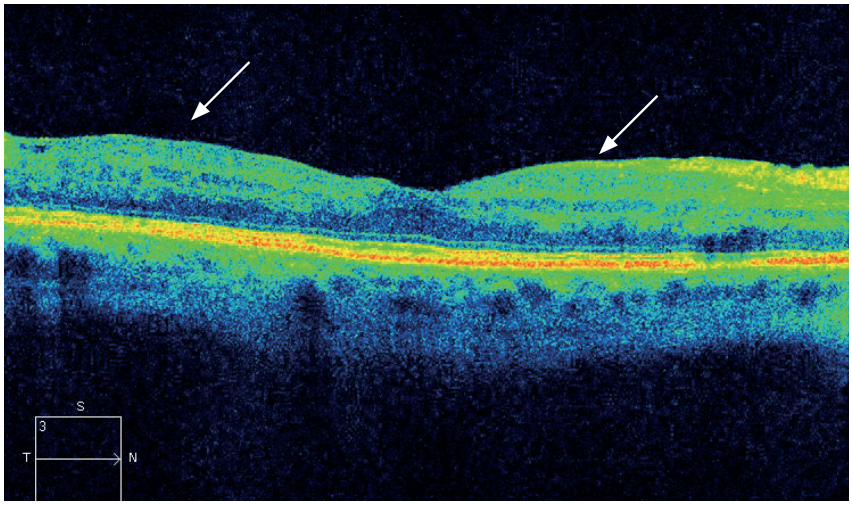


Figure 9. Generalized retinal thickening. Visible spongy swelling of the retina (indicated by arrows). Disturbed foveal profile with minor edema.

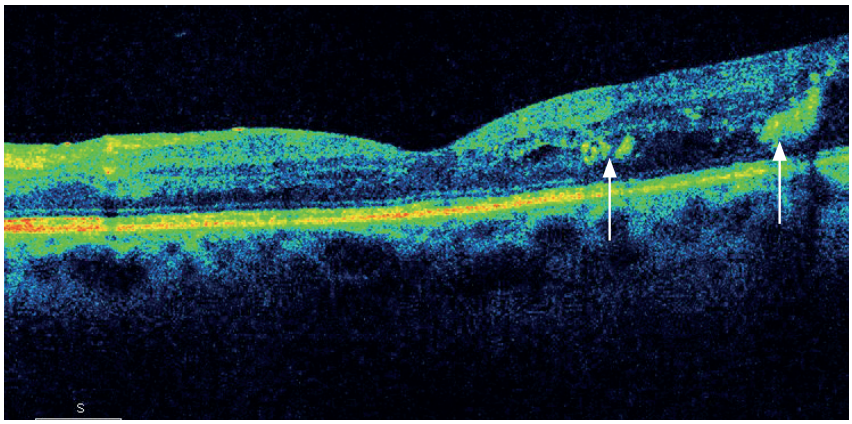


Figure 10. Generalized retinal thickening with hard exudates. Visible spongy swelling on the left side of the scan (nasal sectors). The right side of the scan (temporal sectors) shows the retina with more swelling, partially spongy, with small pseudocysts and hyperreflective foci corresponding to hard exudates (indicated by the arrows).

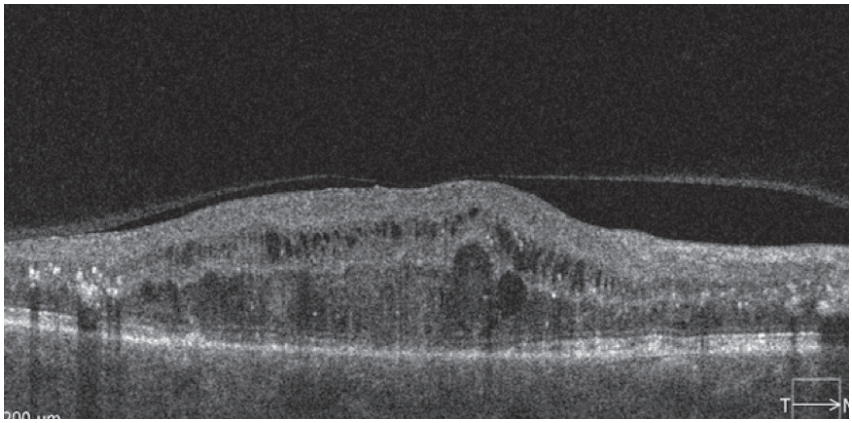


Figure 11. Cystoid edema of the sensory retina. The scan shows numerous cysts located in the external sensory retina. Some of the large cysts extend through most of the thickness of the retina.

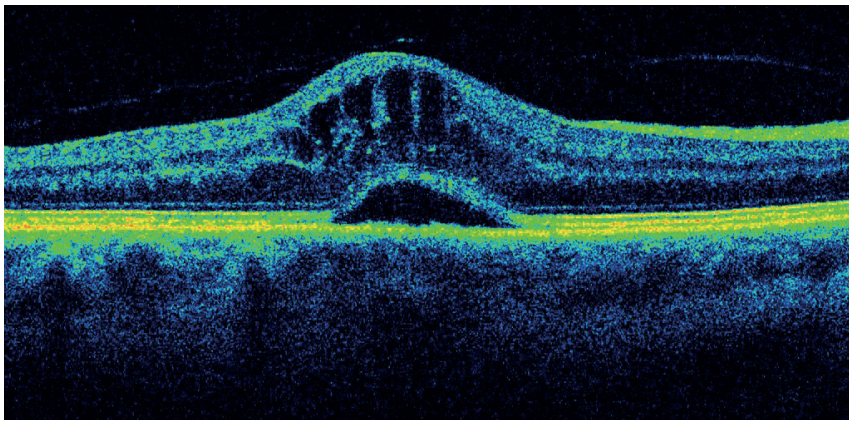


Figure 12. Cystoid retinal edema with subretinal fluid. The scan shows classic cystoid edema of the sensory retina with large cystic spaces. Regular fluid space is visible between the pigment epithelium and the sensory retina.

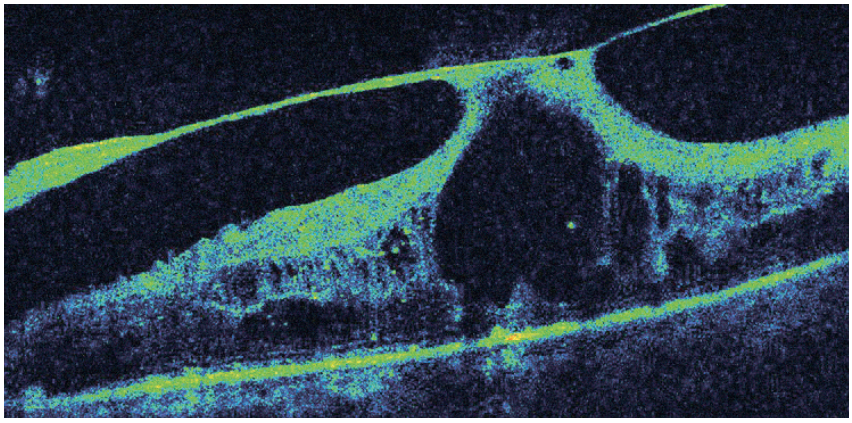


Figure 13. Vitreoretinal traction. The posterior vitreous traction is visible in the scan. Very large pseudocysts and loss of continuity of the ellipsoid layer are present. The treatment for this patient is posterior pars plana vitrectomy.

Optical coherence tomography of the retina

From a practical point of view, the most useful morphological classification of DME is based on OCT images (at present usually SD-OCT)[43]. The most common morphological change seen in OCT in DME is diffuse spongy retinal edema, mainly involving the INL and OPL (Figures 9–10). Generalized thickening of the retina is usually accompanied by a decrease in its reflexivity, associated with fluid accumulation. Quite often, flattening of the contour of the fovea is also present. With prolonged duration of edema, intraretinal hyporeflective spaces (fluid spaces) appear, which over time may cluster into large cysts (Fig. 11). Cystoid edema occurs in approximately half of cases. Less frequently, we encounter serous fluid, located subfoveally under the sensory retina, and posterior vitreous traction (Fig. 12–13).

Otani et al. specify three types of morphological changes visible in OCT in the case of DME (the frequency of the symptom is given in brackets): spongy swelling, especially visible in the outer layers of the retina (88%), cystoid edema (47%) and subretinal fluid (15%)[44].

In turn, Kim et al. describe the following lesions seen in OCT that occur in the course of DME[45].

1. diffuse retinal thickening (97%),
2. cystoid edema (55%),
3. subretinal fluid (7%),
4. edema with vitreoretinal traction (12.7%),
5. tractional retinal detachment (2.9%).

Correlation of the DME image in FA and OCT

Most often, though not always, the leakage seen in FA correlates with an increase in the thickness of the inner layers of the retina. It primarily concerns diffuse edema visible in angiography[46]. Minor leakage from single microaneurysms may not increase in retinal thickness in OCT[47]. The image of cystoid macular edema (CME) revealed by OCT corresponds to stainng in the form of flower petals or honeycombs in fluorescein angiography, although it should be remembered that the sensitivity of CME detection is higher in OCT – by as much as a third[48, 49]. In turn, serous sensory retinal detachment can be precisely diagnosed only with OCT[50]. In the case of focal edema revealed in FA, the OCT image shows an increase in the thickness of the retina, most often with homogenous reflectivity of its layers. Diffuse edema in FA is more often associated with a decrease in the reflectivity of the inner layers of the retina, especially in the case of dominant cystoid lesions[41].

Quantitative analysis with OCT

One vital application of OCT in DME diagnostics is measurement. The examination allows for the measurement of the thickness of the retina and comparison with the results of a standard database (Fig. 14). If multiple examinations are performed at intervals in the same patient, comparative analysis and monitoring of treatment efficacy or disease progression are possible (Fig. 15). Such an analysis makes it much easier to make decisions about continuing a specific regimen or the need to change it. This applies, for example, to intravitreal therapy and/or retinal laser therapy.

Practical remarks on OCT examinations

1. The evaluation of DME morphology is conducive to effective therapeutic pathway, especially when there are several options. Diffuse retinal thickening is more common in edema of a shorter duration, in which cystoid lesions have not yet developed. It should be emphasized that this form of edema may also be present with other macular morphology abnormalities, such as cystoid lesions or SRF. Patients with DME, in whom retinal sponginess is the predominant morphological feature in OCT, usually have relatively good visual acuity.
2. Classic CME, i.e. cystoid macular edema, and subretinal fluid, respond poorly to laser photocoagulation. Thus, in the era of anti-VEGF therapy and micropulse laser therapy, we tend to favour these forms of treatment in such cases.
3. In the presence of vitreoretinal traction, surgical treatment is necessary – pars plana vitrectomy.

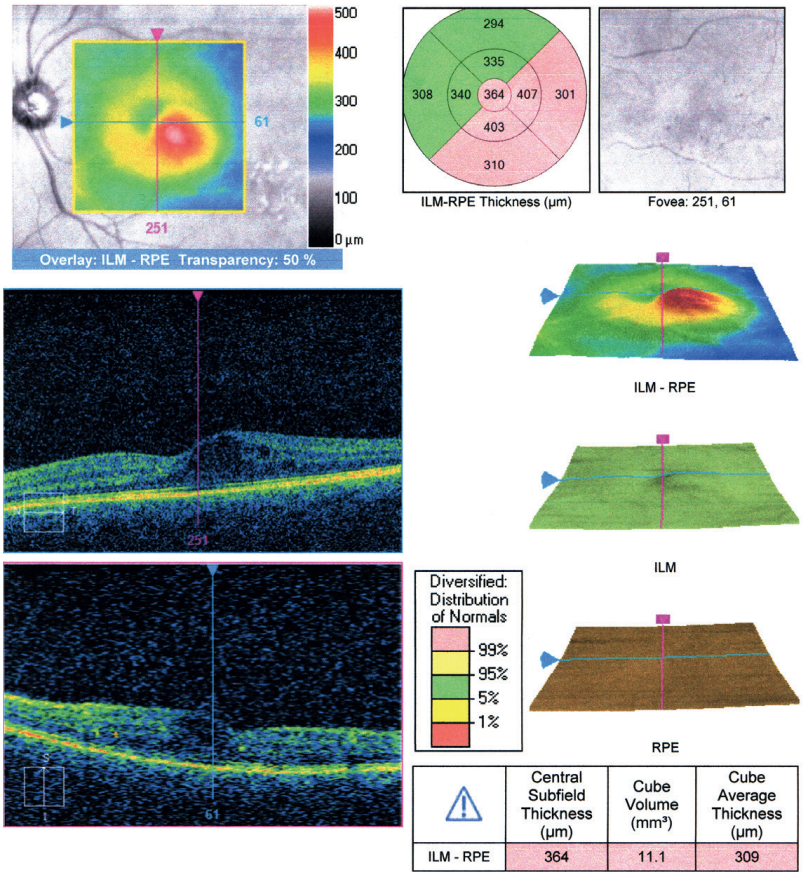


Figure 14. Standard protocol for measuring central retinal thickness in SD-OCT from a Zeiss Cirrus 4000 device. The printout shows a map of the retinal thickness and the areas of edema (marked in red), in the en face image. In addition to the central retinal thickness (CRT), the average central retinal thickness (CRTA) and its volume (CV) are measured. The measurement values apply to the areas marked out by the ETDRS grid, which consists of three concentric circles with diameters of 1 mm, 3 mm and 6 mm. CRT is the mean value of the thickness of the retina in a central circle of 1 mm in diameter, and CRTA is for a circle of 6 mm in diameter.

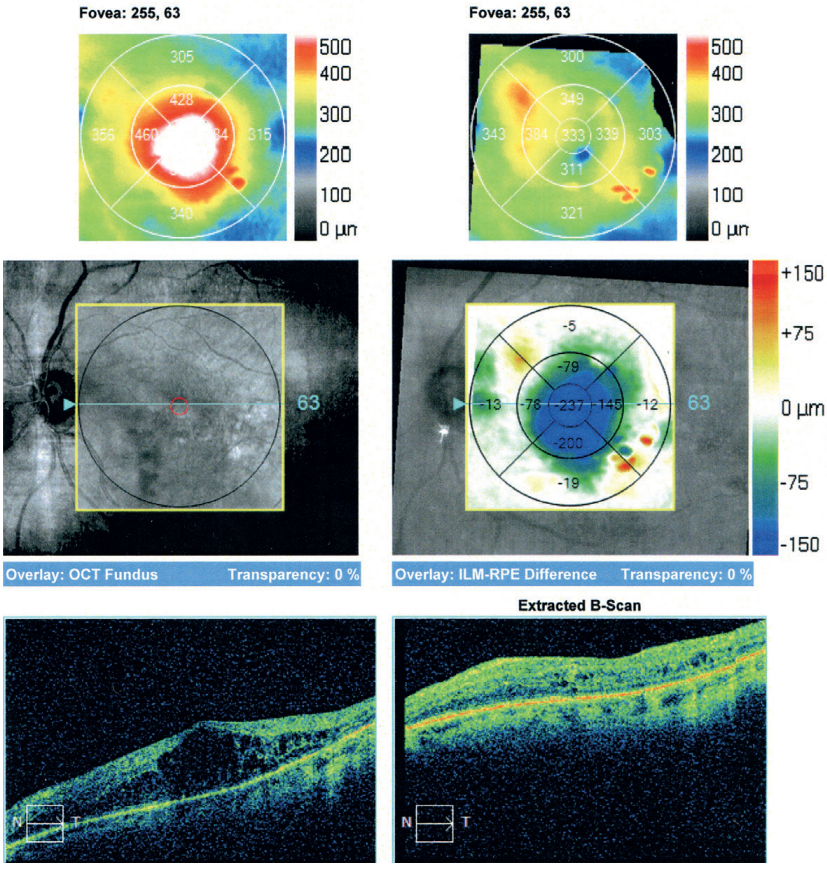


Figure 15. SD-OCT examination protocol (Zeiss Cirrus 4000) comparing two results, in this case before and after subthreshold micropulse laser treatment of the retina. The printout shows maps of the retinal thickness and the amount of edema reduction after the laser procedure (marked in blue).

4. Retinal maps obtained with the use of OCT also allow us to locate the areas of retinal edema accurately. In the case of edema sites located outside the fovea, they facilitate the performance of classic laser photocoagulation. When considering subthreshold micro-pulse laser treatment, SD-OCT maps can identify the area of the retina that will be subjected to such therapy.
5. It should be remembered that the measured size of edema (central macular thickness) does not necessarily correlate with visual acuity in a simple and linear way. Simplifying somewhat, we can say that people with a larger edema have poorer vision, but the acuity can be affected by many other factors, not only the size of the retinal edema (see p. 56). These factors include the duration of DME (often difficult to define), capillary perfusion in the macular area, impairment of function and scarring within the RPE, loss of integrity of the ellipsoid zone (EZ, formerly referred to as a junction of internal and external fragments of photoreceptors – IS/OS) and the outer limiting membrane (ELM), and the opacity of the optical media of the eye.
   Examples:
   a. a patient with long-term DR, with retinal thinning and a decrease in BCVA before the development of DME,
   b. a patient with mild DME and macular ischemia (low BCVA),
   c. patient with small DME and cataract (low BCVA),
   d. patient with retinal atrophy after laser or anti-VEGF therapy and, due to loss of some photoreceptors, no improvement of visual acuity.
6. In the treatment of DME with intravitreal injections, SD-OCT is recommended at monthly intervals at the beginning of the therapy (loading phase)[41]. In the further course of therapy, especially after the local condition and visual acuity stabilize, intervals between follow-up examinations may be prolonged (treat-and-extend scheme). In the case of aflibercept after the loading phase, follow-up examinations are recommended every two months. A flexible treat-and-extend schedule is permissible in the second year of treatment (according to Summary of Product Characteristics (SmPC)).

FA and OCT in diagnosing DME

For many years, fluorescein angiography has been the gold standard in the diagnosis of diabetic retinopathy. It continues to be the primary tool for assessing retinal perfusion and retinal neovascularization.

When planning classic laser photocoagulation in the macular area, FA ensures precise and safe procedure performance. FA is the only reliable diagnostic tool for locating and assessing leakage from microaneurysms. It also remains the primary method for diagnosing macular ischemia (DMI) and an enlarged FAZ, although the introduction of the continuously refined angio-OCT into ophthalmic diagnostics may alter this reliance on angiography.

In recent years, it seemed that the increasing popularity of non-invasive OCT examination would result in the reduced importance of FA in the diagnosis of DME and monitoring its treatment. Undoubtedly, OCT allows a reliable assessment of the presence of edema itself and its morphological characteristics. However, the assessment of perfusion in the macular area with OCT is difficult, and FA performs much better in this regard. In the published guidelines for DME management, EURETINA names FA as the gold standard in diagnosing this condition and monitoring the effectiveness of treatment[42]. In practice, with the necessity of frequent DME control, OCT examination is performed much more often and constitutes the first source of information on the size and character of edema. FA is usually performed at the beginning of the diagnostic process and during follow-up when there is diagnostic doubt.

OCT angiography

The principles of angio-OCT (OCTA) operation are discussed in Chapter 4: *Diagnostic techniques for diabetic retinopathy* section (pp. 70–77). At this point, however,

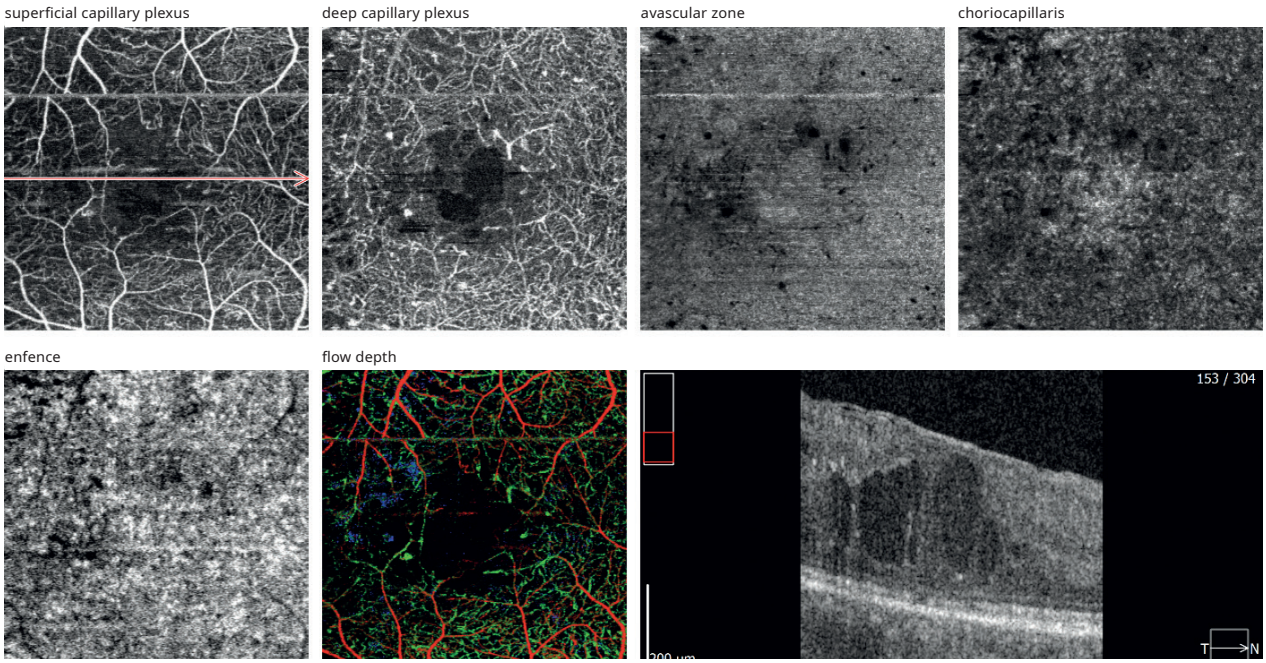


Figure 16. The OCTA scan shows a widening of the foveal avascular zone in both the superficial and deep capillary plexuses. Numerous microaneurysms are visible around the fovea (examination carried out with Optopol's Revo device).

it should be emphasized that the assessment of the macula itself with OCTA, especially FAZ, is one of the best-studied issues in the interpretation of this new diagnostic technique[51, 52]. OCTA allows visualization of the perifoveal capillaries in terms of the superficial capillary plexus (SCP) and deep capillary plexus (DCP). In this way, we can observe the lower density of the vessels and their absence in the perifoveal zone (so-called capillary drop-out). Nowadays, many OCTA devices have modules for measuring the density of these vessels and tools for measuring the FAZ area (Figs. 16–17). Changes in these parameters can also be used to monitor the efficacy of DME treatment. OCTA also allows for the visualization of microaneurysms, although some of them can be missed in that diagnostic modality[53].

Angio-OCT is undoubtedly a valuable complement to macular angiography. In its recommendations, EURETINA emphasizes that both tests are complementary and should be performed at the beginning of the diagnostic process[42].

OCT with enhanced depth imaging function (EDI-OCT) and a tunable laser (swept-source OCT)

The role of choroidal damage in the pathogenesis of diabetic retinopathy has been discussed for several years. In the course of DR, choroidal flow is impaired, which may increase the risk of developing DME and DMI[22]. Choroidal thinning is visible in diabetic patients compared to healthy subjects[54]. In the few available studies, the choroid was also significantly thinner in patients with DMI compared to the group of patients without macular ischemia[55]. Choroidal imaging and thickness measurement are possible in OCT with deeper scanning (EDI-OCT) or OCT with a tunable laser (SS-OCT). For the time being, however, the implementation of the results of these studies in everyday clinical practice is still some way off.

Morphological biomarkers in the treatment of DME

In the past few years, there has been an ongoing search for biomarkers (morphological features, mea-

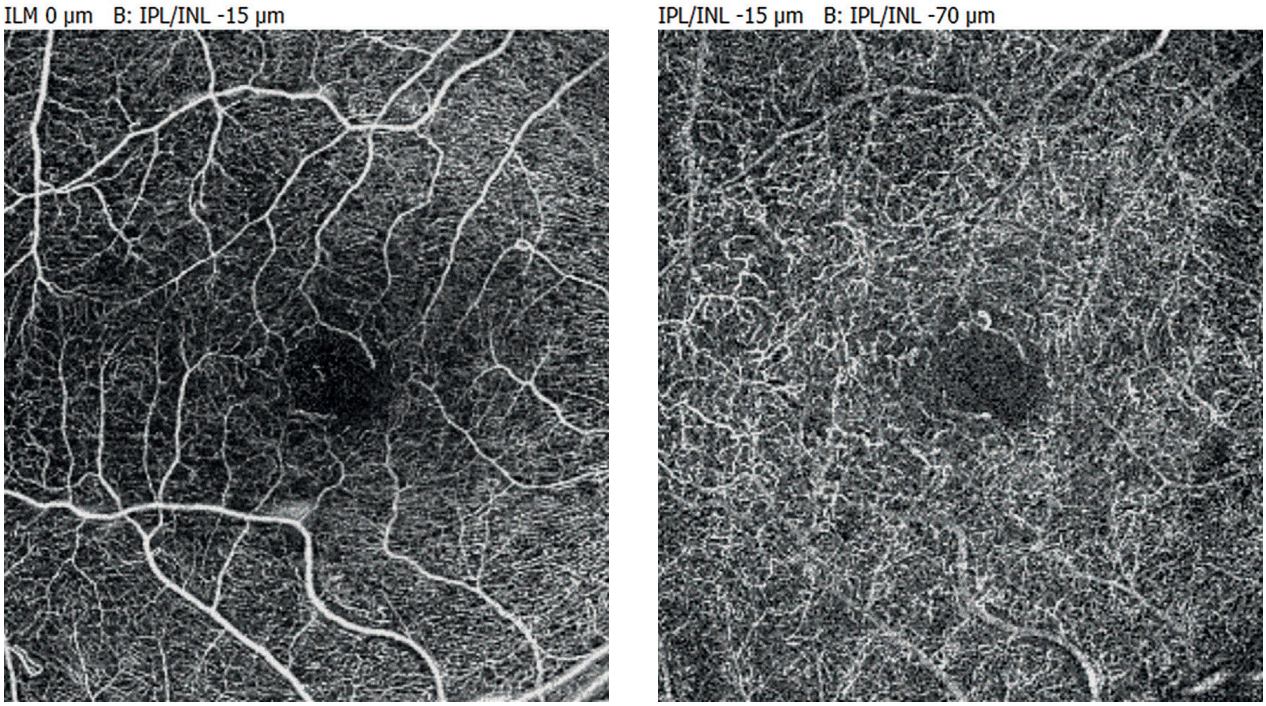


Figure 17. Superficial and deep capillary plexuses in a patient with proliferative diabetic retinopathy. Visible enlargement of the foveal avascular zone and defects in the capillary vascular network in the temporal part of the fovea.

surement values) of the edematous retina that would correlate with visual acuity impairment and response to treatment. The research concerned the following abnormalities of central retinal morphology in DME, along with their correlation with current visual acuity (VA) and response to treatment:

1. increase in central retinal thickness (CRT),
2. presence of intraretinal cysts (IRCs) and their size,
3. the presence of hyperreflective foci (HRF) in the sensory retina,
4. presence of microaneurysms,
5. the presence of SRF,
6. the presence of vitreomacular traction (VMT), including the presence of epiretinal membranes (ERM),
7. morphological abnormalities of the outer retinal layers: EZ (IS/OZ), cone outer segment tips (COST) and ELM,
8. disorganization of the inner retinal layers (DRIL).

Central retinal thickness (CRT) is the primary descriptive parameter in DME, but the relationship between CRT and VA is not strong and direct, and it does not always occur[56, 57]. Studies by the Diabetic Retinopathy Clinical Research Network (DRCR.net) group showed only a moderate correlation in this respect. Also, the relationship between CRT change after retinal laser photocoagulation and VA was not significant. The amount of central retinal edema corresponded to a very wide range of VA, so it was not the size of the edema alone that determined the degree of functional impairment. Similar conclusions were presented in the RESTORE study[58].

The post-hoc analysis of the RESTORE and RIDE/RISE results revealed a protective effect of SRF in relation to photoreceptors. Patients who had subretinal fluid before starting the treatment with anti-VEGF injections showed the highest gain on ETDRS charts in the course of such therapy[58, 59]. Conversely, the presence of more IRCs at the start of the study was associated with poorer visual acuity and lower levels of improvement in BCVA after treatment[58].

Ito et al. found a strong correlation between VA impairment and damage to the outermost structures of the retina: ELM, EZ (IS/OS) and COST. No such relationship was reported in the case of CRT increase, the presence of SRF or hard exudates in that study[57]. Maheshwary et al. similarly showed a correlation between the size of the EZ damage (IS/OS) and loss of VA[60].

Uji et al. also investigated damage to the outer layers of the retina[61]. They showed a correlation between the presence of HRF visible in SD-OCT and located in this region and a decrease in VA. In turn, researchers from the Diabetic Retinopathy Research Group Vienna found the strongest correlation to be between VA impairment and DME morphology in the presence of SRF and large cysts located in the outer nuclear layer (ONL)[62].

As can be seen, the presented findings are often inconclusive and contradictory. They are insufficient to indicate a single morphological parameter that would clearly correlate with visual acuity or predict treatment outcomes. However, in recent years, the concept of disorganization of the inner retinal layers has been introduced into the medical literature. This disruption of retinal architecture may, according to many authors, be an important marker predicting the effects of DME treatment.

Definition of disorganization of the inner retinal layers (DRIL)

DRIL is the term for a disturbance of the retinal architecture in diabetic macular edema. In DRIL, the boundaries between the following retinal layers are blurred: the complex of the ganglion cell layer and the inner plexiform layer, the inner nuclear layer, and the outer plexiform layer.

Consequently, in DRIL, we deal with a conglomerate of cells rather than the layered structure of this part of the retina (Fig. 18). DRIL can vary in extent and location within the central retina. Of practical significance is the central location of DRIL, i.e. in the centre of the fovea, with a diameter of 1 mm. The size of DRIL at its base is usually given in micrometres (the amount of disorganization in the horizontal dimension). It should be emphasized that DRIL can occur both with and without the presence of retinal edema.

Clinical trials with DRIL

A number of clinical trials were conducted, in which study participants had DRIL in the central – i.e. foveal – location. DRIL was assessed on consecutive scans covering the central part of the retina with a width of 1 mm. DRIL size was measured in the horizontal direction and reported in micrometres. Significant central DRIL was defined as the inability to trace the

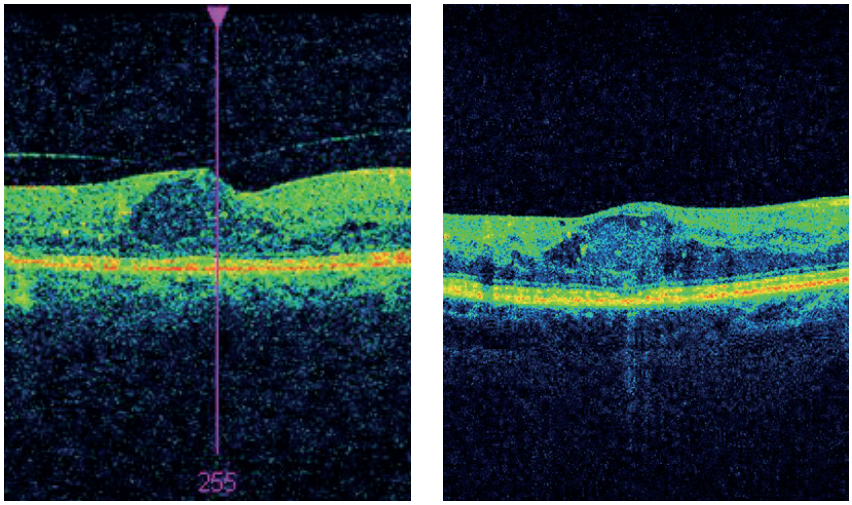


Figure 18. Disorganization of the inner retinal layers (DRIL). Both images show central DRIL. The area of the sensory retina localized over the fovea itself is practically devoid of the layered structure typical of a normal retina seen in SD-OCT.

boundaries between at least two previously reported retina layers over an area exceeding 50%. The analysis was focused on two issues: the relationship between the presence and amount of DRIL and the patient's visual acuity, and the presence of DRIL and the effects of DME treatment – in terms of final visual acuity.

Sun et al. examined both these correlations[63, 64]. The larger range of DRIL clearly correlated with the patient's lower visual acuity at the start of the study. A similar relationship also concerned other morphological features of the retinal edema (greater central thickness, the presence of large cysts, poor visibility of the outer photoreceptor segments, damage to the ELM and EZ (IS/OS)), but in the multivariate statistical analysis, the strong correlation between low VA and retinal morphology was mainly related to the presence and extent of DRIL. The change in the DRIL pattern during DME treatment was of practical importance. An enlargement of the DRIL area four months after treatment correlated with worse VA after eight months of therapy. Changes in other morphological parameters did not strongly correlate with final VA, especially in multivariate modelling.

Radwan et al. analysed the relationship between the presence of DRIL and treatment outcomes in patients who had remission of macular edema (ME) – both in diabetic patients and in ME of different origin[65]. Patients with a larger area of DRIL at the start of treatment showed minor improvement in VA. Also, remission of DRIL alone during treatment correlated with better visual acuity after the cessation of ME.

An analogous study in patients with uveitic cystoid macular edema was performed by Grewal et al.[66]. It showed a correlation between reduced visual acuity and the presence of DRIL in patients before and during CME treatment. It should be noted, however, that a similar relationship also applied to other morphological parameters (greater CRT, presence of intraretinal cysts, or EZ damage).

The EURETINA Society suggests that the features of retinal morphology at the start of treatment indicating a good prognosis for improved vision are: subretinal fluid, small intraretinal cysts and macular vitreoretinal adhesion. In turn, the following features of retinal morphology have poor prognosis at the beginning of therapy: DRIL, discontinuity in EZ and ELM, and subfoveal choroidal thinning[42].

Other diagnostic modalities

The techniques used mainly in scientific research, but not in everyday medical practice, include:

1. microperimetry – shows defects in the central field of vision and a decrease in retinal sensitivity induced by DME[67, 68, 69],
2. multifocal electroretinography (mfERG) – shows impaired electrical response of the retina due to its damage; the defects are clearly visible, especially in the ischemic form of DME[70, 71].

DME diagnostics – summary

- Stereoscopic ophthalmoscopy should be the first-line examination in the diagnosis of DME.
- SD-OCT should be performed whenever DME is suspected, if there is the need to quantify edema, if pathology at the vitreoretinal interface is suspected, and should be the main method used to monitor the disease.
- Fluorescein angiography should be performed at the beginning of the diagnostic and therapeutic process, always before planned retinal laser photocoagulation in the macular area, and when ischemic maculopathy is suspected.
- Angio-OCT is a useful supplement to angiography, especially in the diagnosis of macular ischemia.

Treatment of diabetic macular edema – laser therapy

Introductory remarks

Local treatment of DR is carried out in two ways. On the one hand, we treat the retinopathy itself, for

Table 3. Results of the efficacy study of laser photocoagulation for DME treatment (ETDRS)[72].

Extent of DME	Follow-up time (years)	Control group (% with MVL)	Photocoagulation treated group (% with MVL)
CSME (center not involved)	1	8	1
	2	16	6
	3	22	13
CSME (center involved)	1	13	8
	2	24	9
	3	33	14

DME – diabetic macular edema, CSME – clinically significant macular edema, MVL – moderate visual loss, defined as at least doubling of visual angle

example, proliferative or severe non-proliferative lesions, and on the other hand, we treat diabetic macular edema. Both therapeutic procedures should be carried out simultaneously, without neglecting any element of the therapeutic process. The goal of treatment is to maintain good vision and avoid the need for surgical treatment, i.e. posterior vitrectomy.

The non-surgical procedures in the treatment of DR and DME include:

1. retinal laser photocoagulation,
2. subthreshold laser therapies, especially subthreshold micropulse laser treatment (SMPLT),
3. intravitreal injections.

The use of vitreoretinal surgery in treating DME is discussed in Chapter 10: *Posterior pars plana vitrectomy in diabetic retinopathy*, pp. 204–205.

Laser photocoagulation with diabetic macular edema

For information on how laser photocoagulation of the retina works and the types of lasers, see Chapter 9: *Diabetic retinopathy management*, pp. 177–181.

The ETDRS group researched the effectiveness of laser photocoagulation in treating DME in the 1980s and 1990s. An interesting issue was the assessment of the effectiveness of laser photocoagulation in the prevention of moderate vision loss (MVL)[3, 72]. MVL was defined as at least doubling of the visual angle, i.e. a decrease in visual acuity by half. The patients with DME received laser photocoagulation in the macular area and were followed over several years. The eligibility criterion for the photocoagulation procedure was the presence of clinically significant macular edema. ETDRS introduced this important definition based on the stereoscopic ophthalmic examination and fundus photography (see *Definitions related to diabetic macular edema*, pp. 117–118).

The results of the study are summarized in Table 3. As can be seen, laser photocoagulation in the case of central location of the edema reduces the risk of vision loss by half. It is necessary to emphasize that when referring the results of this milestone ETDRS study to visual acuity, the point is the maintenance of current vision, not its improvement. Nowadays, modern therapeutic methods (anti-VEGF therapy, in-

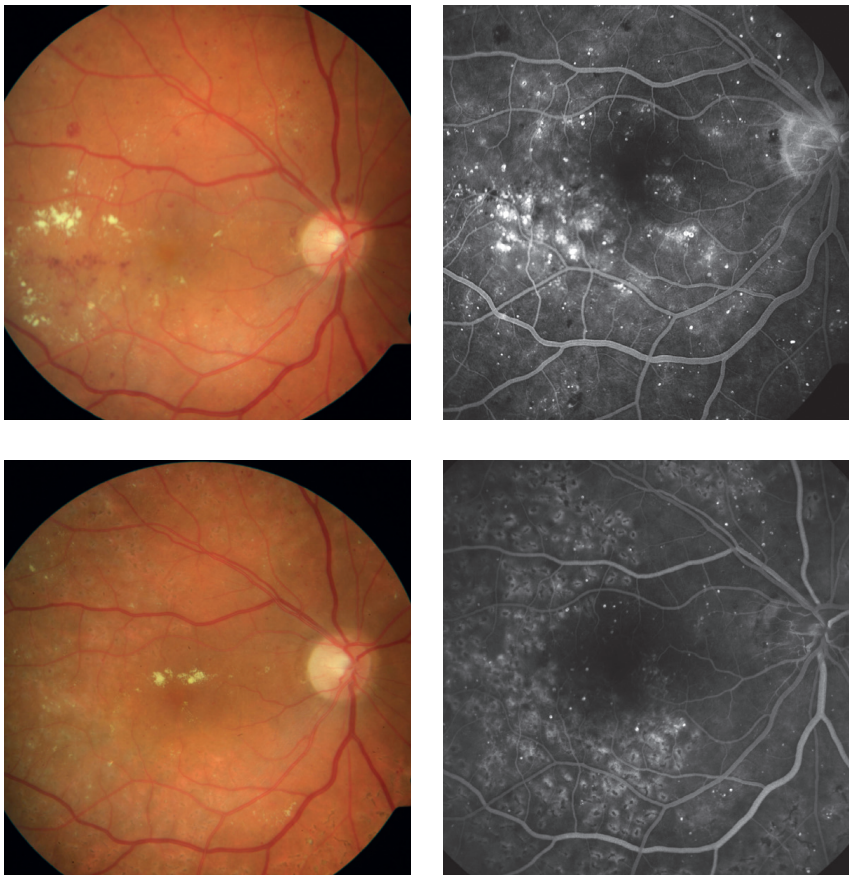


Figure 19. Correctly performed laser treatment in the macular area and panretinal photocoagulation of the retinal periphery. Image of proliferative diabetic retinopathy with clinically significant macular edema – photographs before and after laser therapy. The photos after the procedure show a significant reduction in foveal edema, and a smaller number of hard exudates in the macular area.

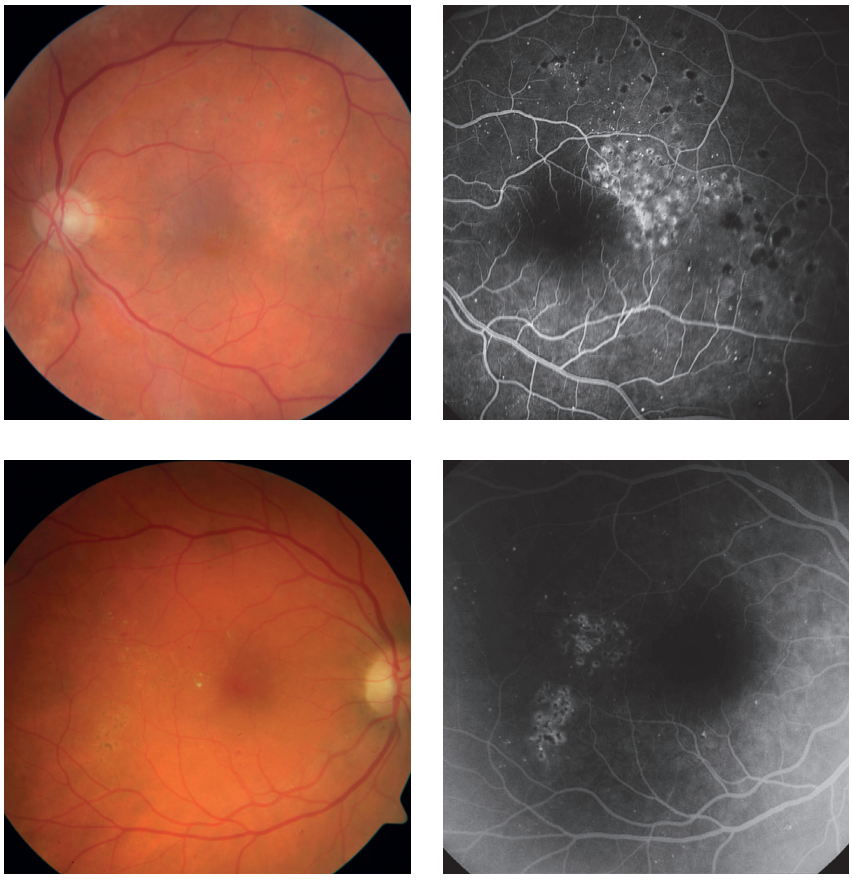
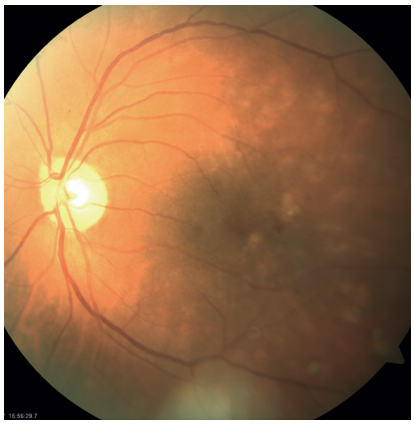


Figure 20. Correctly performed focal laser therapy of the retina. Laser spots are not large and located in the safe distance from the fovea.



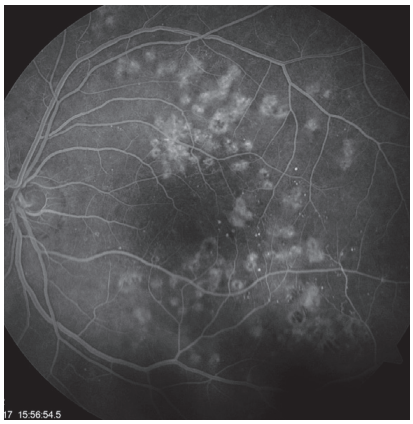
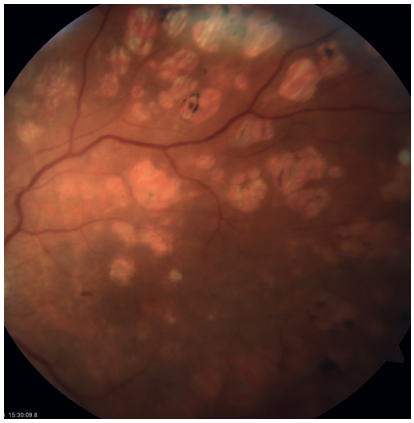


Figure 21. Laser photocoagulation in the macular area. Large laser spots are located too close to the fovea. The patient may experience defects in the central field of vision.



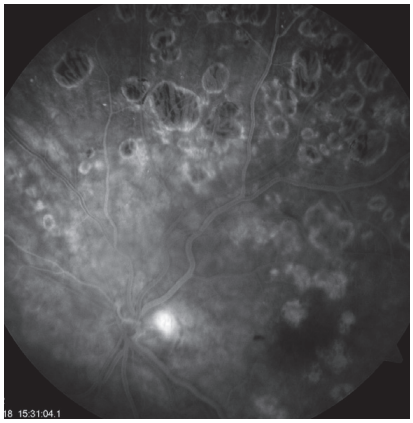


Figure 22. Retinal laser photocoagulation performed many years ago. The laser spots are too large and located too close to the center of the fovea. Too high parameters of laser power and laser spot diameter were used. Angiographic image reveals that neovascularization at the disc is still present.

travitreal steroid therapy or subthreshold micropulse laser treatment), thanks to which we can improve visual acuity and avoid retinal scarring.

The first laser treatment protocol in the macular area according to ETDRS was as follows[73, 74]:

1. focal photocoagulation aimed at microaneurysms in areas of retinal edema in the range of 500–3,000 µm from the macular center, but not closer than 500 µm from the nerve disc,
2. laser spots with diameter from 50 µm to 100 µm, laser power titration until elicitation of clear whitening of the retina: first, photocoagulation is performed with a spot of 100 µm diameter, then a 50 µm diameter hit is directed to the same spot; this should produce a change in colour of the microaneurysm – greying,
3. clusters of microaneurysms, especially those with accompanying hard exudates, treated with 200–500 µm diameter laser spots,
4. impact duration for focal photocoagulation from 0.05 to 0.1 seconds,
5. the extent of GRID laser therapy (treated are areas of diffuse leakage and areas of hypoperfusion beyond the FAZ): area within range of 500–3,000 µm upwards, nasally and downwards from the macular center; 500–3,000 µm temporally from the center; non-laser area closer than 500 µm from the nerve disc,
6. spot diameter for GRID laser therapy: from 50 µm to 200 µm,
7. impact duration for GRID laser therapy: from 0.05 to 0.1 seconds,
8. the distance between spots: one spot diameter in the places of intense leakage, in the case of a smaller leakage, larger spacing between the spots,
9. during the first session, the area closer than 500 µm to the foveal center is not treated; laser photocoagulation at a distance of up to 300 µm is possible during subsequent sessions (after at least

four months), when there is no DME reduction, in eyes with low visual acuity.

The above protocol remains the basis for performing macular retinal laser photocoagulation, but it has been modified in many ways by clinicians and research groups. In general, all these changes have been aimed at reducing retinal damage: lower laser powers and smaller laser spots are used. The original protocol assumed there the destruction of individual microaneurysms, which often required the execution of a few precise impacts of small diameter and greater power. This, in turn, increased the risk of damage to Bruch's membrane and the development of secondary subretinal neovascularization. In addition, the damage to the RPE andother retinal layers was greater with this procedure and resulted in larger scotomas in the central field of view. Hence the tendency for operators to use laser in subthreshold mode, especially for GRID photocoagulation. This shift in approach to retinal laser therapy is also supported by the metabolic theory of how photocoagulation works.

The first modifications to the GRID laser therapy protocol were introduced by R.J. Olk, and later other authors presented their changes[75, 76, 77, 78].

The changes made to the original protocol by the DRCR.net group are as follows[79]:

1. power selected so as to achieve greyish reaction under the microaneurysm (it is not necessary to obtain direct whitening of the microaneurysm),
2. preferred laser spot diameter: 50 μm,
3. for GRID laser therapy, the laser power is set to obtain a barely visible greying,
4. preferred focal spacing for GRID laser therapy: two spot diameters.

The effects of correctly performed laser therapy are shown in Figures 19–20.

Nowadays, photocoagulation laser systems coupled with a fundus camera are being introduced into ophthalmic practice – for example, Navilas ®Laser System. The procedure consists in performing fundus scans and marking them with points corresponding to the planned laser treatment. Then the system performs photocoagulation of the retina based on the planned patterns. Navilas allows for the precise destruction of individual microaneurysms and the laser treatment of specific areas of the retina without damaging healthy tissue[80]. The value of this system is that it is an advanced optical system that enables good visualization of peripheral lesions in the retina. The main disadvantage is the high cost of the equipment.

Complications occurring with laser therapy in the macular area are mainly related to the formation of scotomas in the visual field, related to photoreceptor damage, and secondary glial proliferation on the surface of the retina (ERM)[81, 82]. There is also a risk of inadvertent damage to the fovea. This is especially true of patients who have trouble maintaining fixation. Using too much laser power results in the formation of scars which tend to enlarge with time and can lead to a deterioration of vision, especially if they are located near the fovea (Figures 21–22).

Although retinal laser photocoagulation is much cheaper than intravitreal therapy, it is very rarely performed in the macular area today. It is not a first-line therapy for DME involving the macular center. However, it is acceptable in the case of the extrafoveal localization of the edema, even as the main form of treatment. With the central localization of the edema, laser photocoagulation is used with patients who do not respond to other therapies, such as intravitreal injections. EURETINA permits laser photocoagulation of the retina in the following situations[42]:

- clusters of microaneurysms and leaking capillaries (vasogenic type of edema),
- edema with CRT less than 300 μm,
- edema with vitreomacular adhesion.

Subthreshold micropulse laser treatment

The effectiveness of classic retinal laser photocoagulation comes at a price – it involves side effects and

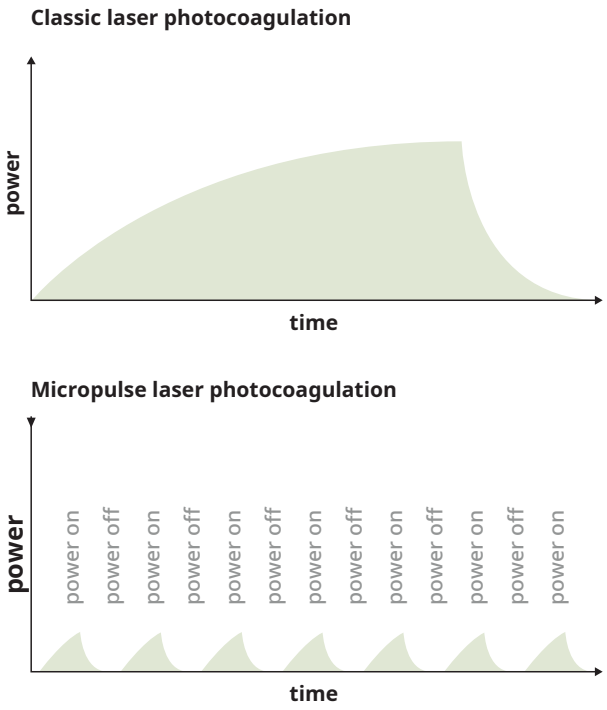


Figure 23. A comparison of the mode of action of classic laser photocoagulation of the retina (continuous wave) with micropulse laser treatment.

potential complications, such as loss of photoreceptors (defects in the central field of view), proliferation of glial tissue (scars, epiretinal membranes, sometimes requiring surgical treatment), and sometimes the formation of secondary neovascular membrane at the site of the scar. Hence, the search continues for non-damaging laser therapies that can spare RPE cells and elicit therapeutic effect by stimulating them, rather than causing a lethal thermal effect (as in the case of classic photocoagulation).

Laser therapies that do not damage the retina include the aforementioned subthreshold micropulse laser treatment (SMPLT) and NRT (non-damaging retinal therapy), which involve using a precise technique of selecting the power and duration of the impulse in the subthreshold mode (EpM – endpoint management). Both techniques, by definition, work at the subthreshold level and involve the induction of similar biochemical processes at the cellular level, but for this purpose, they use laser pulses of different durations. A detailed description of the mechanism and application of subthreshold micropulse laser treatment is presented below.

Micropulse technology was developed in the 1990s, but it is only in recent years that it has become commonly adopted in clinical practice. The idea behind micropulse laser therapy is to optimize the function of the RPE by stimulating it to produce agents that improve the function of the retina without damaging any of its layers.

Research on the biological effects of SMPLT is ongoing. The main theory of micropulse laser operation focuses on the thermal stimulation of the RPE to produce the so-called heat shock proteins (HSPs), which have anti-inflammatory and anti-angiogenic effects[83]. Additionally, the very process of secreting these substances by the cell optimizes its metabolism and often restores its proper functioning. This theory has been confirmed by laboratory tests.

Inagaki et al. demonstrated an increase in HSP70 production in a culture of SMPLT-treated human RPE cells (ARPE-19) in the absence of thermal injury[84]. The increase in HSP70 production depended on the intensity of the laser therapy, i.e. the number of pulses. Other laboratory studies on RPE in mice have shown that SMPLT inhibits VEGF production and increases the production of angiogenesis inhibitors, such as retinal pigment epithelial growth factor (PEDF), while not generating any cell damage[85]. New animal model studies also show that SMPLT restores the oxidative/antioxidative balance in retinal tissue, thus preventing cell apoptosis[86].

Additionally, the latest clinical studies indicate the role of SMPLT in restoring the proper functioning of Müller cells. Midena et al. examined the VEGF levels and biomarkers of Müller cell function in the aqueous humour of patients with DME ≤ 400 μm treated with micropulse laser therapy[87]. In addition, these

researchers measured the change in the thickness of the inner nuclear layer (where the cell bodies of Müller cells are located) on SD-OCT scans in patients after SMPLT. The results showed a reduction in VEGF levels and suggested an improvement in Müller cell function by changing the levels of their biomarkers in the aqueous humour and reducing the thickness of the inner nuclear layer. The effect of SMPLT is also associated with improved retinal perfusion. Vujosevic et al. show that SMPLT therapy in DME reduces the FAZ area at the deep capillary plexus level and reduces the number of microaneurysms and cysts at both the superficial and deep capillary plexus levels[88].

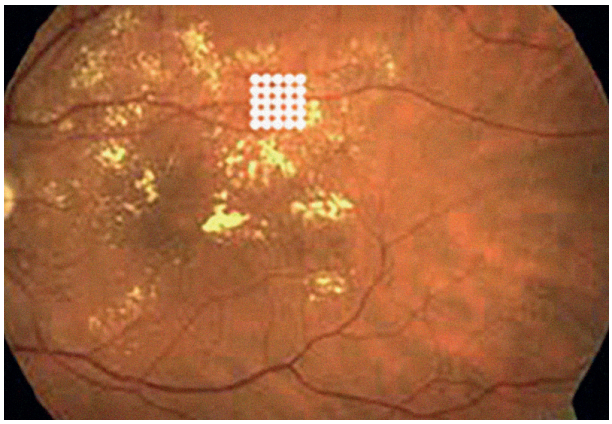


Figure 24. Image of laser spot projection onto the area of retinal edema during SMPLT.

Laser types used in SMPLT

The micropulse mode is a form of energy application used in lasers of various wavelengths: 532 nm, 577 nm and 810 nm. For safety reasons, the 577 nm and 810 nm lasers are usually recommended for macular laser therapy, since their use reduces the likelihood of damage to the sensory retina. In the case of the 577 nm laser (yellow), the xanthophyll present in the sensory retina does not absorb the yellow colour in any practical sense[89]. The 810 nm laser, on the other hand, penetrates the deeper layers of the sensory retina and the choroid, so it is also not absorbed by macular carotenoids. The 810 nm wave is also less absorbed by melanin, which necessitates the use of higher laser powers, but also means the procedure has a wider safety margin[90].

Figure 25. The panel of retinal laser with a micropulse option.

During subthreshold micropulse laser treatment, the laser energy reaches tissues in the form of a series of very short pulses, usually with a duration of 100–300 µs (Fig. 23). The effective laser operating time is known as the duty cycle (DC) and is typically 5 to 15% of the exposure time – for example, in the typical retinal SMPLT time of 0.2 seconds the effective laser operating time is 5% or 0.01 seconds[91]. For the rest of the time, the laser energy is not applied, which allows the tissues to cool down. Additionally, the laser power is set to provide subthreshold mode, i.e. so as not to leave any visible traces in the sensory retina.

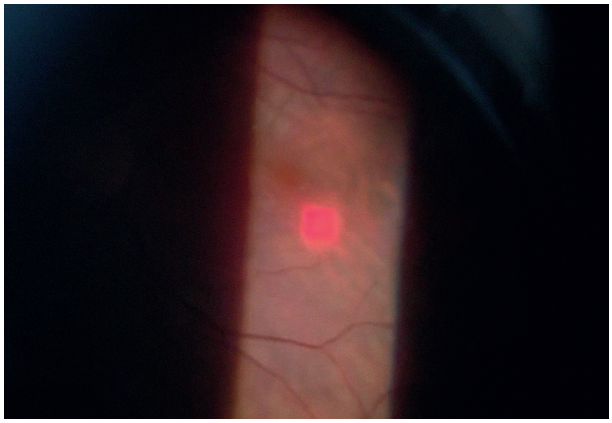


Figure 26. Subthreshold micropulse laser therapy in the macular area – the projection of the laser pilot is visible on the fundus.

When the subthreshold micropulse technique is used, there is no photocoagulation effect typical of classic laser therapy. The photothermal effect applies only to RPE cells – it is negligible and does not damage the tissue.

Consequently, SMPLT does not involve the risk of the complications associated with classic photocoagulation, such as hemorrhages or scars. The absence of scarring at the choroidal level allows the application of laser spots in a confluent mode and its repetition in the same places.

The procedure of preparing a patient for SMPLT is the same as in the case of classic laser treatment (mydriasis and topical anesthesia). During this form of laser therapy the patient does not experience any pain. For macular laser treatment, we use lenses such as Volk's Area Centralis or Ocular Mainster Focal/Grid.

Laser therapy is carried out in a confluent manner – with no gaps between the spots – over the entire area of the edematous retina. The panmacular form of SMPLT covering the entire posterior pole inside the main vascular arcades is sometimes recommended[92]. In micropulse laser therapy, the number of impacts made is significant, because we want to mobilize as many RPE cells as possible. A common mistake made by professionals who are starting to work with a micropulse laser is to apply too few spots. There is disagreement over whether laser therapy should include the foveal area itself. Some researchers include this area in SMPLT[92], while others spare the very centre of the fovea[93].

Figures 24–26 show images from the SMPLT procedure.

The laser power can be selected in two ways. Some sources indicate using lower fixed power parametres for each form of edema: 200–300 mW with a 577 nm laser[94, 87]. Others propose a laser power titration process[93]. The titration is performed on the flat retina just outside the edema border, gradually increasing the laser power. The moment when a barely visible fading of the retina is attained is taken as the threshold point, after which the laser power is reduced by 50%, and sometimes even to 30% of the threshold value. Those reduced power parameters are used to perform SMPLT.

Micropulse subthreshold retinal laser treatment uses a DC of 5%. This value of DC has been considered as safe therefore very seldom clinicians try 10 or 15% for retinal treatment. The recommended impact duration (pulse envelope time) for the 577 nm laser is 0.2 seconds (Quantel Medical). The use of the 810 nm micropulse laser requires different settings. For DME treatment in a micropulse mode, Luttrull et al. used the following parametres: spot diameter 200 μm, 0.15 second pulse envelope time, DC 5% and power 1,400 mW[95]. Recently, the same author reported using spots with a diameter of 500 μm, a power of 1,700 mW and a pulse envelope duration of 0.3 seconds.

Table 4 presents example protocols for subthreshold micropulse laser treatment for different laser wavelengths. It should be borne in mind that there are different clinical experiences and medical equipment manufacturers issue different recommendations. The protocols presented here have been successfully applied in published clinical papers. In all protocols, DC = 5% was used, and the laser power was not titrated.

The SMPLT procedure has been used in the treatment of edema related diseases of the retina: central serous chorioretinopathy (CSCR), DME, and edema secondary to retinal vein occlusion (RVO).

Works presenting the functional effects of DME treatment with SMPLT which go beyond the assessment of BCVA are particularly interesting. A detailed functional assessment of the retina after SMPLT in DME was performed by Vujosevic et al., who examined the change in BCVA and CRT, and the sensitivity of the retina by means of microperimetry, and performed an autofluorescence study of the fundus[94]. Researchers compared the effectiveness of SMPLT and the modified

Table 4. Examples of SMPLT protocols used in published clinical trials.

Wavelength in nm	Power in mW	Laser spot diameter at the retina in µm	Impact time in seconds	Possible range
577	250–300	160–180	0.2	SD-OCT based edema area panmacular
577	425	500	0.3	panmacular
810	1,400	200	0.15	panmacular
810	1,700	500	0.3	panmacular

laser photocoagulation (LPC) protocol as recommended by ETDRS. After twelve months of follow-up, there was no significant difference in BCVA and CRT between the groups. The group subjected to SMPLT showed better contrast sensitivity, while the sensitivity of the central retina decreased in the group subjected to photocoagulation. The autofluorescence test in the SMPLT group did not reveal any retinal damage, while in the LPC group, there were visible scars after photocoagulation. Better functional effects after SMPLT therapy were also confirmed by Venkatesh et al. in electrophysiological examinations of the retina[96].

Chen et al. summarized the functional and morphological effects of DME treatment with SMPLT and classic macular laser therapy, based on the results of six randomized clinical trials. A comparison of the efficacy of SMPLT with conventional photocoagulation in terms of final visual acuity falls in favor of micropulse laser therapy, although the final anatomical effects of both therapies are similar[97]. Inagaki et al. used a combination therapy: SMPLT and classic focal photocoagulation aimed at microaneurysms, achieving good morphological and functional effects[98, 99].

The main dilemma that arises when using SMPLT in DME is how to incorporate it into the treatment of DME, given the availability of commonly used anti-VEGF therapy and intravitreal steroid therapy. The efficacy of DME treatment with intravitreal therapies and their superiority over classic laser photocoagulation has been repeatedly confirmed in large randomized clinical trials[100, 101, 102, 103, 104]. In contrast, the majority of published studies on the use of SMPLT in DME are smaller clinical studies or case series, not large, randomized trials. Table 5 presents the results of the most important clinical studies on the efficacy of SMPLT in the treatment of DME.

Additionally, it should be stressed that so far, there have been no large randomized trials comparing the efficacy of DME treatment with SMPLT versus anti-VEGF preparations or intravitreal steroids. Therefore, there are no precise protocols for managing SMPLT in DME today, especially considering the availability of other forms of treatment. Some authors use SMPLT as first-line therapy for minor edema below 250 µm. For larger central retinal thicknesses, these authors recommend starting the therapy with intravitreal injections of anti-VEGF preparations and introducing SMPLT at a later stage of treatment, after the edema is reduced[105]. Other authors considering the efficacy of SMPLT in DME recommend the value of CRT of 400 µm or less as suitable for SMPLT[106].

It is necessary to emphasize that the morphological effects of SMPLT are often better than the functional effects. BCVA rarely improves by more than five ETDRS letters or one line on Snellen charts. Scholz et al.[107] calculated the mean functional and morphological

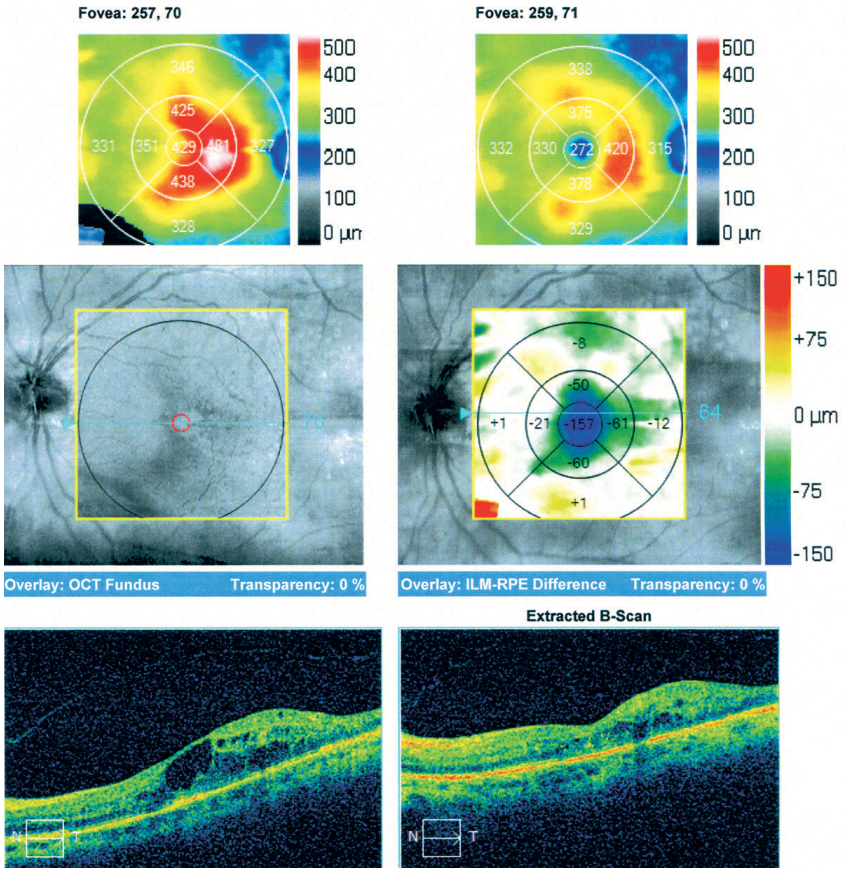


Figure 27. Diabetic macular edema after SMPLT treatment. There was a significant reduction in retinal edema and a reduction in the number of pseudocysts.

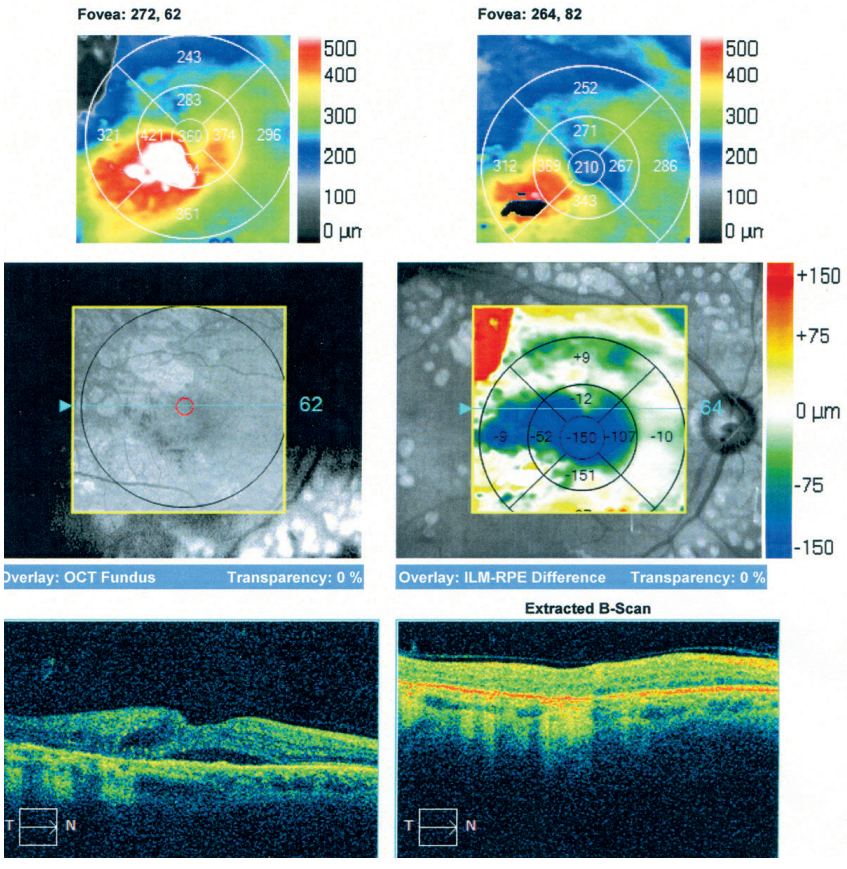


Figure 28. Diabetic macular edema after SMPLT treatment. Complete resorption of the pseudocysts and subretinal fluid as well as a reduction of the central retinal thickness are visible.

Table 5. Major clinical studies of treating diabetic macular edema with SMPLT.

Study	Number of eyes	Study design	Results
Laursen et al. 2004[108]	• SMPLT – 12 • LPC – 11	• comparison of the efficacy of SMPLT versus LPC in the treatment of CSME • evaluation of BCVA and CRT in OCT at 3 months	• significant reduction in CRT for focal edema in both groups • stabilization of BCVA in both groups • no significant difference in outcome between groups
Luttrull et al. 2005[95]	• SMPLT – 95 with CSME	• evaluation of the results of treatment of patients with CSME in patients with mild and moderate NPDR • evaluation at mean 12.2 months	• significant improvement of BCVA in 85% of eyes; reduction of CSME in 96% of eyes, no CSME after treatment in 79%
Sivaprasad et al. 2007[109]	• SMPLT – 25 with CSME	• evaluation of treatment effects (BCVA and FA) at 3 years	• improvement in BCVA in 84% at 1 year, maintained in 92% at 3 years • improvement of CSME in 92% at 1 year and complete regression of CSME in 88% at 1 year • recurrence of CSME in 28% at 3 years
Nakamura et al. 2010[110]	• SMPLT – 28 with DME	• BCVA, microperimetry retinal sensitivity and CRT at 3 months	• a significant reduction of CRT from mean 481 μm to 388 μm • significant improvement of BCVA from mean 0.47 logMAR to 0.4 logMAR • no change in retinal sensitivity in microperimetry
Ohkoshi et al. 2010[111]	• SMPLT – 43 with CSME ≤ 600 μm	• BCVA, CRT and MV at 3 months	• significant reduction of CRT from mean 341.8 μm to 300.7 μm • stabilization, but no improvement in BCVA and MV
Vujosevic et al. 2010[94]	• SMPLT – 32 with CSME • LPC – 30 with CSME	• comparison of the efficacy of SMPLT versus LPC in CSME at 12 months (BCVA, CRT, retinal sensitivity in microperimetry)	• stabilization of BCVA in both groups • significant reduction of CRT in both groups – no difference between groups • improvement in retinal sensitivity in the SMPLT group, decrease in retinal sensitivity in the LPC group

Study	Number of eyes	Study design	Results
Lavinsky et al. 2011[112]	• SMPLT ND – 39 • SMPLT HD – 42 • LPC – 42 (previously untreated patients with BCVA between 20/40 and 20/400)	• comparison of BCVA and CRT in 3 groups at 12 months	• highest improvement in BCVA: by mean 0.25 logMAR in the SMPLT HD group compared with mean 0.08 logMAR in the LPC group and mean 0.03 logMAR in the SMPLT ND group • the most significant reduction in CRT in the SMPLT HD group (by mean 154 µm) and in the LPC group (by mean 126 µm) – no significant difference between these groups
Venkatesh et al. 2011[96]	• SMPLT – 23 with CSME • LPC – 23 with CSME	• comparison of treatment effects in both groups at 6 months (CRT, retinal sensitivity in mfERG, BCVA, contrast sensitivity)	• significant decrease in CRT and improvement of BCVA – no substantial difference between groups • better mfERG results in SMPLT group (fewer areas of signal void)
Takatsuna et al. 2011[113]	• SMPLT – 56 with DME	• BCVA and CRT at 12 months	• reduction in CRT from mean 504 µm to 320 µm • no significant improvement in BCVA in the whole cohort (but improvement > 0.2 logMAR in 17.8% of patients)
Inagaki et al. 2012[98]	• 21 with DME	• treatment with SMPLT plus direct LPC of microaneurysms • evaluation of BCVA and CRT at 6 months	• statistically significant reduction in CRT • no change in mean BCVA
Othman et al. 2014[114]	• SMPLT in CSME without ischemia – 220, of which: » 187 – first-line therapy (group 1) » 33 – second-line therapy after LPC (group 2)	• treatment effects in 2 groups at 12–19 months • BCVA and CRT assessment • DC 15%	• group 1: significant improvement in BCVA at 4 months, stable in subsequent months (0.21 logMAR to 0.18 logMAR) • group 2: stabilization of BCVA without improvement – significant reduction of CRT in both groups
Luttrull et al. 2014[92]	• 39 with CSME and BCVA 20/40 and better	• assessment of treatment effects: CRT and BCVA at 4–7 months	• mean improvement in BCVA of 0.03 logMAR • significant reduction in CRT

Study	Number of eyes	Study design	Results
Mansouri et al. 2014[106]	• 63 with DME	• comparison of the effects of SMPLT (BCVA, CRT) in group 1 (n=33) with CRT ≤ 400 µm and in group 2 (n=30) with CRT > 400 µm (follow-up time – 12 months)	• group 1: significant improvement of BCVA by mean 0.2 logMAR and significant reduction of CRT by mean 55 µm • group 2: no significant change in BCVA and CRT
Inagaki et al. 2015[115]	• 53 with DME, including: » 24 – 810 nm SMPLT » 29 – 577 nm SMPLT	• comparison of treatment effects (CRT and BCVA) with 577 nm versus 810 nm laser using SMPLT combined with focal LPC for microaneurysms	• significant reduction in CRT in both groups, no difference between groups • BCVA stable in both groups
Vujosevic et al. 2015[99]	• 53 with CSME< 400 µm, including: » 26 – 577 nm SMPLT » 27 – 810 nm SMPLT	• comparison of effects in both groups at 6 months (CRT, MV, choroidal thickness, BCVA, retinal sensitivity) • safety assessment: FAF, FA, integrity of outer retinal layers on OCT	• no significant differences in BCVA, CRT, MV and choroidal thickness • significant improvement in retinal sensitivity in both groups • no scarring in FA, FAF, OCT
Fazel et al. 2016[116]	• 68 with CSME < 450 µm, including: » SMPLT – 34 » LPC – 34	• comparison of the effectiveness of SMPLT versus LPC (BCVA, CRT, MV) at 4 months	• significant reduction of CRT in both groups (from mean 357.3 µm to 344.3 µm in the SMPLT group and from mean 354.8 µm to 349.8 µm in the LPC group) • significant improvement in BCVA only in the SMPLT group (from mean 0.59 to 0.52 logMAR)

BCVA – best-corrected visual acuity, CRT – central retinal thickness, CSME – clinically significant macular edema, DC – duty cycle, DME – diabetic macular edema, FA – fluorescein angiography, FAF – fundus autofluorescence, HD – high density, LPC – laser photocoagulation, mfERG – multifocal electroretinogram, MV – macular volume, ND – normal density, NPDR – non-proliferative diabetic retinopathy, OCT – retinal optical coherence tomography, SMPLT – subthreshold micropulse laser treatment

improvement after SMPLT therapy with DME in data from eleven clinical studies (613 patients). The mean improvement in BCVA was +1.26 ETDRS letter (range -6.6 to +19) and the mean reduction in CRT was -74.9 µm (range -138 µm to +48 µm).

Another interesting issue is the use of SMPLT in patients with good visual acuity[92]. With a good baseline BCVA, minor edema and the patient's reluctance to undergo intravitreal therapy, SMPLT may be considered as first-line treatment. In such situations, EURETINA categorizes

Table 6. Major clinical trials on combining anti-VEGF therapy with SMPLT.

Study	Number of eyes	Purpose of the study	Results
Moisseiev et al. 2018[117]	• SMPLT plus ranibizumab – 19 • ranibizumab in monotherapy – 19	• comparison of BCVA and number of injections after 12 months and at the end of the study	• BCVA comparable in both groups • number of injections lower in the combined therapy group (SMPLT plus ranibizumab) than in the ranibizumab alone group (1.7 vs 5.6 at 12 months and 2.6 vs 9.3 at the end of the study)
Inagaki et al. 2019[118]	• combined therapy SMPLT plus injections – 34	• evaluation of BCVA, CRT and number of injections at 12 months	• BCVA: improvement from 0.52 logMAR to 0.41 logMAR at 12 months • stable reduction in CRT • mean number of injections per year: 3.6
Khattab et al. 2019[119]	• aflibercept – 27 (group 1) • aflibercept plus SMPLT – 27 (group 2)	• evaluation of number of injections, BCVA and CS after 18 months	• BCVA similar in both groups, improvement • number of injections: 7.3 (group 1) vs 4.1 (group 2)
Kanar et al. 2020[120]	• aflibercept in monotherapy – 28 • aflibercept plus SMPLT – 28	• randomized clinical trial • evaluation of BCVA, CRT and number of necessary injections at 12 months	• aflibercept group: improvement of BCVA from 0.38 logMAR to 0.20 logMAR, reduction of CRT from 451.28 to 328.8 μm • combination therapy group: improvement of BCVA from 0.40 logMAR to 0.17 logMAR, reduction of CRT from 466.07 to 312.0 μm (no statistically significant difference between groups) • number of injections in the combined therapy group significantly lower: 3.21 vs 5.39 in the monotherapy group
Furashova et al. 2020[121]	• ranibizumab – 7 • ranibizumab plus 2 sessions of SMPLT – 10	• prospective, randomized trial • 2 arms • ranibizumab loading 3 injections and than PRN • ranibizumab loading 3 iniections and 2 sessions of SMPLT at visit 5 and 6 • evaluation of BCVA and CRT and number of injections at 12 months	• latter gain for ranibizumab alone: 5.25±2.06; for combined treatment: 9.50±5.26 – difference not significant • reduction of CRT: ranibizumab alone: -65.25±67.57 vs -117.38±82.71 μm for combined treatment – difference insignificant • number of injections smaller in the combined treatment group: 7.5 vs 9.0

Study	Number of eyes	Purpose of the study	Results
Altinel et al. 2020[122]	• bevacizumab – 40 • bevacizumab plus SMPLT– 40	• evaluation of CRT, BCVA and number of injections at 12 months	• number of injections: bevacizumab: 4.38 ± 0.81; combined treatment: 2.1±0.81 • similar BCVA and morphological improvements
El Matri et al. 2021[123]	• bevacizumab plus SMPLT – 49 • bevacizumab alone – 49	• loading phase of 3 monthly injections followed by SMPLT repeated if needed in group 1 or intravitreal bevacizumab in PRN fashion in group 2 • evaluation at 12 months	• significant improvement of BCVA and reduction of CRT in both groups, no difference between the groups • significant difference in no of injections: 4.1±1.5 in the combined treatment group vs 7.2±1.3 in the bevacizumab alone group

BCVA – best-corrected visual acuity, CRT – central retinal thickness, CS – contrast sensitivity, SMPLT – subthreshold micropulse laser treatment.

SMPLT as an adjunctive therapy, especially in the case of early diffuse retinal edema[42].

Cost and availability are not insignificant factors in the choice of procedure. Micropulse laser therapy is relatively inexpensive, so in some cases it can be an alternative to expensive anti-VEGF therapy. Examples of effective SMPLT in DME are shown in the SD-OCT scans in Figures 27–28.

Combining anti-VEGF therapy with SMPLT is also a promising possibility. Table 6 presents most of the available clinical trials analysing the effects of such treatment.

As can be seen, when compared to anti-VEGF monotherapy, the combination of anti-VEGF and SMPLT allows a significant reduction in the number of injections with comparable functional effects.

However, it should be borne in mind that intravitreal treatment in central retinal edema is nowadays the main form of DME treatment, and the effectiveness of combined therapies requires further clinical trials.

Treatment of diabetic macular edema – intravitreal therapies

Intravitreal therapy was introduced into DR treatment several years ago, primarily as a form of managing of DME. The idea behind the use of intravitreal therapies in DME was to introduce a treatment that spares photoreceptors and is more effective than classical laser photocoagulation in terms of improving visual acuity.

Currently, two types of intravitreal agents are used to treat DR and DME: steroids and anti-VEGF preparations.

Intravitreal therapy with steroid agents

Studies on the intravitreal application of steroids in DME have their basis in the pathomechanism of its formation. The release of pro-inflammatory mediators,

the pro-edematous action of which may be inhibited by steroid therapy, is of great importance here. The most important studies on the use of intravitreal steroids and their relation to laser photocoagulation of the retina are presented in Table 7.

Most of the early studies of steroid drugs in the treatment of DME involve triamcinolone acetonide and show the efficacy of such therapy in the short term only. After several years of observation, intravitreal therapy usually has no advantage over classic laser photocoagulation. Additionally, steroid therapy is associated with complications, mainly with the development of cataract and the possibility of an increase in intraocular pressure and glaucoma. In a study by Gillies et al. with triamcinolone, the proportion of patients receiving glaucoma medications during the study was 44% versus 3% in the sham group, and 5.9% of patients trabeculectomy. Cataract surgery had to be performed in 54% of the treated patients versus 0% in the placebo group[124].

The approach to the use of intravitreal steroids in DME has changed with the introduction of new drugs to the market. In certain situations, such steroid therapy can be applied with success, especially with the use of sustained release implants. This is especially true of patients after cataract surgery (pseudophakia) and situations where DME does not respond to other forms of treatment (such as anti-VEGF therapy or laser therapy)[125]. Also, patients with cardiovascular diseases may be candidates for first-line intravitreal therapy with steroids due to the potential side effects of anti-VEGF medications.

Good results are observed with the use of a slow-release implant: dexamethasone 700 μg (Ozurdex) – see Table 7. What is crucial, a good therapeutic effect is maintained with a relatively small number of injections. The mean number of injections administered to patients with DME in the MEAD study (Ozurdex 700 μg implant registration study) over three years of treatment was 4.1 in the 700 μg group and 4.4 in the 350 μg group. Cataracts occurred in the majority of patients treated with dexamethasone (67.9% in the 700 μg group and 64.1% in the 350 μg group). Increases in intraocular pressure of more than 10 mmHg from baseline occurred in 27.7% of patients in the 700 μg group and 24.8% in the 300 μg group, with only 3.7% in the sham group but were easily controlled with topical anti-glaucoma medications. A small number of cases required trabeculectomy (0.6% in the 700 μg group and 0.3% in the 350 μg group)[126]. The RELDEX study[127] is also noteworthy. It is a real-life study, i.e. it evaluates the use of drugs in everyday practice. The average number of Ozurdex injections per patient during DME treatment over three years was only 3.6. Cataract surgery was performed in 47% of phakic eyes.

In patients with long-standing and refractory DME, a therapeutic option is fluocinolone acetate, administered as a drug-releasing implant for three years (Iluvien). The FAME study demonstrated the efficacy of a dose of 0.2 μg per day in improving BCVA by 15 letters on ETDRS charts in approximately 1⁄3 patients. Virtually all phakic patients treated with fluocinolone required cataract surgery. The need for surgical treatment of secondary glaucoma occurred in 4.8% of patients at a dose of 0.2 μg per day (at a dose of 0.5 μg per day, this percentage was 8.1%, which in the context of virtually the same functional results determined the registration of a dose of 0.2 μg per day for intravitreal administration)[128, 129].

It should be remembered that patients undergoing intravitreal steroid therapy must be under strict ophthalmological supervision (for cataract and secondary glaucoma). In all likelihood, the majority will have to undergo cataract surgery.

The intravitreal steroid drugs currently in use include:

1. Triamcinolone acetonide (Trivaris, Triesence, Vitreal S) – a drug administered by intravitreal injection at a dose of 4 mg/0.1 ml in a preservative-free form; with a half-life of about 19 days.It is

Table 7. Selected clinical trials using intravitreal steroid therapy in the treatment of diabetic macular edema.

Study	Substance	Purpose	Result
Gilles et al. 2006[130]	intravitreal triamcinolone acetonide – IVTA	comparison of the efficacy of IVTA versus placebo in LPC-resistant DME	at 2 years BCVA better in the IVTA group (mean difference 5.7 ETDRS letters)
DRCR.net (Protocol B) 2008, 2009[131, 132]	intravitreal triamcinolone acetonide – IVTA	comparison of efficacy of intravitreal doses of 1mg and 4mg IVTA versus LPC; IVTA injection interval 4 months	better BCVA and lower CRT in patients receiving 4 mg IVTA at 4 months; at 2 and 3 years BCVA better in patients after LPC, regardless of lens condition (phakia, pseudophakia)
Haller et al. 2010[133]	dexamethasone slow-release implant	comparison of 700 µg and 350 µg dexamethasone with placebo	better BCVA and lower CRT in the 700 µg dexamethasone group at 90 days compared to the placebo group
Campochiaro et al. FAME 2011 [128, 129, 134]	fluocinolone acetate (Iluvien) extended-release implant	patients with long-standing DME after previous laser therapy; fluocinolone at a dose of 0.2 µg/day or 0.5 µg/day versus sham	at 3 years improvement in BCVA by ≥15 letters: 28.7% 0.2 µg group, 27.8% 0.5 µg group versus 18.9% sham; in patients with DME lasting ≥ 3 years, improvement of BCVA by ≥15 letters: 34% 0.2 µg group, 28.8% 0.5 µg group versus 13.4% sham
Boyer et al. MEAD 2014[135]	dexamethasone slow-release implant	dexamethasone 700 µg, dexamethasone 350 µg, versus sham	at 3 years BCVA improvement by ≥15 letters: 22.2% in DEX 0.7, 18.4% in DEX 0.35 and 12% in sham group; CRT reduction by 111.6 µg in DEX 0.7, 107.9 µg in DEX 0.35 and 41.9 µg in the sham group
Augustin et al. MEAD 2015[136]	dexamethasone slow-release implant	dexamethasone 700 µg in patients previously treated with other methods versus sham	at 3 years BCVA +3.2 letters ETDRS in DEX 0.7 versus +1.5 in sham; CRT -126.1 µm for DEX 0.7 versus -39.0 µm sham
Heng et al. OZLASE 2016[137]	Ozurdex (dexamethasone 700 µg after registration)	Ozurdex in combination with LPC versus LPC alone	at 56 weeks no difference in BCVA between groups
Malclès et al. RELDEX 2017[127]	Ozurdex (dexamethasone 700 µg after registration)	effectiveness of Ozurdex treatment at 3 years	BCVA at 3 years +9.5 ETDRS letters, gain of at least 15 letters in 25.4%; reduction of CRT at 3 years from 451 µm to 280 µm; mean number of injections over 3 years = 3.6

BCVA – best-corrected visual acuity, CRT – central retinal thickness, DEX – dexamethasone, DME – diabetic macular edema, IVTA – intravitreal triamcinolone acetonide, LPC – laser photocoagulation

used worldwide off-label for treatment of DME because it is not registered as a drug for management of that condition. Triesence and Trivaris have been registered in the US for intravitreal administration in sympathetic inflammation, temporal arteritis, uveitis, and inflammatory conditions that do not respond to topical steroids, and as a visualization tool during vitrectomy. Vitreal S is commonly used as a visualization substance during vitrectomy.

2. Dexamethasone (Ozurdex) – a sustained release implant, contains a dose of 700 μg of slow-release dexamethasone in a disposable applicator. Following intravitreal implantation, trace amounts of dexamethasone were detectable in the vitreous after six months. According to the SmPC, a subsequent injection can be administered after at least six months. Simultaneous implantation in both eyeballs is not recommended, however. The drug has been approved for the treatment of DME, ME secondary to retinal vascular occlusions, and non-infectious uveitis. In the case of DME, it is licensed for administration to pseudophakic patients or patients insufficiently responsive to other forms of treatment. In practice, Ozurdex is used in many more clinical cases than those indicated in the SmPC. It is also not uncommon for it to be used more frequently than every six months. The retrospective real-life CHROME study, which examines the use of Ozurdex in DME, RVO, and uveitis, reports a mean re-injection interval of 2.3–4.9 months[138].
3. Fluocinolone (Iluvien) – an implant with extended release, amounting to 0.19 mg of fluocinolone acetate. The drug is administered into the vitreous by means of an applicator. The implant releases small doses of the drug (starting at 0.25 μg per day) over 36 months. The preparation is registered for administration with patients who have been treated with corticosteroids in the past without increases in intraocular pressure during this therapy (USA), and for the treatment of chronic DME in patients with unsatisfactory results of therapy with other methods – refractory DME (UK). In practice, it is used as a second-line and third-line drug when other forms of therapy are not effective.

Recommendations of EURETINA[42]

Nowadays, injections of steroids in the treatment of DME are a second-line therapy, used mainly in patients who do not respond to anti-VEGF preparations after 3–6 injections. Steroids may be the drugs of choice for patients with DME and significant cardiovascular burdens, and in patients who do not wish to undergo monthly injections during the initial treatment period. Dexamethasone is recommended first, and in cases of chronic and refractory DME – fluocinolone. Pseudophakic patients are preferred for steroid injections.

It is necessary to reiterate that some authors allow intravitreal steroid therapy in the first line of treatment. This mainly applies to pseudophakic patients at risk of cardiovascular disease and patients who do not wish to undergo frequent – i.e. monthly – intravitreal injections[139].

Intravitreal therapy with anti-VEGF preparations

Nowadays, by far the most common treatment of the central form of DME is with injections of agents which inhibit the VEGF. VEGF causes a very strong increase in vascular permeability, which is at the root of the formation of central macular edema. There are currently four anti-VEGF preparations on the market: ranibizumab, aflibercept, bevacizumab and brolucizumab. Bevacizumab is not licensed for intravitreal administration and is therefore used worldwide in the off-label treatment of DME. Brolucizumab, on the other hand, is a new drug that has been so far registered for the treatment of neovascular form of age related macular degeneration, but not yet for DME.

The effectiveness of the first three products in the management of DME has been confirmed in numerous

Table 8. Efficacy of anti-VEGF therapy in the treatment of diabetic macular edema (selected studies).

Study	Design	Results
Nguyen et al. READ-2 2009[140, 141] Do et al. READ-2 2013[142]	arms of the study: **1.** ranibizumab 0.5 mg **2.** laser treatment only **3.** ranibizumab followed by laser treatment	BCVA at 6 months (ETDRS letters): **1.** +7.24 **2.** -0.43 **3.** +3.80 CRT at 6 months – reduction in edema by: **1.** 50% **2.** 33% **3.** 45% at 2 years (continuation of treatment with ranibizumab only) improvement of BCVA (ETDRS letters): **1.** +7.4 **2.** +0.5 **3.** +3.8 mean number of injections over 18 months: **1.** 5.3 **2.** 4.4 **3.** 2.9 results at 3 years (intensive ranibizumab therapy – injection at CRT of 250 µm and more) BCVA improvement (ETDRS letters): **1.** +10.3 **2.** -1.1 **3.** +5.8
Massin et al. RESOLVE 2010[100]	arms of the study: **1.** ranibizumab 0.3 mg **2.** ranibizumab 0.5 mg **3.** sham ranibizumab administered at monthly intervals for 3 months, then PRN; rescue laser therapy allowed	results at 12 months BCVA (ETDRS letters): +10.3 for group 1 and 2 combined -1.4 in sham group CRT reduction (µm): -194 for groups 1 and 2 combined -48.4 in sham group mean number of injections in ranibizumab group: 10.2
Mitchell et al. RESTORE 2011[101]	arms of the study: **1.** ranibizumab 0.5 mg **2.** ranibizumab 0.5 mg plus laser treatment **3.** laser treatment only ranibizumab administered at monthly intervals for 3 months, followed by PRN	results at 12 months BCVA (ETDRS letters): **1.** +6.1 **2.** +5.9 **3.** +0.8 CRT reduction (µm): **1.** -118.7 **2.** -128.3 **3.** -61.3 mean number of injections in groups 1 and 2: 7

Study	Design	Results
Nguyen et al. RISE and RIDE 2012[143] Brown et al. RISE and RIDE 2013[144]	arms of the study: **1.** sham **2.** ranibizumab 0.3 mg **3.** ranibizumab 0.5 mg ranibizumab administered at monthly intervals for 24 months; rescue laser treatment allowed	results at 24 months for RISE percentage of patients with a gain of ≥15 ETDRS letters: **1.** 18.1% **2.** 44.8% **3.** 39.2% results after 24 months for RIDE percentage of patients with a gain of ≥15 ETDRS letters: **1.** 12.3% **2.** 33.6% **3.** 45.7% results after 36 months for RISE percentage of patients with a gain of ≥15 ETDRS letters: **1.** 22% **2.** 51.2% **3.** 41.6% results after 36 months for RIDE percentage of patients with a gain of ≥15 ETDRS letters: **1.** 19.2% **2.** 36.8% **3.** 40.2%
Elman et al., Bressler et al. DRCR.net 2010, 2011, 2016[102, 145, 146]	arms of the study: **1.** laser **2.** 0.5 mg ranibizumab plus immediate laser **3.** 0.5 mg ranibizumab plus deferred laser **4.** 4 mg triamcinolone plus immediate laser	BCVA at 12 months (ETDRS letter gain): **1.** +3 **2.** +9 **3.** +9 **4.** +4 BCVA after 24 months (ETDRS letter gain): **1.** +3 **2.** +7 **3.** +9 **4.** +2 BCVA at 5 years (from week 74 of the study, groups 1 and 4 could also receive ranibizumab injections): **1.** +5 **2.** +8 **3.** +10 **4.** +7 mean number of injections per year at 2 years of treatment: 3–5 depending on the group; the lowest number (3–4) in the ranibizumab groups
Do et al. DA VINCI 2012[147]	arms of the study: **1.** 0.5 mg aflibercept every 4 weeks **2.** 2 mg aflibercept every 4 weeks **3.** 2 mg aflibercept every 8 weeks after the first 3 doses every month **4.** 2 mg of aflibercept in the PRN regimen after the first 3 doses **5.** macular laser treatment	BCVA (ETDRS letter yield) after 12 months: **1.** +8.6 **2.** +11.4 **3.** +8.5 **4.** +10.3 **5.** +2.5 percentage of patients with a gain of ≥ 15 ETDRS letters after 12 months: **1.** 40.9% **2.** 45.5% **3.** 23.8% **4.** 42.2% **5.** 11.4% CRT reduction at 12 months (in µm): **1.** -165.4 **2.** -227.4 **3.** -187.8 **4.** -180.3 **5.** -58.4

Study	Design	Results
Korobelnik et al. VIVID and VISTA 2014[103] Brown et al. VIVID and VISTA 2015[148] Heier et al. VIVID and VISTA 2016[149]	arms of the study: **1.** 2 mg aflibercept every 4 weeks **2.** 2 mg aflibercept every 8 weeks after 5 doses at monthly intervals **3.** laser photocoagulation	BCVA (ETDRS letter gain) at 52 weeks (VISTA/VIVID): **1.** +12.5 / +10.5 **2.** +10.7 / +10.7 **3.** +0.2 / +1.2 percentage of patients with a gain of ≥15 ETDRS letters at 52 weeks (VISTA/VIVID): **1.** 41.6% / 32.4% **2.** 31.1% / 33.3% **3.** 7.8% / 9.1% CRT reduction at 52 weeks in µm (VISTA/VIVID): **1.** 185.9 / 195 **2.** 183.1 / 192.4 **3.** 73.3 / 66.2 BCVA (ETDRS letter gain) at 100 weeks (VISTA/VIVID): **1.** +11.5 / +11.4 **2.** +11.1 / +9.4 **3.** +0.29 / +0.7 percentage of patients with a gain of ≥15 ETDRS letters at 100 weeks (VISTA/VIVID): **1.** 38.3% / 38.2% **2.** 33.1% / 31.1% **3.** 13.0% / 12.1% BCVA (ETDRS letter gain) at 148 weeks (VISTA/VIVID): **1.** +10.4 / +10.3 **2.** +10.5 / +11.7 **3.** +1.4 / +1.6 percentage of patients with a gain of ≥ 15 ETDRS letters at 148 weeks (VISTA/VIVID): **1.** 42.9% / 41.2% **2.** 35.8% / 42.2% **3.** 13.6% / 18.9%
Michaelides et al. BOLT 2010[106] Rajendram et al. BOLT 2012[150]	DME patients after at least one laser therapy; follow-up 12 months arms of the study: **1.** bevacizumab 1.25 mg every 6 weeks (min. 3, max 9) **2.** laser treatment every 4 months (min. 1, max. 4)	results at 12 months BCVA (median ETDRS letter gain): **1.** +8 **2.** -0.5 CRT reduction (mean): **1.** from 507 µm to 378 µm **2.** from 481 µm to 431 µm median number of injections: 9 median number of laser treatment: 3 results at 24 months BCVA (median ETDRS letter gain): **1.** +9 **2.** +2.5 CRT decrease (mean): **1.** by 146 µm **2.** by 118 µm median number of injections over 24 months: 13 median number of laser treatment over 24 months: 4

Study	Design	Results
Soheilian et al. 2009[151]	duration: 36 months arms of the study: **1.** bevacizumab 1.25 mg **2.** bevacizumab 1.25 mg plus triamcinolone 2 mg **3.** laser photocoagulation	change in BCVA at 36 weeks (logMAR): **1.** -0.28 **2.** -0.04 **3.** +0.01 no synergistic effect of triamcinolone
Wells et al. (DRCR.net group) 2016[152]	duration: 24 months arms of the study: **1.** 2.0 mg aflibercept **2.** 1.25 mg bevacizumab **3.** 0.3 mg ranibizumab injections a maximum of once a month	BCVA (ETDRS letter gain) after 24 months: **1.** +12.8 **2.** +10.0 **3.** +12.3 BCVA (ETDRS letter gain) at 24 months for VA 20/50 to 20/320: **1.** +18.1 **2.** +13.3 **3.** +16.1 median number of injections (at 2 years/second year): **1.** 15/5 **2.** 16/6 **3.** 15/6 statistically significant advantage of aflibercept over bevacizumab but not over ranibizumab

BCVA – best-corrected visual acuity, CRT – central retinal thickness, PRN – pro re nata (as needed)

clinical trials (Table 8). The introduction of anti-VEGF therapy to the treatment of ocular complications of diabetes is a breakthrough in the therapeutic management of this disease. After the application of anti-VEGF therapy, a significant functional (visual acuity) and morphological (reduction of CRT) improvement is noted. In terms of improving visual acuity in patients with DME, anti-VEGF therapy is more effective than classic laser photocoagulation of the retina, which for years has been the primary treatment of DME. Combined therapy: anti-VEGF with retinal laser also proved to be successful (the studies of the DRCR.net group).

Intensive anti-VEGF treatment in the first year results in fewer injections in the following years (in the DRCR.net and RESTORE studies, patients treated in the first year with ranibizumab alone or in combination with laser therapy required an average of only 2–4 injections in the second and third years of the study). The studies emphasize the role of the loading dose at the beginning of the therapeutic process: usually 3–5 injections at monthly intervals (depending on the drug used).

This fact is also confirmed by "real-life studies", i.e. relating to everyday clinical practice. An analysis of the efficacy of aflibercept in the treatment of DME carried out at Moorfields Hospital in London showed that during the first twelve months of treatment, patients received an average of 6.92 injections. This means that after the administration of the five loading doses, only two injections were required over the next seven months[153] (the drug was administered in the PRN regimen, or pro re nata, already in the first year of treatment, although the SmPC allows this regimen for aflibercept from the second year).

It is worth noting that clinical trials of DME do not show an advantage of using anti-VEGF in monotherapy over combined anti-VEGF plus laser therapy. In fact, one large

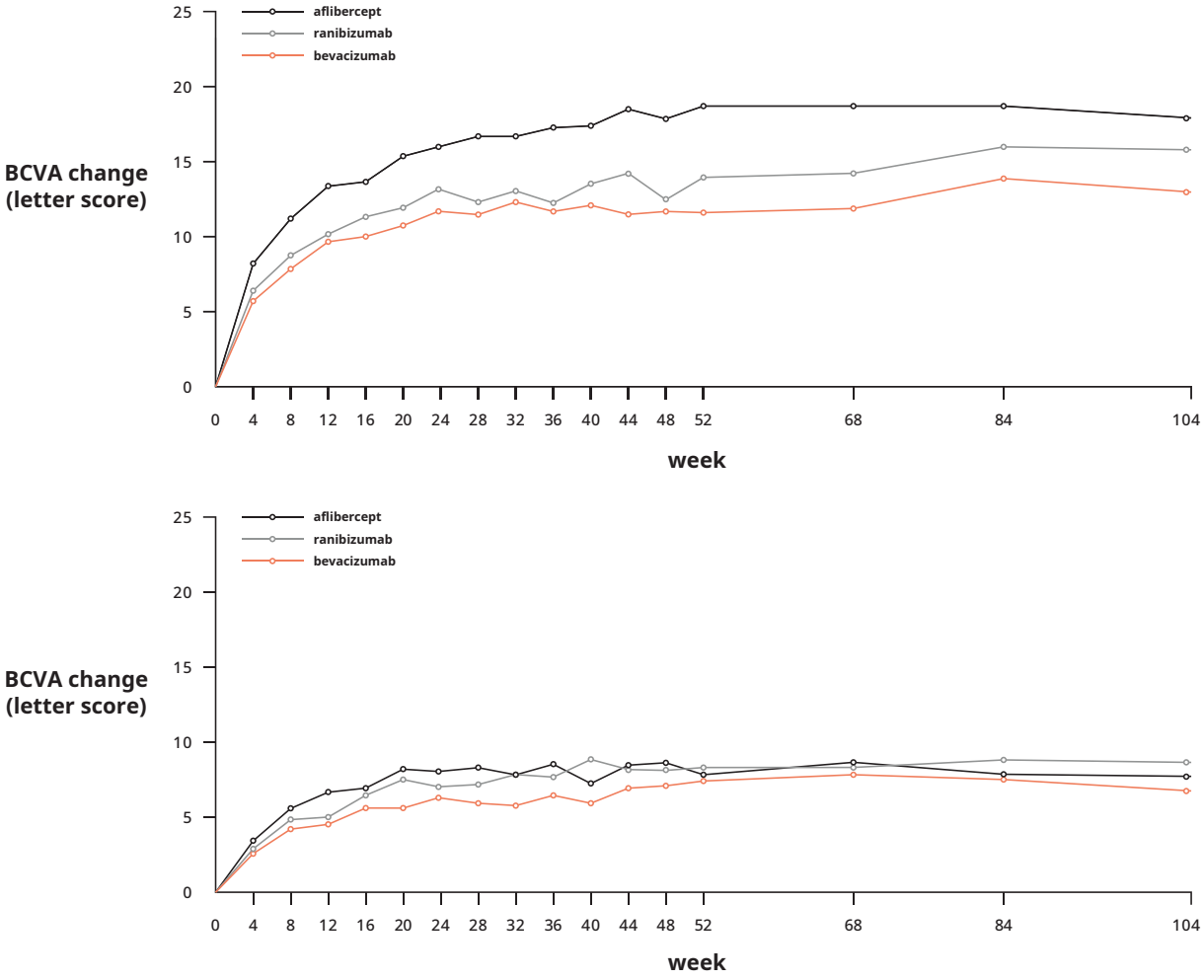


Figure 29. Comparison of the efficacy of aflibercept, ranibizumab, and bevacizumab in the treatment of diabetic macular edema over two years (Protocol T of the DRCR.net group). The top graph relates to a group of patients with visual acuity of 20/50 and worse, and the bottom one to a group of patients with visual acuity ranging from 20/40 to 20/32. After one year of treatment, patients with low visual acuity had better results with aflibercept. After two years of therapy, this difference in BCVA was no longer statistically significant. The effects of treatment in patients with better baseline visual acuity were similar for all three agents.

clinical trial of the DRCR.net group from 2010 showed the benefits of deferred laser therapy in the course of DME treatment with ranibizumab[102]. Most clinicians who have the option of conducting anti-VEGF therapy for DME, use it as monotherapy, avoiding the damage to the central retina with a photocoagulating laser. In practice, classic photocoagulation is used in the course to anti-VEGF therapy as a rescue procedure or when it is no longer possible to continue intravitreal therapy.

An important consideration is the choice of anti-VEGF medication. Aflibercept and ranibizumab have been approved for intravitreal administration, but for bevacizumab, this way of administration remains off-label. For some physicians, this fact may be significant in the context of legal security, but it should be noted that due to its low price, bevacizumab is currently the most frequently administered intravitreal agent in the world.

Apart from legal issues, there is also the question of the effectiveness of the discussed drugs in the treatment of DME. A study on the best medication to choose was carried out by the DRCR.net group (Protocol T)[154, 155] (Fig. 29). A comparison of the effectiveness of the three described agents in terms of BCVA improvement at one year showed the advantage of aflibercept over the other two drugs in patients with low baseline visual acuity (20/50 – 20/320). However, after 24 months, the analysis showed that there was no such statistically significant difference for aflibercept and ranibizumab. The only statistically significant difference concerned the advantage of aflibercept over bevacizumab in this group of patients. It should be noted, though, that in the DRCR.net study ranibizumab was used at a dose of 0.3 mg in accordance with the US approval, while in Europe a dose of 0.5 mg is recommended.

The results of the DRCR.net Protocol T study were reflected in the 2017 recommendations of the EURETINA society, which recommend aflibercept or ranibizumab in the treatment of DME in patients with a baseline visual acuity of 20/50 or lower. EURETINA also emphasizes that aflibercept is the preferred drug for these patients, as its use will result in faster improvement of visual acuity. In patients with a baseline visual acuity of 0.5 and better, each of the three available drugs can be used with an equivalent effect[42].

It should also be stressed that practical real-life studies are usually less optimistic than large clinical trials conducted for the purpose of drug registration. In the US, the mean ETDRS letter gain in patients treated with each of the three intravitreal drugs was similar, ranging from 4 to 5.5 after twelve months of treatment[156]. In the real-life APOLLON study of aflibercept monotherapy, there was a gain of 7.8 letters in previously untreated patients with DME and 5 letters in previously treated patients. An evaluation was performed after twelve months. The mean number of injections in both groups was 7.6[157]. Nevertheless, large clinical trials show a significant improvement in the quality of life in patients treated with anti-VEGF agents (e.g. AQUA)[158].

If one intravitreal medication is ineffective, the intravitreal therapy should be continued with another drug (switch). Many clinical trials have demonstrated the therapeutic efficacy of such a switch, although the morphological effect was usually better than the functional one[159, 160, 161, 162]. Switching from bevacizumab to the original drugs usually produces better functional effects.

It should be emphasized that anti-VEGF therapy in DME has a time horizon, unlike treatment of the exudative form of age-related macular degeneration (AMD), which is carried out for the rest of the patient's life. The extended arm of the READ-2 study[141], as well as the RESTORE[163] and DRCR.net[146] studies show that DME patients treated intensively with anti-VEGF medications in the first year require significantly fewer injections in the next two years.

DME treatment regimens with anti-VEGF medications

1. Fixed regimen – treatment is carried out according to the principles of the SmPC for each drug. After the loading phase, treatment with injections is continued at two-month (aflibercept) or monthly (ranibizumab and bevacizumab) intervals. Currently, this treatment regimen is rarely used, due to the need for frequent monitoring and treatments, as well as the high cost.
2. Flexible PRN scheme – consists of the loading phase specified for each drug, and then switching to the system of monitoring at specified intervals (most often monthly checks; in the case of aflibercept, according to the SmPC, PRN is possible in the second year of treatment). Changes in BCVA and the morphology of the retina in SD-OCT determine the administration of the next dose.
3. Treat-and-extend regimen – a recent alternative to the PRN regimen. The basic principles of both regimens are similar – the loading phase and the re-

injection decision based on BCVA and retinal morphology. The difference is in changing the patient's follow-up regimen from regular to flexible: in the case of stabilization of functional and anatomical parameters, the intervals between control examinations may be gradually prolonged (the aflibercept SmPC does not define the time interval for such an extension, and the ranibizumab SmPC allows for a maximum one-time extension of such an interval by one month). In the event of recurrence, the intervals between follow-up visits are shortened. For aflibercept, the treat-and-extend regimen is acceptable from the second year of treatment (according to the SmPC).

Rigid dosing schedules for intravitreal drugs are always used in registration trials (RISE, RIDE, VIVID, VISTA). Everyday practice verifies the use of such a treatment regimen: frequent procedures and follow-up visits are usually difficult for patients to accept, put a heavy burden on healthcare systems, and generate high costs. Hence, there are attempts at using intravitreal drugs in flexible schemes, in which the administration of injections depends on the morphology of the retina and the dynamics of changes in visual acuity.

The efficacy of the PRN regimen for the administration of anti-VEGF drugs in the treatment of DME has been confirmed in many clinical trials. The DRCR.net group conducted a Protocol I study that used a specific ranibizumab re-injection algorithm[164]. (Re-injection was not performed if the BCVA was 20/20, if the CRT in SD-OCT was less than 250 μm, or if the change from the last injection was less than five ETDRS letters and less than 10% CRT in SD-OCT). The number of visits and injections clearly decreased in the subsequent years of the patient's treatment. In the fifth year of treatment, the patients practically did not require injections, and the number of follow-up visits fell to four or five.

The PRN regimen also turns out to be effective in treatment with aflibercept (recommendations of a panel of Italian experts), but requires strict monthly monitoring[165]. The efficacy of the PRN regimen in treatment with aflibercept has also been confirmed in other real-life studies[153, 166]. Both cited studies started with a loading phase with five injections at monthly intervals, and then continued with reinjections depending on changes in BCVA and retinal morphology, and achieved good anatomical and functional effects. (Note that this treatment regimen is not SmPC compliant).

Clinical trials have also shown the effectiveness of DME treatment with anti-VEGF medications in the treat-and-extend mode. The RETAIN study compared DME treatment using two regimens: treat-and-extend versus PRN[167]. The results showed that treatment with the treat-and-extend regimen did not produce inferior functional effects to treatment with the PRN regimen but required significantly fewer follow-up visits. In turn, the TREX-DME study compared the efficacy of DME treatment with monthly ranibizumab versus treat-and-extend (TREX). After two years, TREX patients had no inferior functional or anatomical parameters compared to patients treated with the fixed regimen, but they required significantly fewer injections[168]. Good functional results with fewer ophthalmic consultations have also been reported with aflibercept under the treat-and-extend regimen[169]. The use of different treatment protocols (fixed, PRN, and treat-and-extend) for aflibercept in the second year was evaluated in the VIOLET study[170]. Both flexible regimens turned out to be no worse than the rigid schema with regard to the final functional and anatomical parameters.

The analysis of the factors that influence the effects of DME treatment is an interesting issue which is the focus of ongoing research. Diabetic retinopathy and DME are diseases of multifactorial etiology, so it is difficult to identify unequivocally which factors determine therapeutic success before the therapy is undertaken. When analysing the functional effects of DME treatment with anti-VEGF medications, the so-called ceiling

effect should be borne in mind. A meta-analysis of nine large clinical trials by Dugel et al.[171] showed that the mean visual acuity after twelve months of treatment was approximately 70 ETDRS letters (approximately 0.5 on Snellen charts) in each trial. Although the mean ETDRS letter gain after twelve months of treatment differed from study to study (ranging from 6.8 to 13.1), good visual acuity at baseline also meant lower letter gain at the end of the study.

The pre-treatment retinal morphology is also important for the final outcome[172]. This issue is discussed in the section on the role of OCT in the diagnosis of diabetic maculopathy (pp. 123–128 of this chapter).

Available anti-VEGF agents for use in the treatment of DME

Ranibizumab (Lucentis) is a fragment of a recombinant humanized monoclonal antibody directed against human vascular endothelial growth factor A (VEGF-A). Ranibizumab binds to VEGF-A isoforms, preventing VEGF-A from binding to its receptors in tissues. This results in inhibiting the proliferation of vascular endothelial cells, and hence vascular proliferation.

In addition to its use in DME treatment, Lucentis has been registered for the treatment of exudative age-related macular degeneration (AMD), choroidal neovascularization (CNV) of non-AMD etiology, including neovascularization in myopia, and the treatment of macular edema secondary to retinal vein occlusion (RVO).

Key information from the Lucentis SmPC[173]:

1. Dosage
   In Europe, the recommended dose of Lucentis is 0.5 mg in 0.05 ml of solution (in the USA, a dose of 0.3 mg is allowed). Treatment is started with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity, i.e. no change in visual acuity and other signs of disease with continued treatment. In patients with wet AMD, DME and RVO, an initial three or more monthly injections may be needed. Thereafter, treatment and follow-up intervals should be determined by the physician and should be based on disease activity as assessed by visual acuity and/or anatomical parameters. If the physician determines, based on the assessment of visual acuity and anatomical parameters, that continued treatment is not improving the patient's condition, treatment with Lucentis should be discontinued. Monitoring disease activity may involve a clinical examination, functional tests, or imaging studies (for example, optical coherence tomography or fluorescein angiography). In patients treated with the treat-and-extend regimen, after maximum visual acuity and/or no disease activity are achieved, the dosing intervals may be gradually extended until either there is evidence of disease activity or vision worsens. Dose intervals should not be extended by more than two weeks at a time in patients with exudative AMD and may be extended by up to one month at a time in patients with DME.
2. Discontinuation of Lucentis
   Dosing of the drug should be withheld and treatment should not be restarted before the next scheduled visit in the event of the following:
   a. deterioration of best-corrected visual acuity (BCVA) by ≥ 30 ETDRS letters when compared to the last assessment of visual acuity,
   b. intraocular pressure ≥ 30 mmHg,
   c. retinal detachment,
   d. subretinal hemorrhage involving the centre of the retinal fovea, or if the hemorrhage size is ≥ 50% of the total lesion area (applies to AMD),
   e. furthermore, intra-ocular surgery should not be planned or performed within 28 days before or after the administration of the drug.

Aflibercept (Eylea) – a recombinant fusion protein consisting of fragments of extracellular domains of human VEGF 1 and 2 receptors fused to the Fc fragment of human IgG1. Aflibercept acts as a decoy receptor that binds VEGF-A and PlGF (placental growth factor) with greater affinity than their natural

receptors and thus inhibits their activation. It thus inhibits vascular proliferation.

Like Lucentis, Eylea is also registered for the treatment of AMD, CNV in myopia and for the treatment of macular edema secondary to retinal vein occlusion.

Key information from the Eylea SmPC[174]

1. Dosing in DME
   The recommended dose of Eylea is 2 mg aflibercept in 50 ml of solution. Treatment with Eylea starts with one injection per month for five consecutive doses, followed by one injection every two months. There is no requirement to monitor the thickness of the retina between injections. After the first twelve months of treatment with Eylea, on the basis of visual and/or anatomical observations, the dosing interval may be extended, for example, by using a treat-and-extend dosing regimen in which the dosing interval is gradually extended so as to maintain response in visual and/or anatomical parameters; however, there are insufficient data to quantify the length of these intervals. If the visual and/or anatomical parameters deteriorate, the dosing interval should be shortened accordingly. Therefore, the monitoring schedule should be determined by the treating physician and may be more frequent than the injection schedule.
   If the patient is not benefiting from continued treatment, based on visual and anatomical evaluation, Eylea should be discontinued.
2. Discontinuation of Eylea
   The medication should be stopped and treatment should not be restarted until the next scheduled appointment if the following occur:
   a. best-corrected visual acuity deterioration (BCVA) ≥ 30 letters ETDRS compared to the last assessment of visual acuity,
   b. subretinal hemorrhage involving the centre of the fovea, or if the hemorrhage involves ≥ 50% of the total area of the lesion.

   Patients with rhegmatogenous retinal detachment or stage 3 and 4 macular holes should be withdrawn from treatment. If a retinal break occurs, the dose should be withheld and treatment should not be restarted until the rupture has healed. The administration of the drug should be suspended 28 days before or after performed or planned intraocular surgeries

Bevacizumab (Avastin) – is a recombinant humanized monoclonal antibody, synthesized by recombinant DNA. Like ranibizumab, bevacizumab binds to VEGF, preventing it from attaching to tissue receptors and thus inhibiting angiogenesis.

Bevacizumab is approved for the treatment of ovarian, fallopian tube, breast, colon and peritoneal cancers, most often combined with other chemotherapeutic agents[175]. It is not registered for intraocular administration and is used off-label worldwide.

In ophthalmology, Avastin is used with the same recommendations as Lucentis or Eylea. In intravitreal therapy, the dose is 1.25 mg in 0.05 ml of solution (the dosing regimen is usually the same as for ranibizumab).

Due to the mechanism of action, anti-VEGF agents are potentially teratogenic drugs, although there are no clinical studies on their use in pregnancy. Therefore, the use of anti-VEGF drugs is contraindicated in pregnant women (unless the potential benefit outweighs the potential risk to the fetus). Women of childbearing potential should use effective contraception during treatment, and women wishing to become pregnant should wait at least three months after the last dose of the drug. It is not known whether anti-VEGF drugs are excreted in human milk, so patients on such regimens are advised not to breastfeed.

Key principles of anti-VEGF therapy in the treatment of DME

1. The use of each of the available drugs requires a loading phase:
   a. For aflibercept, the recommended dose is five monthly injections followed by injections every

two months during the first year of treatment. In the following years, aflibercept can be administered in a flexible regimen, i.e. depending on changes in BCVA and morphological parametres (SmPC information). The use of aflibercept in a flexible regimen already after the loading phase is used in practice, but it requires strict monitoring.

b. When using ranibizumab, the initiating monthly injections are used to achieve maximum visual acuity, which in practice means applying at least three injections. Further treatment can be carried out in a flexible schedule.

c. Treatment with bevacizumab is usually analogous to that of ranibizumab.

2. The continuation and frequency of subsequent injections depend on the stabilization of BCVA and CRT – PRN or a treat-and-extend regimen can be employed.
3. The treat-and-extend regimen can be used for all three drugs after reaching maximum BCVA and in the absence of disease activity. The intervals between injections can be gradually extended until symptoms reappear. In the event of recurrence, the frequency of follow-up visits should be increased.

New intravitreal drugs

Clinical trials are being carried out on new anti-VEGF drugs that could be introduced into the treatment of chronic eye diseases, including DME. The aim of such studies is to find a substance that could be administered less frequently than the drugs used so far. (In the case of anti-VEGF drugs, we cannot currently expect a higher mean ETDRS letter gain, due to the so-called ceiling effect).

At the time of publishing this book, a new anti-VEGF product has appeared on the Polish market: brolucizumab (the Beovu medication), which for the time being, has been registered for the treatment of wet AMD (nAMD). However, it should be expected that in the near future this drug will also be approved for the treatment of DME.

In the treatment of nAMD, a dose of 6 mg of the agent in 0.05 ml of solution is used. The drug requires a loading phase of three injections, given four weeks apart. Subsequently, the SmPC allows for individual dosing intervals, depending on disease activity as assessed by visual acuity and anatomical parametres[176]. In patients without disease activity, dosing every twelve weeks is possible.

When Beovu has been registered for DME treatment, it will be possible to assess whether the drug is effective in treating this entity with less frequent dosing.

Faricimab (YOSEMITE study) is another drug developed with a lower dosing frequency in DME[177]. The drug is currently undergoing phase III trials[178].

The technique for performing intravitreal injections

Information on treatment with intraocular injections usually arouses emotional reactions and fears in patients, but the facts indicate that it is a practically painless and safe procedure. During the injection, the needle passes through the flat part of the ciliary body, so the sensory retina is not affected.

Intravitreal injections can be performed at an outpatient clinic; it is not necessary to perform them in the operating theatre. Topical and systemic antibiotic therapy is not necessary, indeed – taking into account the number of injections performed in the same patient – it may even lead to complications such as changes in the natural bacterial flora of the conjunctival sac and growth of bacterial species resistant to commonly used antibiotics[179]. A meta-analysis conducted by Benoist d'Azy et al. did not show a higher incidence of ocular inflammation in patients without the protection of topical antibiotics during intravitreal therapy (the incidence of endophthalmitis was 0.051% in the antibiotic group and 0.048% in the group without antibiotics)[180]. There is no contraindication to injecting into both eyes at the same procedure, but this requires the use of separate instrument sets. Disposable sterile

kits are convenient and usually include a drape, speculum, caliper or marker and cotton tip applicators. Prior to injection, informed consent must be obtained from the patient. The treatment technique is shown in Figures 30–36.

It is important to follow certain procedures during intravitreal injection, as follows[181]:

1. position the patient on a treatment chair or operating table, preferably in a supine or semi-recumbent lying position,
2. disinfect the skin of the eyelids, forehead and cheek with a 10% povidone-iodine solution (preoperative lid scrubs are not recommended),
3. cover with a sterile drape with an opening for the eye,
4. administer topical anesthesia ex: proparacaine or lidocaine drops (anesthetic drops are also administered several times before entering the treatment room),
5. position a speculum on the eyelids,
6. rinse the conjunctival sac with a 5% iodopovidone solution (it should remain in the conjunctival sac for at least 30 seconds), and then rinse with saline solution,
7. measure a distance of 4 mm from the limbus for phakic patients or 3.5 mm for pseudophakic patients,
8. stabilize the eyeball with tweezers or a caliper,
9. perform the injection using the supplied injection kit or an insulin needle (a 30G needle is recommended for aqueous solutions and a 27G needle for crystalline solutions): point the needle perpendicular to the wall of the eyeball, slowly administer the drug, then slowly withdraw the needle, and press the injection site with a cotton tip/sponge (it can be soaked with 5% iodopovidone),
10. after the injection, perform an approximate assessment of visual acuity (hand movement); in the case of a negative response, urgent ophthalmoscopy is required,
11. check intraocular pressure 30 minutes after injection; in the case of a significant increase in IOP, the patient may be given oral acetazolamide or intravenous Mannitol.

After the injection, the patient should be instructed to seek an urgent appointment if redness, pain or decreased visual acuity occurs. Follow-up on the next day is not necessary.

Table 9 shows the recommendations of EURETINA[182] for performing intravitreal injections.

Complications following intravitreal therapies

Complications after intravitreal therapy can be divided into local, i.e. related to the injection procedure itself, and general, i.e. related to the systemic effects of the administered drug.

1. Local complications are rare and are usually related to the surgical technique.
2. Among temporary local complications, the following may occur:
   a. subconjunctival hemorrhage – has no clinical significance and is associated with vessel damage at the injection site,
   b. temporary increase in intraocular pressure – usually lasts up to 60 minutes and is associated with the injection of a certain volume of the drug into the vitreous chamber,
   c. subjective symptoms reported by the patient: pain, foreign body sensation, floaters and spots in the visual field – these are transient, related to the injection procedure itself and the presence of the drug in the vitreous; they disappear with time and with the absorption of the drug.
3. Serious local complications include:
   a. endophthalmitis – a rare but very serious complication that directly threatens eyesight; the primary reported symptoms are pain and deterioration in vision; on microscopic examination, the eyeball is severely irritated, usually with hypopyon and flare in the anterior chamber, and the ultrasound of the eyeball also shows vitreous exudate; endophthalmitis usually

Figure 30. Preparation of a set of disposable instruments for intravitreal injection.

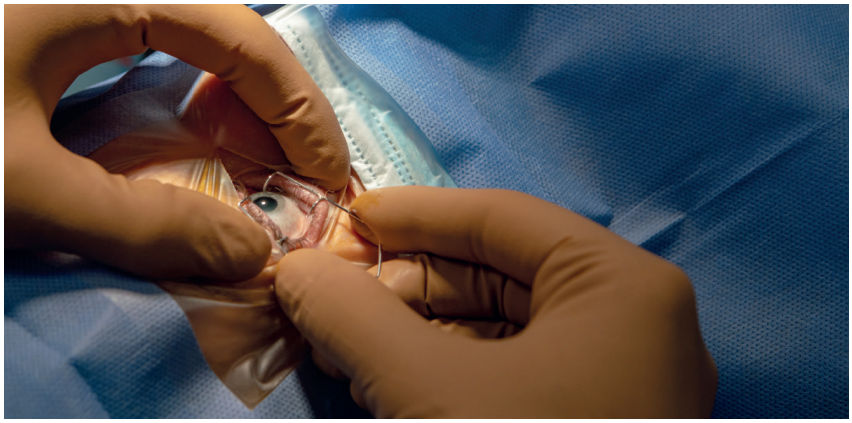


Figure 31. Fitting the eyelid speculum.

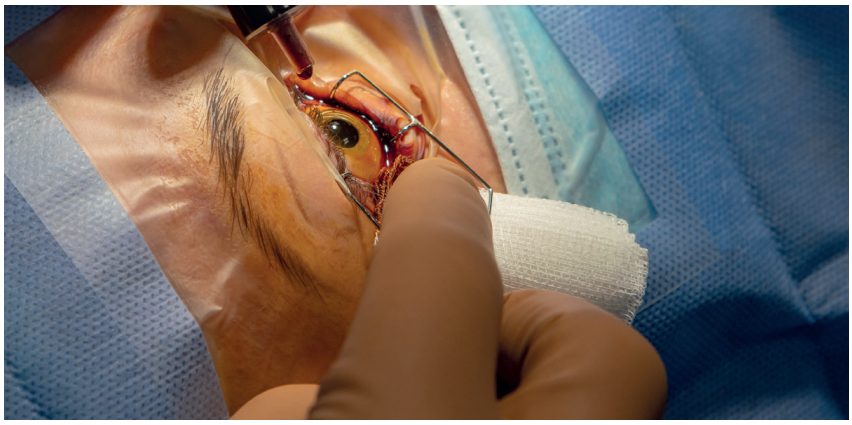


Figure 32. Rinsing the conjunctival sac with a 5% iodopovidone solution.

Figure 33. Flushing out iodopovidone from the conjunctival sac after 30 seconds.

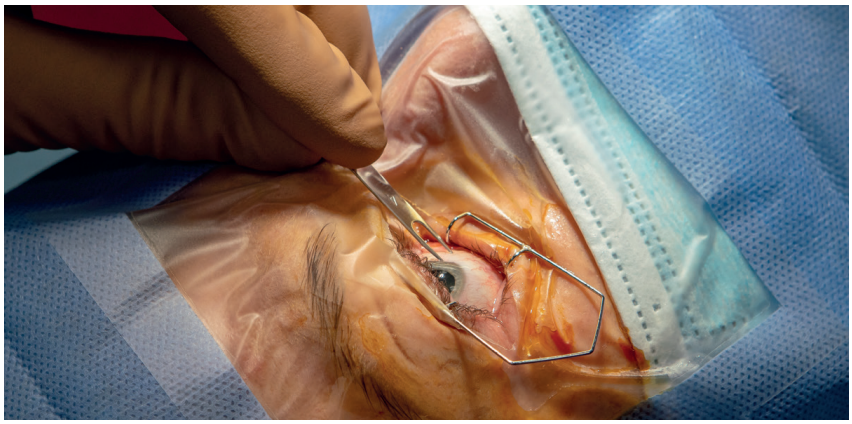


Figure 34. Measuring the distance from the injection site to the limbus of the cornea (4 mm).

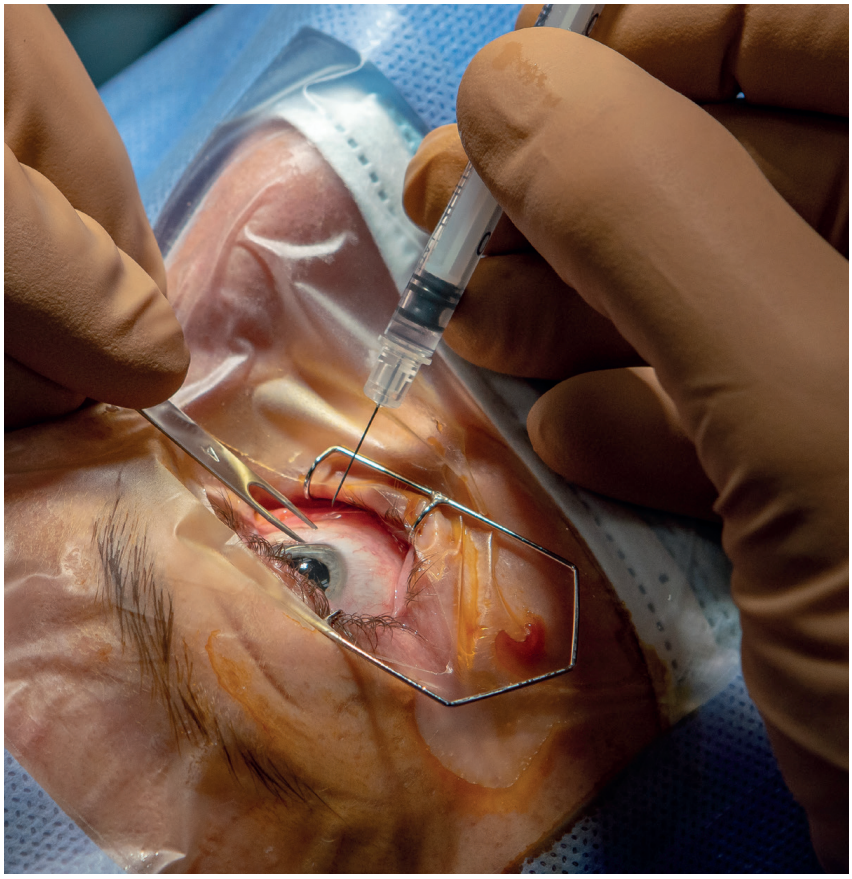


Figure 35. Performing the intravitreal injection. The operator stabilizes the eyeball with the help of a marker.

Figure 36. Disinfection of the injection site with a cotton swab soaked in 5% iodopovidone.

Table 9. EURETINA society recommendations for performing intravitreal injections[182].	
Clinical setting for intravitreal injections	operating theatre, dedicated room or ophthalmologist's office
Local antisepsis	5% povidone-iodine into the conjunctival sac for at least 30 seconds; chlorhexidine for patients allergic to povidone-iodine
Perioperative antibiotic therapy	not recommended
Anaesthesia	topical (drops)
Site of injection	through the pars plana, 3.5–4 mm from the limbus it is necessary to switch the quadrant of administration for subsequent injections
Lid speculum	sterile speculum recommended
Type of needle	recommended needle 30G or thinner for the administration of liquid substances (larger needles used if necessary)
Binocular injections	should be performed as two separate procedures
Use of gloves and drapes	sterile gloves are recommended; draping may be irrelevant
Surgical masks	recommended

requires urgent surgical treatment (pars plana vitrectomy),

b. retinal tear and detachment – serious complications, usually requiring surgical intervention; the retinal tear itself, without its detachment, can be secured with laser photocoagulation, rhegmatogenous retinal detachment must be treated surgically,

c. intravitreal hemorrhage – due to a significant deterioration of visual acuity, the complication may be very burdensome for the patient, but it does not necessarily have serious consequences: a vessel is damaged during puncture and bleeds into the eyeball; in the absence of any features of retinal detachment (ophthalmoscopic evaluation and ultrasound of the eyeball are required), the patient can be observed while waiting for the spontaneous resorption of the hemorrhage; in the case of accompanying retinal detachment, surgical treatment is necessary,

d. dislocation of the lens, iatrogenic cataract – a complication usually related to improper injection technique or lack of patient's cooperation; lens damage always requires surgical intervention.

The incidence of serious local complications after intravitreal injections is very low. Endophthalmitis remains the most common among sight-threatening sequelae of this procedure. Benoist d'Azy et al. report the occurrence of this complication in 0.052% of cases[180], Dossarps et al. in 0.021%[183], and Cheung et al. in nine cases out of 15,895 injections (0.031%)[184]. Severn et al. presented a report on serious complications in patients with nAMD treated with anti-VEGF medications in the UK in 2008–2014[185]. Endophthalmitis occurred in 0.04% of patients, retinal tear

in 0.014%, retinal detachment in 0.002%, significant vitreous hemorrhage in 0.009%, and complications related to lens damage in 0.005%. A similar analysis was carried out in the USA by Day et al.[186]. The authors report the following rates of serious complication per injection: ocular inflammation 0.09%, retinal detachment 0.1%, retinal tear 0.06%, and vitreous hemorrhage 0.23%. In contrast, an analysis of patients receiving ranibizumab in the RESTORE study after three years did not reveal a single case of ocular inflammation, retinal tear, or retinal detachment[163]. Some authors report a higher incidence of ocular inflammation after bevacizumab use, but these rates are still low[187].

The issue of general complications developing after the use of anti-VEGF medications has been discussed in the medical literature. Systemic complications were analysed during large randomized clinical trials. In the RESTORE study discussed earlier, one in 102 patients experienced a myocardial infarction, which could be related to ranibizumab administration[125]. The rates of vascular and thromboembolic complications were the same in the ranibizumab and sham groups. The study also did not show any effect of administration of ranibizumab on the levels of HbA1 and proteins in the urine.

Schlenker et al. analysed a population of 57,919 patients over 65 years of age treated with ranibizumab and bevacizumab for AMD or disorders with retinal edema. The study showed a greater risk of thromboembolic events in this group compared to the rest of the population of the same age[188].

Avery et al. conducted a meta-analysis of randomized clinical trials on the side effects of chronic anti-VEGF therapy (ranibizumab and aflibercept) in patients with DME[189]. The analysis showed an increased risk of death from vascular causes and the occurrence of cerebrovascular events in the group of patients treated with intravitreal agents. The risk of myocardial infarctions and thrombotic complications did not increase. In some studies, the safety profile of bevacizumab was slightly worse than that of the other two anti-VEGF inhibitors[190]. In the CATT study, the number of hospitalizations for serious systemic complications was higher with bevacizumab. However, these reports have not been confirmed in other studies. Wang et al. conducted a meta-analysis of data from the literature comparing the safety profile of ranibizumab and bevacizumab in the treatment of AMD. The analysis showed no statistically significant differences in the safety profiles of the two drugs[191]. Similar conclusions were presented by Moja et al.[192].

Also in the previously discussed DRCR.net (Protocol T) study[154, 155] comparing the efficacy of ranibizumab, aflibercept, and bevacizumab in the treatment of DME, the rate of systemic complications was examined in each of the three groups. The total percentage of serious complications and hospitalizations did not differ between the groups. However, systemic vascular complications – stroke and death due to vascular causes – were more common in patients treated with ranibizumab.

Anti-VEGF agents inhibit angiogenesis, so this also applies to repair processes taking place in the body after myocardial infarction or strokes. As some clinical trials have shown an increase in the incidence of thromboembolic complications in patients undergoing anti-VEGF therapy, everyday practice is to avoid using them within six months after myocardial infarction or stroke. However, the summaries of product characteristics for these drugs do not explicitly state this.

Anti-VEGF medications should be used with caution in patients suffering from vascular diseases. However, since the risk of such complications is low, this therapy should not be abandoned entirely in patients receiving treatment for other conditions.

There are no reports of systemic complications following the use of intravitreal steroids. In exceptional circumstances, they are used in pregnancy, but at

present, this is an off-label practice (no large clinical trials on the use of these drugs during pregnancy are available)[193].

Diabetic macular ischemia

General remarks

In the past, diabetic macular ischemia (DMI) arising in the course of diabetic retinopathy was rarely discussed in the medical literature as a separate clinical entity, possibly due to diagnostic difficulties and lack of therapeutic options. Today, this disease is receiving more attention due to the advances in diagnostics, in particular the development of the angio-OCT technique.

DMI can accompany any stage of diabetic retinopathy, but its incidence increases as retinopathy progresses[194]. Figures 37–38 and 41 show a significant enlargement of the FAZ already at the stage of non-proliferative retinopathy. The risk factors for developing DMI are virtually the same as those for developing DR.

The essence of macular ischemia is the loss of capillaries in this region of the retina (Figs. 39–40). Such deficits in microcirculation are a consequence of structural changes in the vascular wall, particularly pericytes and endothelial cells[195]. In addition, thrombotic events occur in the altered capillaries, which in turn causes their occlusion and atrophy[196]. At a later stage, atrophy occurs within the sensory retina[197].

Diagnosis of diabetic macular ischemia

The main subjective symptom of diabetic macular ischemia is decreased visual acuity and disturbances in the visual field. The often difficult to explain visual impairment in a patient with DR, especially in the absence of central retinal edema, can be explained by macular ischemia. Performing perimetry may reveal defects in the central part of the visual field and decreased sensitivity of the retina. Microperimetry in particular clearly indicates the loss of retinal function in such situations.

In the presence of DMI, ophthalmoscopic examination of the macular area often reveals sectors completely devoid of microaneurysms and hemorrhages, and "ghost vessels" devoid of blood flow.

Fluorescein angiography remains the gold standard in the diagnosis of DMI[42].

With the help of fluorescein angiography, we are able to visualize the widening and/or irregular shape of the FAZ and areas devoid of capillary perfusion. In angiographic images, they appear as dark areas lacking fluorescence. In its recommendations, the AAO suggests that fluorescein angiography should be performed in the event of a decrease in visual acuity that is difficult to explain, i.e. suspected ischemic maculopathy[40] (Fig. 41).

DMI can occur with or without retinal edema, as evidenced by OCT. In the presence of retinal edema, the actual image of retinal damage may be disturbed because the edema masks the thinning of individual retinal layers (Fig. 43). DMI can also be obscured by concomitant macular pathologies such as the preretinal membranes, which are not uncommon in DR. However, in cases without edema, OCT clearly shows thinning of the retina and loss of its inner and outer layers[198, 199] (Fig. 42). The blurring of the boundaries between the inner layers of the retina (NFL, GCL, and IPL) is characteristic[200]. Some authors point to the loss of ganglion cells as an indicator of ischemia in diabetic retinopathy[201, 202]. Others emphasize the EZ (IS/OS) lesion, the finding frequently observed in eyes with DMI[203, 204]. Thus, the extent of the damage affects practically the entire retina to a varying degree, although in SD-OCT the most characteristic and pronounced are changes in the inner retinal layers (Fig. 43).

The introduction of OCTA to clinical practice has brought completely new diagnostic information about DMI. This non-invasive examination, which

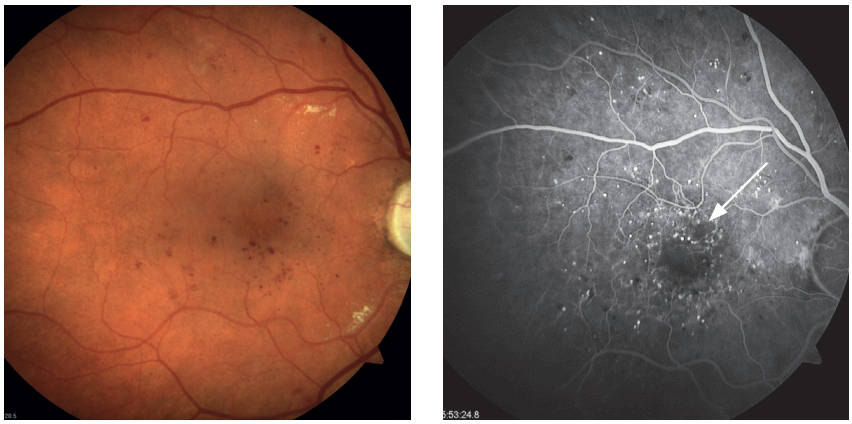


Figure 37. Moderate non-proliferative diabetic retinopathy with maculopathy. The angiographic image shows numerous microaneurysms, especially around the fovea. Noticeable widening of the foveal avascular zone and the lack of capillaries, mainly in the upper part of the fovea (indicated by the arrow).

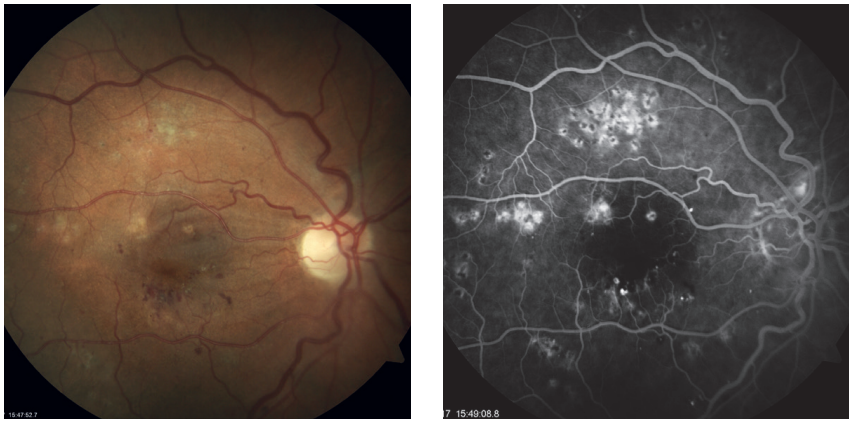


Figure 38. Moderate non-proliferative diabetic retinopathy after focal laser therapy. Angiography shows a marked widening of the foveal avascular zone.

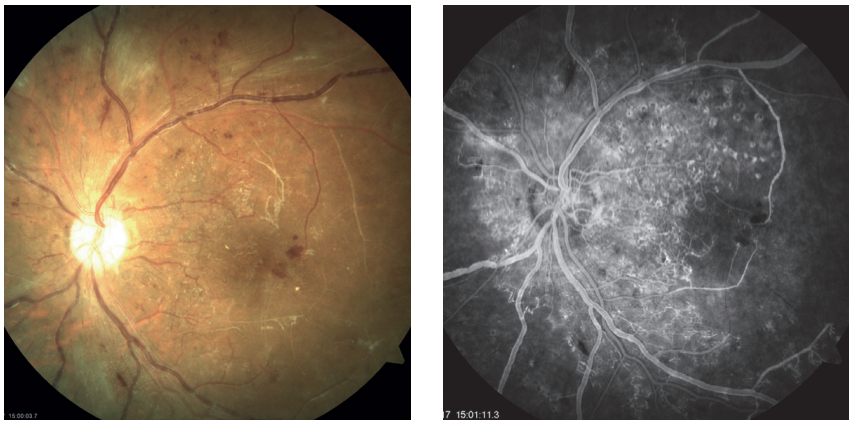


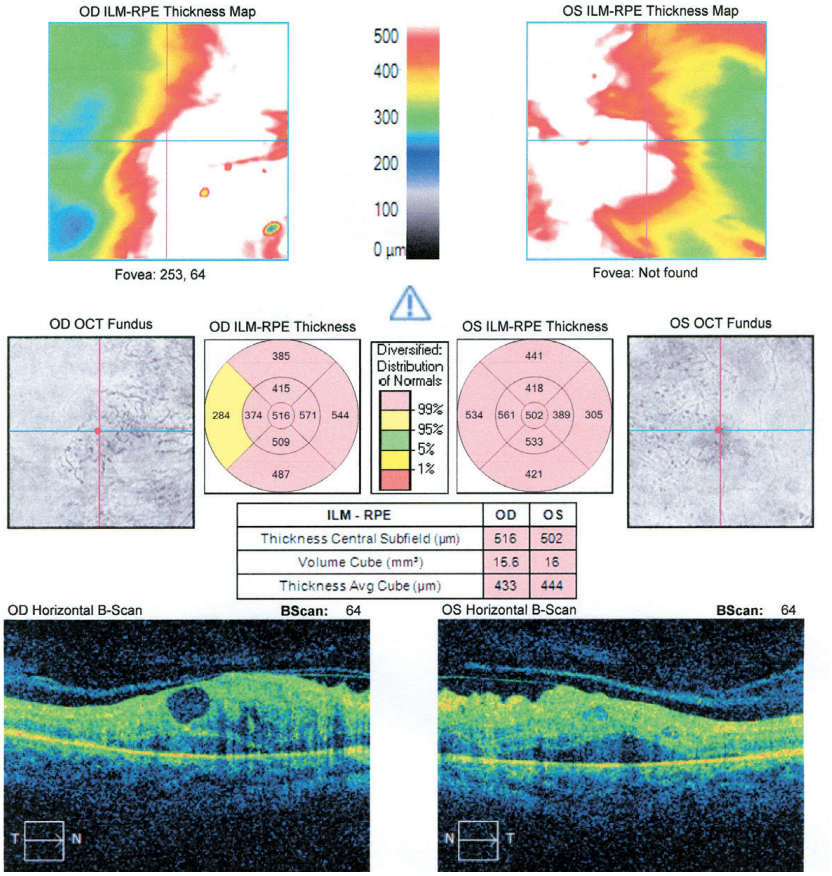
Figure 39. Proliferative diabetic retinopathy. The colour image shows the absence of visible vessels in the temporal part of the retina. Angiography shows a complete lack of perfusion in the temporal sectors of the retina, including significant ischemia of the temporal macula.

does not require dye administration, shows changes in two capillary plexuses: superficial and deep[205] (Figs. 44–45). FA cannot differentiate between these two vascular networks.

OCTA can be used to measure the size of the FAZ and monitor the lesions in this area[206]. In DMI, measurements of the FAZ and areas of capillary loss provide opportunities for grading the severity of ischemic maculopathy[207]. The size of the FAZ measured by OCTA correlates with a decrease in BCVA in patients with DMI[208].

Treatment of diabetic macular ischemia

Currently, there is no algorithm for the management of DMI. In general, it can be said that in the presence of DMI, diabetic retinopathy is treated, along with DME, according to current principles, but there is



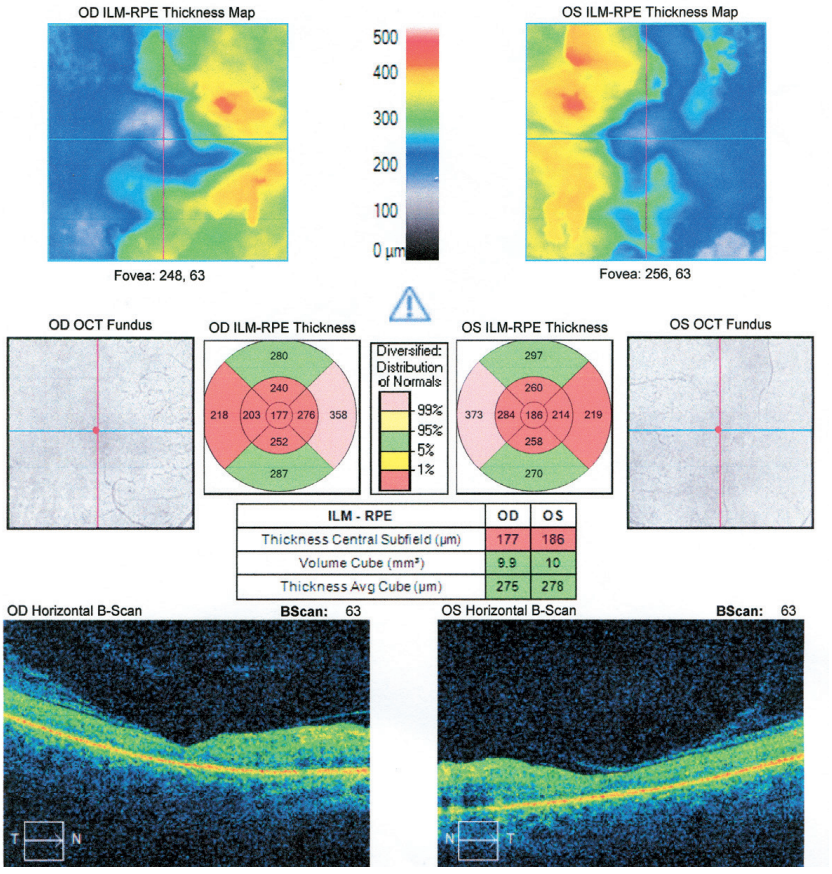


Figure 40. SD-OCT of the patient from Figure 39 before and after anti-VEGF treatment. Before treatment, there is visible fluid under the sensory retina and significant edema within the sensory retina. The remission of edema reveals the actual condition of the retina and explains the poor visual acuity in this patient. Significant thinning of the sensory retina is visible.

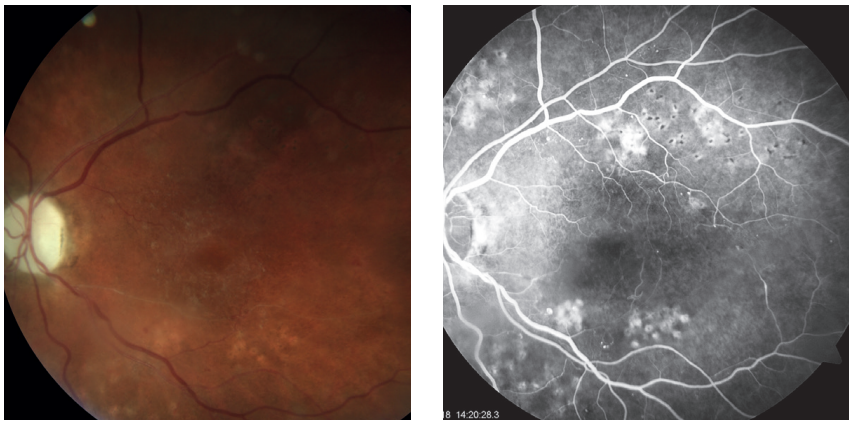


Figure 41. Ischemic maculopathy in non-proliferative diabetic retinopathy. Colour photos show retinal vessels devoid of perfusion and a pale appearance of the fovea and optic disc. Lack of perfusion in the foveal area is revealed by angiography.

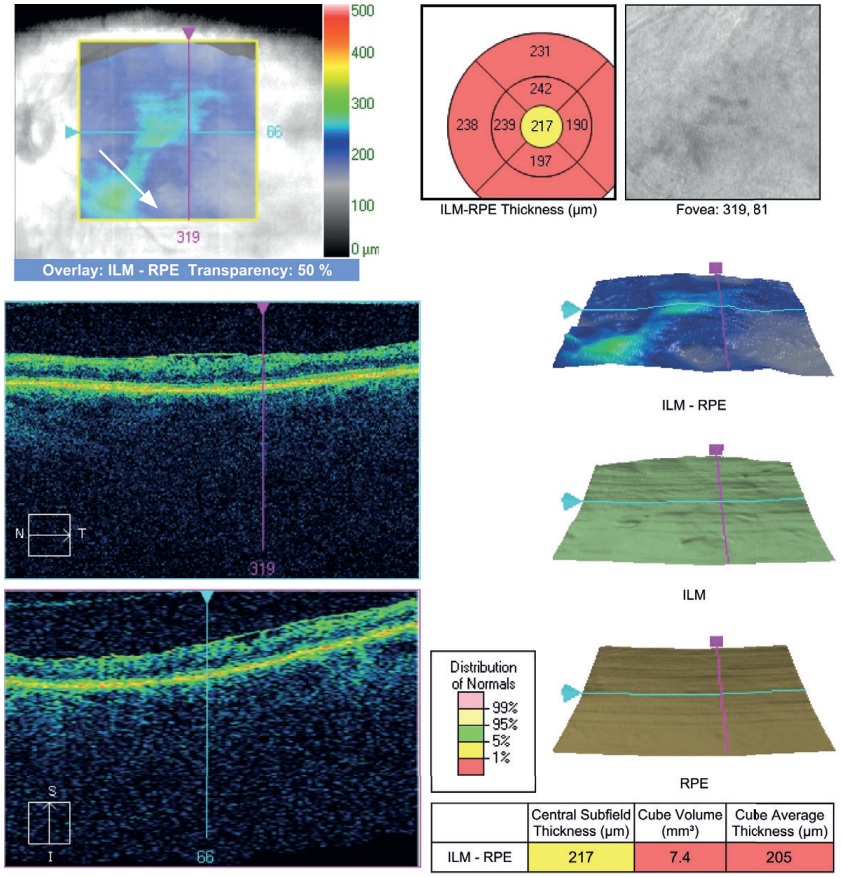


Figure 42. SD-OCT of the patient's retina from Figure 41. Scans show generalized retinal thinning in the posterior pole and a small epiretinal glial membrane.

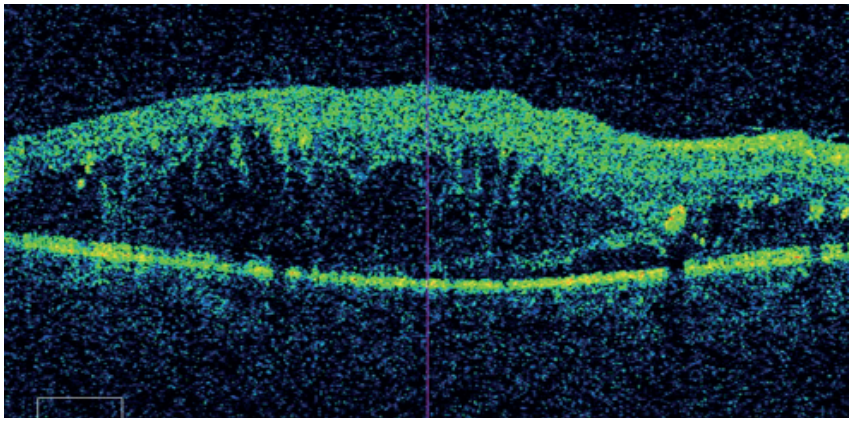


Figure 43. Ischemic maculopathy with foveal edema. The SD-OCT scan shows complete blurring of the boundaries of the inner layers of the retina. Significant cystoid edema located mainly in the outer plexiform layer.

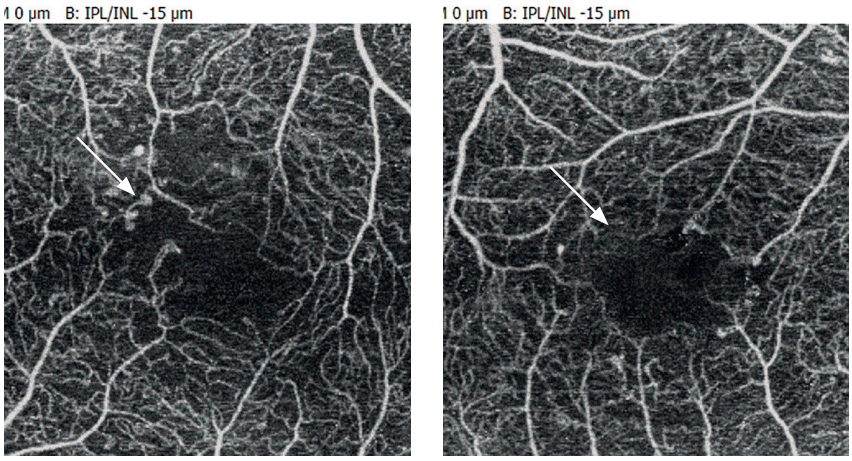


Figure 44. Scans of the superficial capillary plexus. There is a marked widening of the foveal avascular zone and loss of capillaries, more pronounced on the left scan (indicated by the arrows). Small hyperreflective spots suggestive of microaneurysms are also visible.

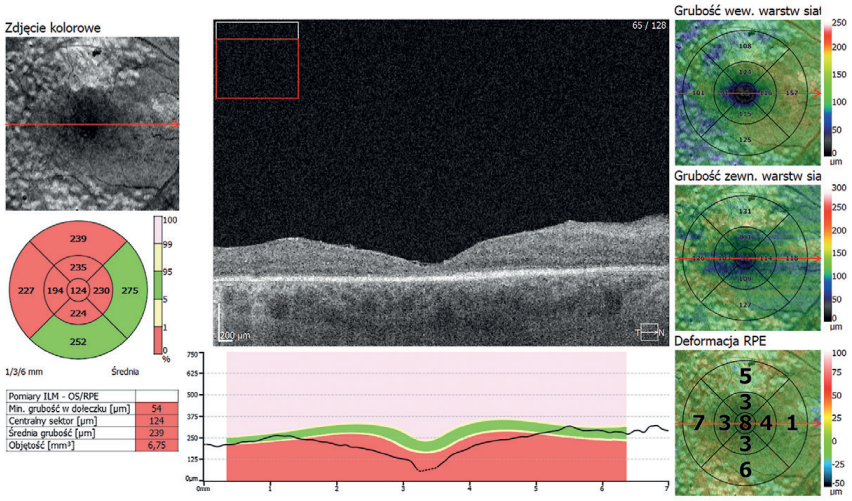
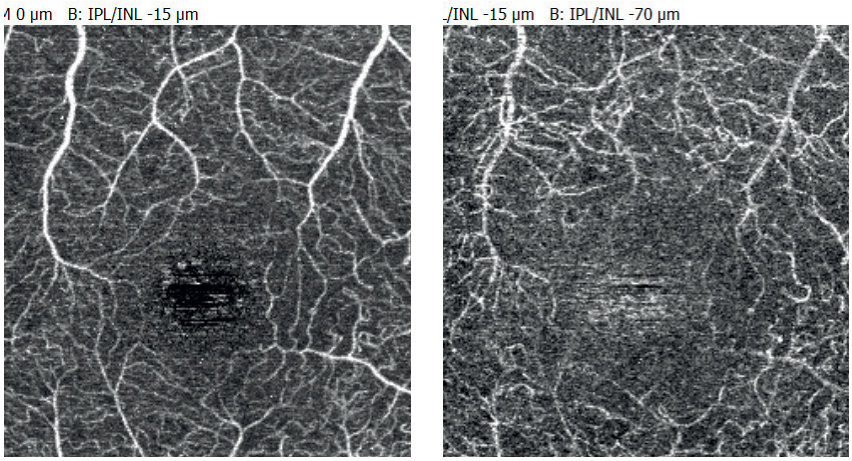


Figure 45. Patient with macular ischemia in the course of diabetic retinopathy. SD-OCT scans show significant thinning of the sensory retina. OCTA reveals significant widening of the foveal avascular zone and loss of capillaries in both capillary plexuses, especially in the deep capillary plexus.



no established form of therapy for macular ischemia itself. Unfortunately, the results of DR treatment in the presence of macular ischemia are poor. This applies to laser photocoagulation, anti-VEGF therapy and posterior vitrectomy[209, 210, 211].

ETDRS allows for classic photocoagulation in the treatment of DMI, but recommends caution, especially in the presence of extensive ischemia[212]. Cases of macular ischemia in the presence of foveal edema can also be problematic. We do not know

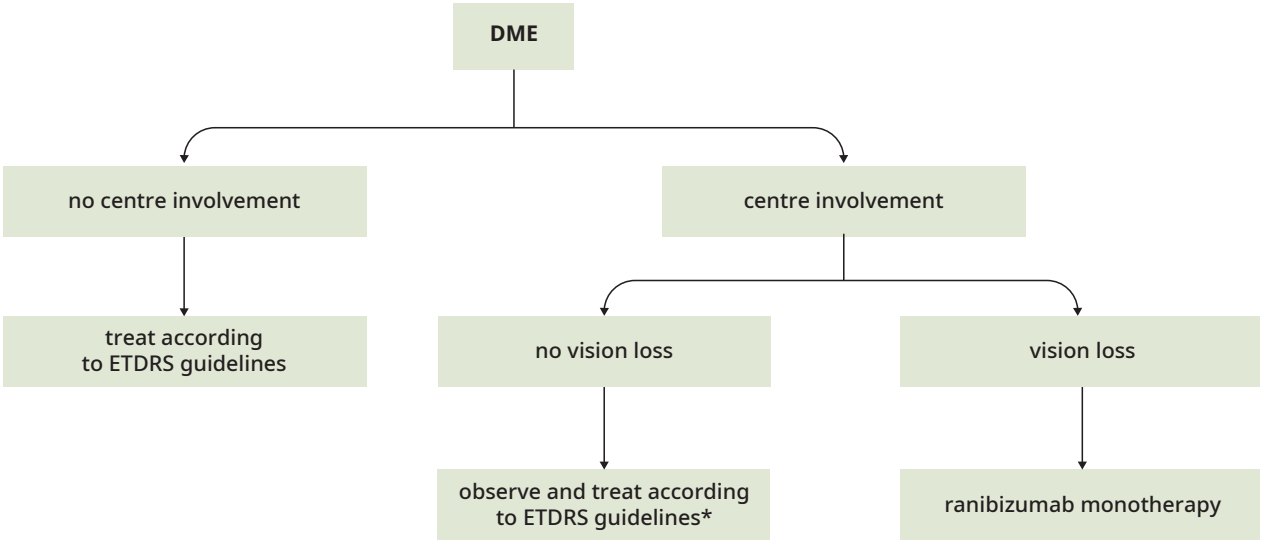


Figure 46. An algorithm for the management of diabetic macular edema (DME) recommended by an expert panel led by Francesco Bandello. The regimen was proposed before the introduction of other intravitreal drugs. Nowadays, other available anti-VEGF medications can also be used instead of ranibizumab.

*Summary of ETDRS recommendations for laser photocoagulation (FA): (1) focal photocoagulation of single microaneurysms filling and/or leaking in FA and other sources of leakage such as small-vessel abnormalities, (2) GRID laser therapy of areas of thickened retina with visible area of leakage or impaired perfusion in FA.

then whether the reduction in visual acuity is due to the edema itself or the consequences of ischemia. The use of anti-VEGF therapy in the presence of significant macular ischemia may be dubious[213]. Anti-VEGF agents inhibit vascular proliferation, and thus may also exacerbate the symptoms of macular ischemia[214, 215].

Algorithms for the management of diabetic macular edema

Treatment for DME has evolved over the years. The introduction of new therapies has changed our approach to the use of, for example, classic retinal laser photocoagulation in the treatment of this disease. One simple treatment algorithm may not always be applicable, but there are several basic principles of DME management:

1. Intravitreal anti-VEGF therapy is the basic treatment in the presence of the central form of DME. The choice of medication may depend on the patient's initial visual acuity.
2. Intravitreal steroid therapy is usually the second-line therapy in the treatment of DME, in the absence of a satisfactory response to anti-VEGF therapy. The decision to switch to a steroid drug is usually made after 3–6 injections. The use of steroids as first-line drugs may be considered for pseudophakic patients with cardiovascular stress and for patients who are unwilling or unable to undergo monthly monitoring and monthly injections. Intravitreal steroid therapy may also be effective in the case of long-term DME after retinal laser photocoagulation (fluocinolone).
3. Retinal laser photocoagulation is currently in the background of the treatment of DME. It is used for DME located outside the centre of the retina, especially in its vasogenic form, and for refractory cases. Photocoagulation of the retinal periphery in the presence of areas of hypoperfusion and/or neovascularization is, however, necessary to achieve the effect of treating DME itself.

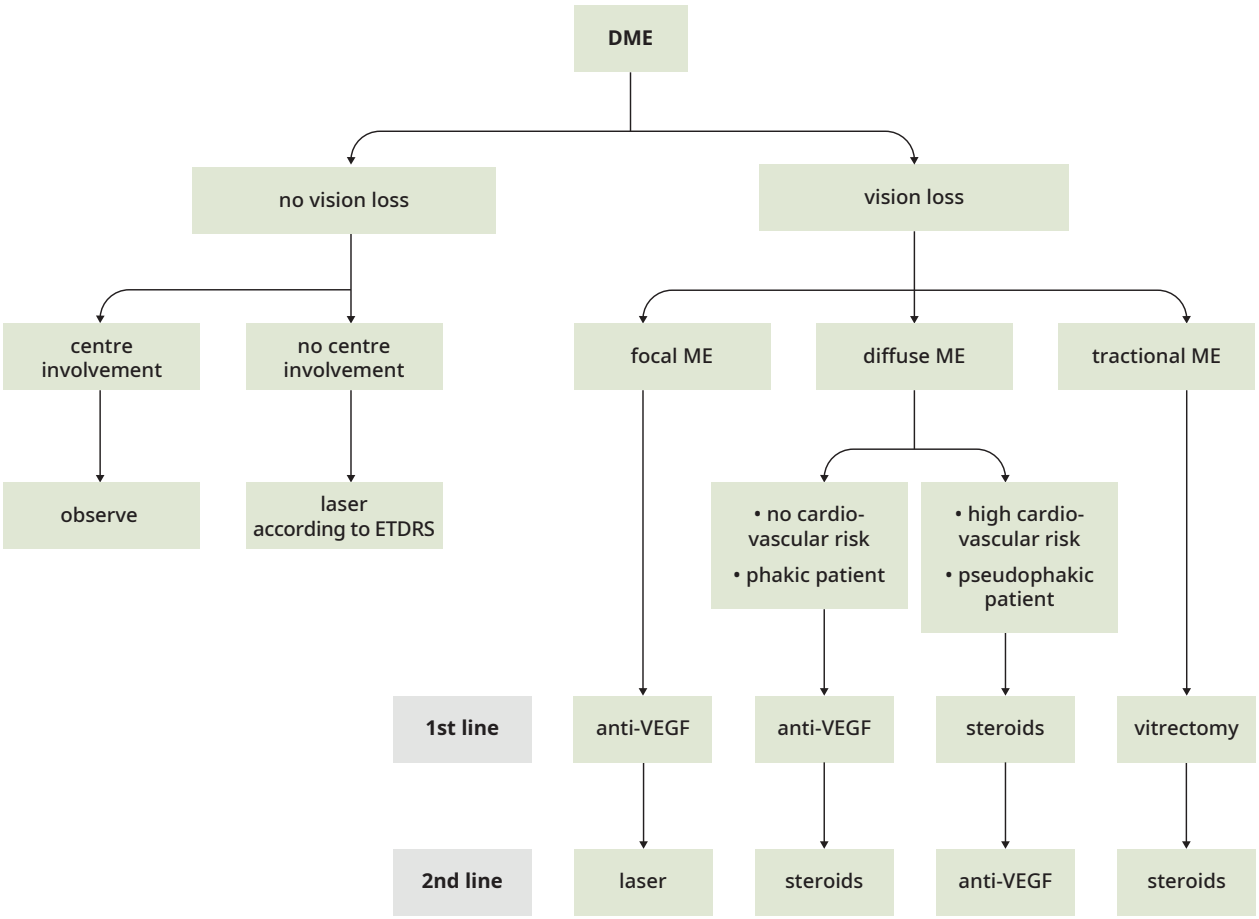


Figure 47. An algorithm for the management of DME proposed by Anat Loewenstein.

4. Forms of laser therapy that do not damage the retina, primarily subthreshold micropulse laser treatment (SMPLT), can be used as an adjunct therapy for small, diffuse and central retinal edema (usually below 400 μm) with good visual acuity.
5. Surgical treatment, or pars plana vitrectomy (PPV), is currently used in the treatment of disorders of the vitreoretinal interface accompanying DME (epiretinal membranes, VMT). PPV may be considered for patients without traction in the absence of response to other forms of therapy.

Sample DME algorithms are presented below.

1. Recommendations of the Polish Ophthalmological Society (PTO)[216]:
   a. local (focal) DME at a distance greater than 500 μm from the centre of the fovea:
      - focal laser or GRID photocoagulation (photocoagulation of each microaneurysm at a distance of 500–3,000 μm from the macular center),
      - anti-VEGF intravitreal therapy (when laser therapy is contraindicated);
   b. local (focal) DME at a distance less than 500 μm from the centre of the fovea:
      - anti-VEGF intravitreal therapy,
      - micropulse laser (when anti-VEGF is contraindicated);
   c. local DME with foveal involvement/diffuse DME (clinically significant macular edema):
      - anti-VEGF intravitreal therapy,
      - micropulse laser (when anti-VEGF is contraindicated),
      - corticosteroids (for contraindications to the above treatments; for pseudophakic eyes);

d. edema with vitreomacular traction or epiretinal membrane: posterior vitrectomy.

2. The panel of experts from F. Bandello recommended the DME treatment algorithm presented in Figure 46. The recommendations were established in 2012, before the approval of aflibercept for DME treatment. Nowadays, aflibercept or bevacizumab can also be used instead of ranibizumab[217].

3. The algorithm proposal of A. Loewenstein[218] is presented in Figure 47. The place of intravitreal steroid therapy in the treatment of DME is noteworthy. The author suggests the use of intravitreal steroids as first-line treatment for diffuse macular edema in patients at cardiovascular risk and for pseudophakic patients.

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Chapter 9: Diabetic retinopathy management

Introduction

The ophthalmological management of diabetic retinopathy (DR) depends on the advancement and characteristics of the retinopathy itself and the coexistence of diabetic macular edema (DME). The patient's general condition is also important, including glycemic control, concomitant arterial hypertension or renal dysfunction. The patient's compliance with medical recommendations plays a significant role as well, especially in terms of undergoing regular ophthalmological monitoring.

The primary ophthalmological treatments for diabetic retinopathy are:

- retinal laser treatment,
- intravitreal therapies, mainly anti-VEGF therapy,
- surgical procedures (discussed in Chapter 10: *Posterior pars plana vitrectomy in diabetic retinopathy*, pp. 197–205).

Retinal laser therapy

General remarks

For many years, the primary treatment for proliferative diabetic retinopathy (PDR) was laser photocoagulation (LPC). Studies from the Diabetic Retinopathy Study (DRS) group have shown its effectiveness in preventing severe vision loss in patients with high-risk proliferative diabetic retinopathy (HR PDR). Panretinal photocoagulation (PRP) can also sometimes be considered in initial PDR and in severe non-proliferative diabetic retinopathy (NPDR).

The first successful photocoagulation attempts were made by Gerhard Meyer-Schwickerath in the 1950s, using a xenon arc lamp[1]. In the following years, significant technological advances were made – ruby and argon lasers were invented and emerged as therapeutic tools in ophthalmology.

Retinal LPC was commonly performed in ophthalmic clinics, but it was not until the 1970s that large randomized clinical trials were conducted on its efficacy and application. The DRS and Early Treatment Diabetic Retinopathy Study (ETDRS) studies led to formalized guidelines for PRP and focal photocoagulation in DR and DME[2].

Types of lasers

All lasers are based on the emission of a highly directional, monochromatic and coherent electromagnetic wave. The stimulation of a specific physical body (gas, liquid or solid) causes the excitation of its atoms and then the forced emission of electromagnetic waves[3].

The radiation generated during stimulated emission has the following characteristics:

1. low beam divergence – the beam generated by the laser shows a high degree of focus (the diameter of the beam expands very slowly with the distance from the source),
2. monochromaticity – laser radiation has a very narrow spectral range, i.e. a beam with a specific wavelength is emitted,
3. coherence – the generated electromagnetic waves have a coherent phase.

The features of the wave generated by the laser are the reason for its use in medicine. For example, the strong focus of the beam allows precise photocoagulation, and the use of a specific wavelength makes it possible to obtain specific tissue reactions selectively.

The type of laser and its properties are determined by the medium which is the source of the emitted electromagnetic wave. We distinguish between lasers:

1. gas – e.g. argon, krypton, CO_2,
2. dye – dye particles, which are usually suspended in a liquid solvent, are the source of emission,
3. solid-state – usually based on crystals – Nd:YAG, Er:YAG, ruby,
4. semiconductor (sometimes called diode) lasers; most commonly used nowadays (810 nm, 577 nm and 532 nm).

Krypton and argon lasers were quite widely used in ophthalmology in the 1960s–1980s. Nowadays, diode lasers with a specific single wavelength are more frequently used, due to their safety, low price and small size.

The argon laser had two emission peaks: 488 nm (blue spectrum) and 514 nm (green spectrum). Most of the energy in these ranges is absorbed by the retinal pigment epithelium (RPE). The use of 488 nm was hazardous due to its absorption by the macular pigment (xanthophyll). The 514 nm wavelength was used for photocoagulation in the macular area due to its non-significant absorption by the macular pigment.

The krypton laser had emission peaks in the red (647 nm) and yellow (568 nm) spectra. The red spectrum was used for some time in laser photocoagulation as the macular pigment does not absorb it. It turned out, however, that the retinal pigment epithelium is very sensitive to power fluctuations in this spectrum, leading to complications: hemorrhages and tears within the RPE. The yellow spectrum, on the other hand, is successfully obtained from dye and diode lasers, which in practice came to replace krypton lasers.

In the case of widely used diode lasers, yellow lasers with a wavelength of 577 nm have had the most widespread application. This wavelength is well absorbed by hemoglobin, which facilitates the photocoagulation of microaneurysms. Green diode lasers (532 nm) have also found practical application because in order to obtain a thermal effect, they need less power than argon lasers. As mentioned earlier, RPE remains the primary target of photocoagulation at this wavelength.

Infrared diode lasers operating in infrared (810 nm) are also used in treating retinal diseases. At this wavelength, only 9% of the energy is absorbed by the RPE. Most is absorbed by melanocytes located in the choroid. After this laser is used, the changes visible in the retina are pale grey – in contrast to the clear fading visible after the application of green or yellow lasers. Therefore, the selection of power parameters may present difficulties for a novice ophthalmologist.

The crystal-based neodymium YAG laser with a wavelength of 1064 nm has been used both in laser photocoagulation and in photodisruption (Q-switch function) in posterior capsulotomy and iridotomy. Retinal photocoagulation occurs with a wavelength of 532 nm, obtained due to the beam passing through non-linear KTP crystals, which enables second-harmonic generation.

Laser application in the multispot pattern

The multispot function applies to lasers of different wavelengths, most often green (532 nm) and yellow (577 nm). Technically the application of this innovation consists in making a whole series of photocoagulation spots in a short time. A single exposure time usually ranges from 0.01 to 0.02 seconds (compared to the standard time in classic photocoagulation: 0.1 to 0.2 seconds).

Using the multispot laser for retinal photocoagulation results in delivering less energy to the tissue than in the case of a classic photocoagulator. Admittedly, making a spot with such a short exposure time (0.01–0.02 seconds) requires the use of high laser power, but the total fluence (pulse energy per unit area) is lower. A short exposure time results in the formation of smaller scars, less damage to the ad-

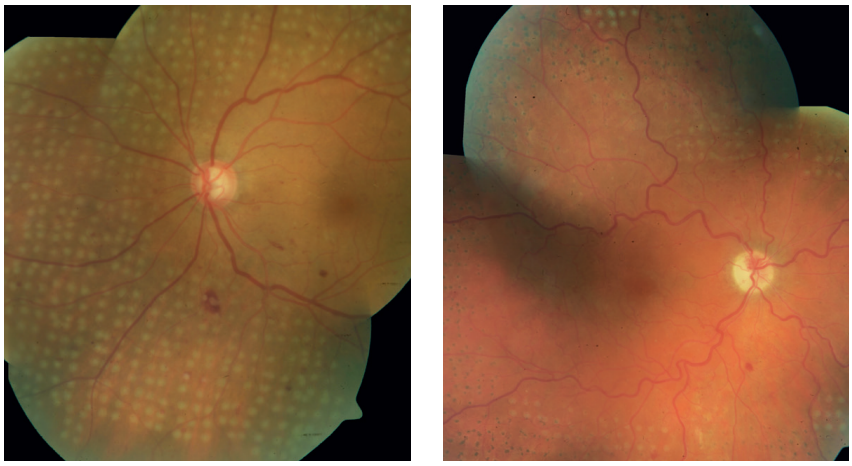


Figure 1. The fundus of the eye of patients after panretinal photocoagulation performed with a multispot laser. It can be seen that the resulting spots are very regular, with equal spacing between them.

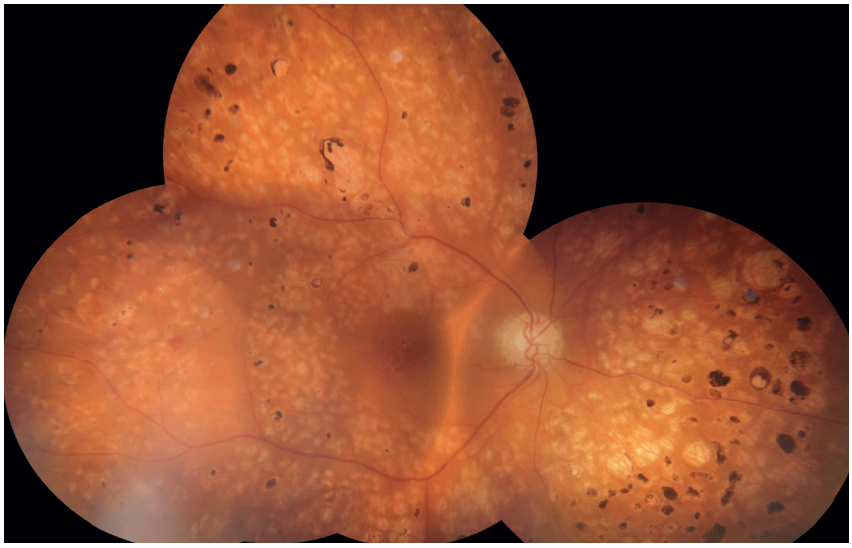


Figure 2. A patient after panretinal photocoagulation with a traditional laser. There are visible multiple treatment spots on the retinal periphery and GRID in the macula. It is evident that the peripheral photocoagulation spots are less regular than those seen in the images after multispot laser therapy.

jacent retina, and consequently smaller defects in the field of vision[4, 5]. In addition, the scars formed do not tend to enlarge over time; in fact their size sometimes decreases.

Multispot laser therapy is more patient-friendly, as it causes significantly less pain[6]. Research shows that performing full PRP with a multispot laser in one session achieves the same results as conventional PRP spread over several sessions[7, 8, 9, 10]. As a consequence, performing full PRP (1,500 spots) in one session is possible, safe and effective[7]. It has also been shown that performing PRP with a multispot laser in one session does not cause thinning of nerve fibers, which was observed a few months after the PRP procedure performed with a classic laser within a few sessions[11]. Moreover, completion of PRP in a single session resulted in better regression of neovascularization compared with a procedure spread over several sessions.

Due to the smaller size of the scars, sometimes more spots are needed in this procedure than in standard photocoagulation. Examples of PRP performed with a multispot laser, and a conventional laser are shown in Figures 1–2.

The theoretical foundations of photocoagulation

Although retinal LPC has been widely used in ophthalmology for several decades[1, 12, 13], its mechanism is still not fully understood. There are two main theories of

laser action on tissues: the first one is referred to as the oxygen theory, and the second can be described as the metabolic theory.

The oxygen theory assumes that during photocoagulation of the retina, a thermal reaction occurs at the level of the RPE cells, which results in the destruction of these cells and the formation of scars. While most of the laser energy is absorbed by the melanin of the RPE, where the strongest effect occurs, some photoreceptors are also destroyed. The inner parts of the retina should remain intact. The resulting scar allows oxygen transfer from the choroid to the retina, bypassing photoreceptors which normally consume large amounts of oxygen[14, 15]. The oxygen demand of the retina decreases. As a consequence, the oxygenation of the inner layers of the retina improves (Fig. 3). The effect of increased oxygen concentration in the sensory retina is the contraction of arterioles and a decrease in vascular flow. Hydrostatic pressure in the retinal vascular system is reduced and retinal edema is decreases, as per the Starling's law. Another consequence of improving the oxygen supply to the retina is reducing the production of vasoproliferative factors – primarily vascular endothelial growth factor (VEGF). Many studies have shown a lower concentration of VEGF in the blood and plasma of DR patients after PRP[16, 17]. This occurs due to the reduction in tissue hypoxia and the improvement in its oxygenation[18, 16] (Fig. 4).

In contrast, the metabolic theory assumes that the photocoagulation effect at the RPE level stimulates the epithelium to produce cytokines which act antagonistically to VEGF, thereby reducing the proedematous effects of this factor. Those cytokines do not have their source in the coagulated RPE cells, which are destroyed, but the adjacent surviving tissue. During photocoagulation, cells adjacent to the laser focus are subjected to a thermal shock and consequently produce the so-called heat shock proteins (HSP), i.e. the cytokines mentioned above which – besides edema-reducing action – also have protective properties with regard to other cellular proteins. In addition,

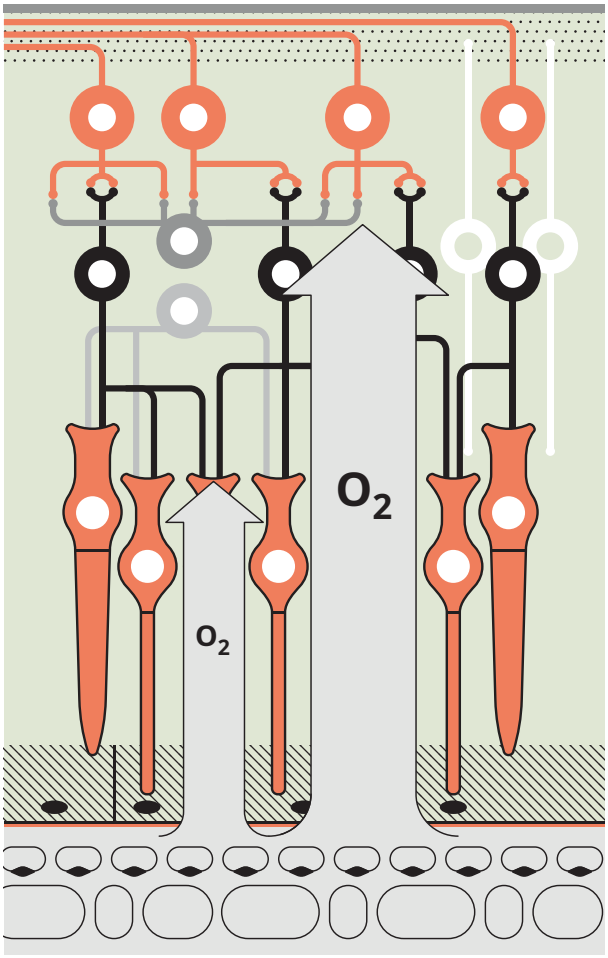


Figure 3. Oxygen transfer from the choroid to the retina through the photocoagulation scar (indicated by the longer arrow). Oxygen enters the choroid directly into the inner layers of the retina, bypassing the photoreceptor layer. Under normal circumstances, oxygen from the choroid supplies practically only the outer layers of the retina (indicated by the shorter arrow).

the production of these proteins itself regulates the metabolism of RPE cells and improves their function (for example, RPE works better as a pump).

Laser photocoagulation in macular edema

Three factors play a role in macular photocoagulation. The first is the direct destruction of leaking microaneurysms and thus the reduction of retinal edema. The second is the reduction of the number of photoreceptors in the photocoagulated sites, an

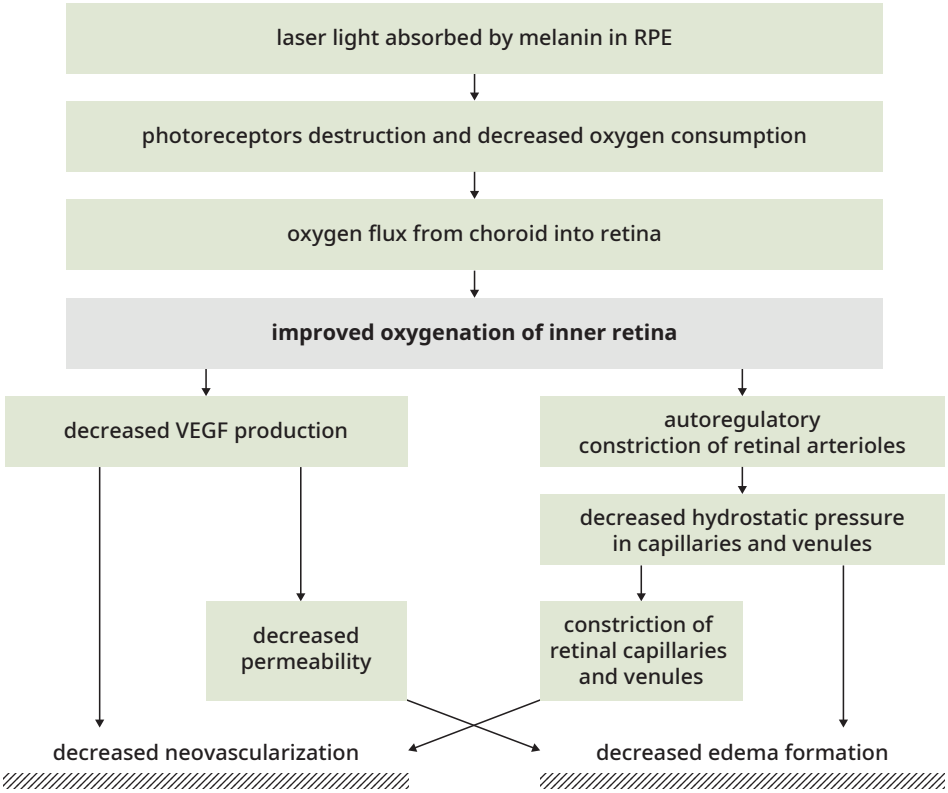


Figure 4. Functional diagram of retinal laser photocoagulation. | RPE – retinal pigment epithelium, VEGF – vascular endothelial growth factor

improvement in retinal oxygenation and the reduction of the production of proedematous VEGF. The third factor, which seems to be the most important considering the pathomechanism of DME formation, is the contraction of arterioles and, consequently, the reduction of fluid leakage from the vessels into the tissues. In turn, the reduction of hydrostatic pressure in the macular capillary system enables fluid resorption into the venous system and edema reduction.

The above theory explains the importance of reducing hydrostatic pressure in the vessels for the treatment of DME. This is especially true in patients with diabetes mellitus (DM) and hypertension, for whom the reduction of systemic pressure is of paramount importance for improving the local condition.

Obviously, the secretory effect of RPE, described in the metabolic theory, is also vital in the reduction of macular edema with laser therapy. This fact is confirmed by the good results of subthreshold laser therapy see Chapter 8: *Diabetic maculopathy (diabetic macular edema) – diagnosis and treatment*, pp. 133–143). Nowadays, methods that do not damage the retina (intravitreal drugs and subthreshold micropulse laser treatment) predominate in DME treatment.

Panretinal laser photocoagulation and scatter laser treatment

Historically, the first form of retinal laser therapy was panretinal photocoagulation to prevent the progression of proliferative retinopathy, used in clinical trials by the DRS group. Photocoagulation in the macular region was introduced later, following the ETDRS study (see Chapter 8: *Diabetic maculopathy (diabetic macular edema) – diagnosis and treatment*, pp. 130–133).

The DRS and ETDRS studies have shown that early PRP significantly reduces the risk of severe vision loss in patients with HR PDR (from 44% to 20% in the fourth year of follow-up; see Table 1 on p. 187)[19, 20, 21]. Both clinical trials also showed a reduction in the risk of severe NPDR progression to PDR after early photocoagulation, but due to the numerous side effects of laser therapy performed in the 1970s and 1980s, new guidelines clearly recommended that PRP should only be performed when the DR has progressed to the proliferative stage.

The basic aim of PRP is to exclude a significant area of the retina from oxygen uptake and thereby improve the oxygenation of the remaining areas, especially the macula. The total area of the retina is estimated at 1,100–1,400 mm^2[22]. ETDRS and DRS suggested 236 mm^2 as the minimum area of the retina that must undergo panphotocoagulation in PDR and severe NPDR to achieve a therapeutic effect. In 1995, Reddy et al. determined the area of the retina that should be subjected to PRP at the level of 510–1,280 mm^2 (which corresponds to 2,600–6,500 spots 500 µm in diameter), with the intensity of the procedure dependent on the severity of retinopathy and the presence of risk factors[23]. In severe PDR, ETDRS recommends extending PRP into regions of the peripheral retina.

The main indications for PRP:

1. HR PDR (definition on p. 97),
2. neovascularization of the angle and/or neovascularization of the iris,
3. in some situations severe NPDR and initial PDR (PDR without high-risk characteristics).

The DRS and ETDRS studies do not recommend PRP in mild and moderate NPDR. Intensive laser therapy of the retina in severe NPDR remains debatable, especially nowadays with the availability of intravitreal therapies. The ETDRS study showed that the use of full PRP in severe NPDR reduces the risk of progression to the PDR stage by 50%[20]. However, the risk of severe vision loss (SVL) in severe NPDR is not significant. In the ETDRS study, after five years, SVL occurred in 2.6% in the early PRP group and in 3.7% in the group in which PRP was performed after reaching.

Despite the positive results of clinical studies on the efficacy of PRP in various stages of retinopathy, ETDRS and DRS recommended its use only in the proliferative phase. This was largely due to complications after using xenon or ruby lasers. Contemporary multispot lasers, as already mentioned, operate with a very short exposure time, which results in the formation of small scars without the tendency to enlarge over time. The visual field defects are smaller, and the procedure is not as painful as classic PRP. Accordingly, PRP may be considered for severe NPDR approaching the proliferation stage, especially in the presence of additional risk factors.

The Royal College of Ophthalmologists (RCO) recommends considering PRP for severe NPDR in the following situations[24]:

- in older adults with type 2 diabetes (DM2),
- when examination of the fundus is difficult,
- before scheduled cataract surgery,
- in the better eye, when the other one has lost vision due to PDR,
- when there are difficulties with regular follow-up.

Once HR PDR is diagnosed, full PRP should be performed as soon as possible, within a maximum of two weeks from diagnosis. The number of sessions is not defined and depends on the patient's perception of pain. In such a situation, multispot laser therapy is very useful, because – as mentioned earlier – it is usually possible to perform full PRP in one or two sessions.

The PRP technique has evolved along with the technological development of lasers. Originally, ETDRS recommended laser ablation of the retina with an area of at least 236 mm^2, which corresponds to 1,200–1,600 spots 500 µm in diameter. As a standard, the exposure time was set at 0.1 seconds, and the laser power was adjusted to obtain a slight retinal fading at the target spot. The distance between the spots should be

0.5 to 1 of the diameter of the impact. This number of burns was performed over two or more sessions. In the era of multispot lasers, shorter exposure times are used: from 0.01 to 0.05 seconds and often smaller spots, for example 300–400 μm in diameter. In such a situation, it is sometimes necessary to perform more burns, but – as I emphasized earlier – the procedure can be performed in a single session.

PRP protocol

- Setting the laser spot diameter to 500 μm and the time to 0.1 seconds in the case of classic photocoagulation; with multispot lasers, typically the time setting is 0.01–0.02 seconds and the spot diameter 300–500 μm.
- Setting the laser power (titration) to obtain a slight fading of the retina at the laser spot.
- Determining the extent of laser treatment (boundaries) with 1–2 rows of photocoagulation spots:
  - temporally at a distance of 2 DD from the border of the foveal avascular zone (FAZ),
  - along the main vascular arcades,
  - nasally at a distance of 1 DD from the margin of the optic nerve disc.
- We perform PRP peripherally from the designated boundaries.
- The laser power is reduced when performing PRP on the periphery.

Practical remarks

- In advanced, non-regressive PDR, PRP should be extended to the retinal periphery.
- The intensity and extent of PRP depend on the severity of the retinopathy.

In terms of the procedure technique, complete panretinal photocoagulation can be planned and conducted in two ways. In the first scenario, after marking the boundaries of the laser therapy as individual rows of photocoagulation spots, the procedure is divided into individual quadrants of the retina and performed successively in each quadrant. In the second form of PRP, which is used by more experienced clinicians, scatter laser therapy is conducted in all quadrants simultaneously, the spacing of spots is successively condensed and the procedure itself is moved peripherally in subsequent sessions.

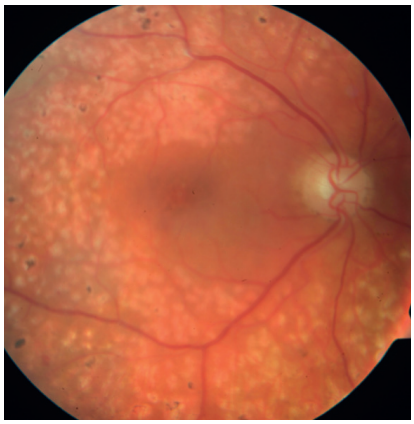
The RCO, based on the recommendations of ETDRS, recommends the following strategies for performing primary PRP (in the case of multispot lasers, a larger number of spots should be considered):

1. early PDR (early neovascularization (NV): neovascularization elsewhere (NVE) and at the disc (NVD) when NV is flat and less than ⅓ DA): 1,200–1,800 spots over two weeks; follow up after four months (unless the patient is pregnant – see Chapter 11: *Ophthalmic care for special diabetic patients: children, adolescents and pregnant women*, pp. 209–214);
2. moderate PDR (NVD > ⅓ DA, forward NVD beyond disc margin or forward NVE in any quadrant, NVE in four quadrants): 2,000–2,500 spots in two weeks; follow up after three months, unless there is poor glycemic control or the patient is pregnant – in which case, after a shorter period;
3. severe PDR (large NVE in any quadrant, NVE with tractional retinal detachment, large NVD covering the entire optic disc, NVD with tractional retinal detachment): 3,000 exposures over 3–4 weeks; for vitreous hemorrhage, photocoagulation of the visible areas of the retina; photocoagulation of the remaining ones is performed as blood is absorbed; additional anti-VEGF intravitreal therapy is possible.

In the case of severe PDR with hemorrhages and traction, immediate surgical treatment, i.e. posterior vitrectomy, is usually recommended. The ETDRS recommendations date back to the years when the vitrectomy technique was not as developed as it is today.

The number of spots in panretinal photocoagulation

The most common mistake made by ophthalmologists in laser treatment of severe DR is producing an insufficient number of burns. For example, in the United



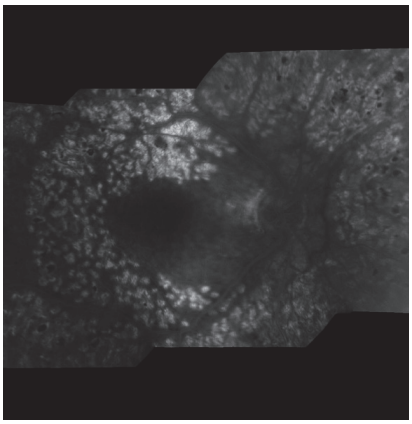
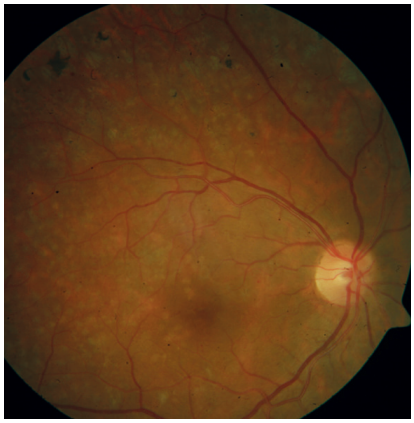


Figure 5. Correctly performed classic panretinal photocoagulation is visible in the colour and angiographic image.



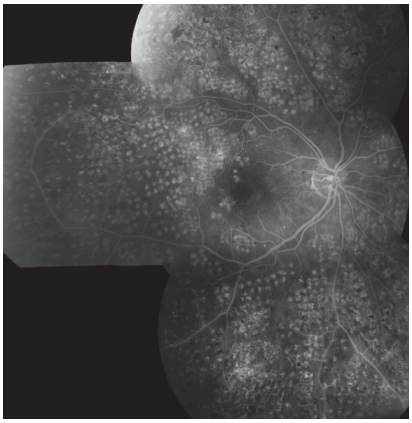
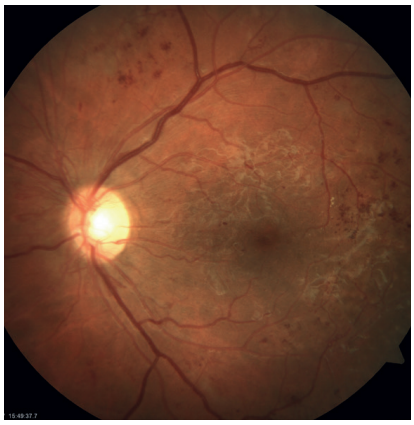


Figure 6. A patient with proliferative diabetic retinopathy after correctly performed panretinal photocoagulation with a multispot laser.



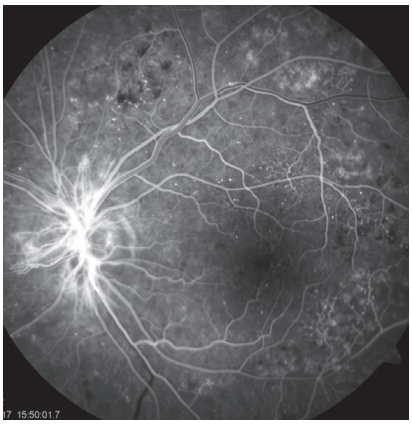
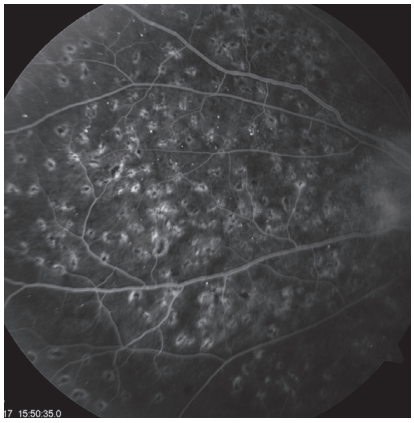
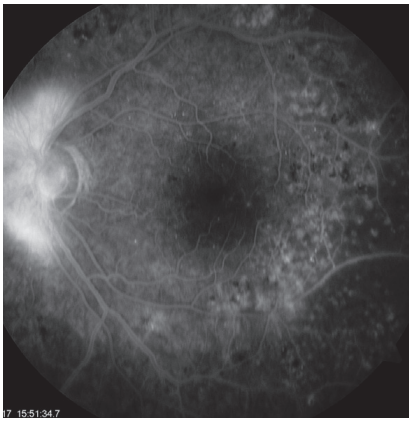


Figure 7. Proliferative diabetic retinopathy after panretinal photocoagulation. A visible leak from neovascularization on the optic disc. Necessary supplementation and condensation of photocoagulation spots.





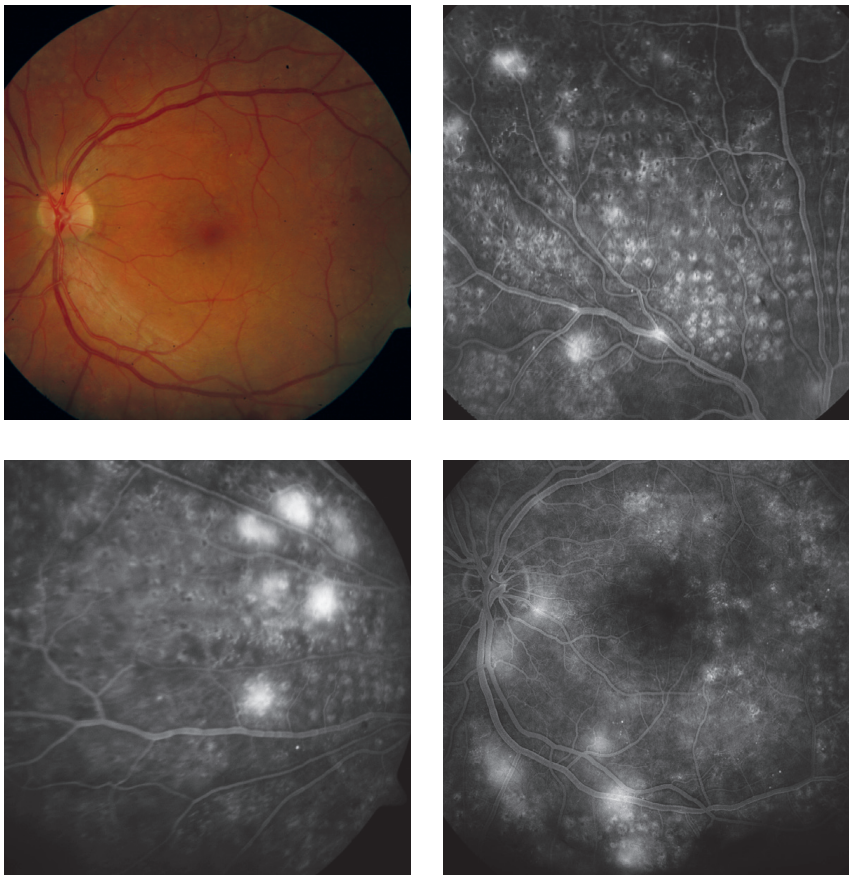


Figure 8. A patient after panretinal photocoagulation with a multispot laser. Angiographic images show neovascularization on the optic disc and numerous neovascularizations outside the optic disc. Necessary condensation of photocoagulation spots.

Kingdom, in 1995, the mean area of the retina subjected to PRP was 98.2 mm^2, with the ETDRS and DRS recommending a minimum area of 236 mm^2[25]. This corresponds to a minimum of 1,200–1,500 spots that should be performed. In the case of advanced PDR, this number should be much higher (Figs. 5–7).

Due to the frequent use of multispot lasers for PRP, it is worth considering the number of spots required for this photocoagulation technique (Fig. 8). The RCO suggests that this number should be larger than for classic PRP. The MAPASS study determined the mean cumulative number of multispot laser burns required to achieve PDR regression in patients treated within the 18 months' follow-up period: mild PDR required an average of 2,200 spots (an of area 264 mm^2), moderate PDR 4,000 spots (an area of 456 mm^2), and advanced PDR required 7,000 spots (an area of 836 mm^2)[26]. (Data for Pascal laser from Topcon Medical Laser System).

Panretinal photocoagulation intensity

The metabolic theory of the photocoagulation laser induces considering laser powers used in PRP. The question arises whether the formation of visible scars after PRP is necessary to achieve the desired effect – a reduction of neovascularization or a reduced risk of its development.

Bandello et al.[27] compared the effectiveness of mild PRP with classic PRP in HR PDR. Mild PRP relied on the use of low power argon laser: only barely visible retinal fading was targeted during laser therapy. The study results showed that mild PRP had comparable efficacy to classical PRP, with fewer complications.

Lenses for laser therapy

Panfundoscopes are used to perform panretinal photocoagulation, i.e. wide-angle imaging lenses (Fig. 9), for example Super Quad or Equator Plus (Volk) or NMR Mainster PRP 165 (Ocular). A Goldmann three mirror

lens is not recommended for performing PRP. It is important to remember that the photocoagulation burn that is produced on the retina with the panfundoscope is twice as large as the laser setting, i.e. a 200 µm setting will produce a 400 µm diameter burn.

Most panretinal laser photocoagulation procedures are performed under topical anesthesia with tetracaine or proparacaine drops. In some situations, when we want to perform panretinal photocoagulation quickly, and the patient is unable to withstand a longer session (for instance, because of pain), periocular or extraocular anesthesia is used. Some authors also recommend topical drops of non-steroidal anti-inflammatory drugs a few days before the scheduled laser procedure.

Figure 9. Contact lenses for retinal laser treatment. Left: a panfundoscope for performing PRP; right: lens for laser treatment for the central part of the retina.

Complications of PRP and focal laser treatment

1. Pain – pain symptoms are experienced by a significant percentage of patients undergoing laser therapy (up to 80%), mainly with panretinal photocoagulation[28, 29]. The source of the pain is probably the posterior ciliary nerves. The discomfort is greater when more burns are generated and more power is used. It usually occurs during laser therapy of the retinal periphery, so it is advisable to reduce the laser power parameters while targeting this region.
2. Preretinal or vitreous hemorrhage – it is rare and may occur in the presence of significant vascular proliferation. This complication was more common when krypton lasers were in use[30, 31].
3. Reduction of the field of view – the reduction of the field of view is assessed as 40–50% loss after full classic panretinal photocoagulation[32, 33]. In practice, however, this does not mean significant restrictions in everyday life (less than 20% of patients lose their driving license for this reason)[34, 35]. In the case of multispot laser therapy, the changes in the field of view are much smaller[5].
4. Visual quality disturbances – a decrease in the contrast sensitivity of the retina is noted after PRP. In the case of laser therapy in the macular area, scotomas may appear in the visual field, or there may be a decrease in visual acuity in the case of the photocoagulation spot located too close to the fovea. Other visual quality disturbances concern accommodation (reduction of the range). Moreover, patients may experience transient photophobia, moderate nyctalopia and colour vision disturbances in the blue spectrum[36, 37, 38].
5. Secondary choroidal neovascularization (CNV) – a rare complication that occurs after photocoagulation in the macular with small burns, such as 50 µm, and too much laser power. Bruch's membrane ruptures occur and neovascularization from the choroid follows. Treatment of CNV requires anti-VEGF therapy[39, 40]. Damage to Bruch's membrane during photocoagulation may also cause subretinal fibrosis without obvious features of CNV[41].
6. The occurrence or worsening of macular edema – intense panretinal photocoagulation may aggravate macular edema. For this reason, treatment of diabetic maculopathy should be planned prior to

Table 1. Studies demonstrating the effectiveness of subthreshold micropulse laser therapy in the treatment of proliferative diabetic retinopathy.

Study	Number of eyes	Study design	Results
Luttrull et al. 2008[48]	99 with severe NPDR or PDR	• retrospective study • the following parameters were assessed: BCVA, the presence of VH, the need for PPV after 12 months	• no change in BCVA • estimated probability of VH = 12.5% and of PPV = 14.6%
Jhingan et al. 2018[49]	20–10 patients with symmetric severe NPDR or low-risk PDR	• prospective, randomized study • each eye randomized to classic PRP or SMPLT • assessed parameters: BCVA, contrast sensitivity, visual field and ERG in both groups at 9 months	• one eye of the SMPLT group developed VH and required classic PRP • the classic PRP group had worse retinal sensitivity compared to the SMPLT group, but the difference was not statistically significant

BCVA – best-corrected visual acuity, ERG – electroretinography, NPDR – non-proliferative diabetic retinopathy, PDR – proliferative diabetic retinopathy, PPV – pars plana vitrectomy, PRP – panretinal photocoagulation, SMPLT – subthreshold micropulse laser therapy, VH – vitreous hemorrhage

peripheral photocoagulation or in parallel. The anti-VEGF/PRP combination therapy effectively prevents DME in patients undergoing panretinal photocoagulation. Sometimes anti-VEGF therapy is applied before intensive photocoagulation[42, 43, 44].

7. Preretinal fibrosis – glial proliferation occurs in the epiretinal membranes (ERM) after intensive photocoagulation, especially with excessive laser powers. Preretinal glial growth is visible primarily after photocoagulation in the macular area. The resulting membranes tend to shrink, inducing traction, which causes additional damage to the photoreceptors[45].
8. Vision deterioration related to the enlargement of photocoagulation scars – using too much power may result in the formation of large scars, which tend to enlarge in the months or even years after the laser treatment. Laser therapy performed too close to the fovea may lead to vision deterioration: BCVA decrease and permanent scotoma formation[46].
9. Choroidal detachment – a rare complication which occurs after very intense photocoagulation[47].

Subthreshold micropulse laser therapy in proliferative diabetic retinopathy

Subthreshold micropulse laser therapy (SMPLT) is not a standard form of PDR treatment, but studies indicating its effectiveness in treating this disease are worth noting (Table 1). Luttrull et al. emphasize the lack of fibrovascular tissue shrinkage after PRP performed with micropulse laser[48]. However, it is a long and tedious procedure, and its effectiveness requires confirmation in a larger number of clinical trials. The use of micropulse panretinal photocoagulation in cases of severe NPDR remains an open issue. According to recent reports, SMPLT in severe NPDR is not less effective than classic panretinal photocoagulation[48]. Due to the small number of clinical trials on PRP performed in PDR in the SMPLT mode, this form of laser treatment should be classed as experimental for the time being.

Intravitreal therapies and combination therapies

Anti-VEGF therapy and intravitreal steroid therapy in the treatment of proliferative diabetic retinopathy

Combined therapies – intravitreal injections plus laser treatment – have been used to treat PDR, but on a relatively small scale. The reason for this is the insufficient number of clinical trials defining the principles for the application of such therapy. Adding intravitreal therapy to PRP may have two benefits: a reduction in the risk of macular edema following intense panretinal photocoagulation and regression of neovascularization. The question remains regarding what regimen should be used in this kind of combination therapy.

Reducing the risk of developing macular edema

There have been many studies that have investigated the effectiveness of combination therapies in PDR, usually of a short-term nature. Most of them have shown that both intravitreal anti-VEGF agents and intravitreal steroids administered before laser therapy reduced the risk of developing macular edema (ME) after PRP. Cho et al. compared the effects of combination therapy: PRP plus intravitreal triamcinolone (IVTA), PRP plus intravitreal bevacizumab (IVB), and the effects of PRP alone[50]. After three months, in the group receiving only laser therapy, BCVA decreased, while in the groups receiving combined therapy, BCVA was maintained. Additionally, improvement in BCVA was observed in patients with clinically significant macular edema (CSME) who received combination therapy with IVTA. Morphological improvement (reduction in central retinal thickness – CRT) occurred in patients with CSME who received combined therapies. Similar results were reported by Mason et al.[51]. The administration of bevacizumab injections prior to PRP was protective, preventing the vision loss associated with the occurrence of macular edema following intense photocoagulation.

Regression of neovascularization

In a small sample, Ernst et al.[52] compared the regression of neovascularization after classic PRP and anti-VEGF therapy (bevacizumab). Patients were monitored for twelve months. The group IVB received bevacizumab every two months. In the bevacizumab group, complete regression of NV occurred in 4 out of 5 patients and in the PRP group in 1 in 5. A larger trial of this type was analysed by Filho et al.[53]. The comparison was made between patients with HR PDR treated with PRP alone and PRP combined with ranibizumab. Ranibizumab was administered at 0.5 mg, 60 minutes after the first PRP session. The study allowed for repeated injections at 16 and 32 weeks if NV activity was detected. After 48 weeks of the study, the regression of NV (reduction of leakage by fluorescein angiography) was greater in the group treated with the combination therapy than in the group treated with PRP alone. At 48 weeks, BCVA did not change in the combination group, while patients on PRP alone showed a decrease in visual acuity at all stages of the study.

Mirshahi et al.[54] investigated the effect of a single injection of bevacizumab on the regression of NV in combination with PRP. The positive effect was short-term: NV regression was significantly greater in the PRP plus bevacizumab group than in the PRP only group after six weeks. At week 16 of the study, this difference was no longer observed.

A similar NV regression analysis was also performed by Tonello et al.[55]. The study lasted sixteen weeks and involved patients with HR PDR but without CSME. After sixteen weeks, the regression of NV was greater in the IVB plus PRP combination group than in the PRP alone group, but there was no difference in BCVA between the groups. A similar trial with IVB and PRP was carried out by Preti et al.[56]. At the end of the study, the group treated with PRP alone showed a deterioration in visual acuity and an increase in CRT, while visual acuity and CRT remained unchanged in the combined group. The authors conclude that

HR PDR combination therapy prevents vision loss and provides better morphological outcome in the retina compared to PRP monotherapy, although it does not significantly improve BCVA.

In the discussed studies, the frequency of administering intravitreal injections was low and did not follow a long-term regimen. Clearly better effects after anti-VEGF plus PRP combination therapy were seen in clinical trials when the patients received more injections and at regular intervals, and when PDR was accompanied by CSME. The regimen involving only single injections in addition to PRP turned out to produce better short-term effects, but the long-term effects (BCVA, NV regression) were comparable to PRP monotherapy.

In 2013, the results of a study on the efficacy of treating non-resorbing vitreous hemorrhage with intravitreal injections of ranibizumab (Protocol N of the DRCR.net group) were published[57]. Patients were randomized for treatment with ranibizumab or saline (three injections at monthly intervals), and the need for vitrectomy was assessed in both groups sixteen weeks after initiation of treatment. At the end of the study, there was no significant difference between the rates of necessary vitrectomy in the two groups (12% for ranibizumab and 17% for saline). However, full PRP was more frequently performed in the ranibizumab group due to better resorption of hemorrhage compared to patients in the control group (44% versus 31%).

Recent studies on the efficacy of anti-VEGF therapy in the treatment of proliferative diabetic retinopathy

In 2017 and 2018, three large randomized trials investigating the effectiveness of anti-VEGF therapy in treating PDR were conducted, and these merit a separate discussion.

1. **Protocol S of DRCR.net**
   Protocol S from DRCR.net is a study that unequivocally confirms the effectiveness of anti-VEGF therapy in PDR[58]. This is the first such large randomized trial comparing the effectiveness of intravitreal injections of ranibizumab and PRP in treating PDR. The study included 394 eyes, of which 203 received panretinal photocoagulation, and 191 were given intravitreal injections of ranibizumab according to a specified schedule, with a maximum frequency of every four weeks (the number of injections over two years was: in patients without DME – seven in the first year and three in the second year of the study; in patients with DME – nine in the first year and five in the second year of the study). After 24 months, the change in BCVA and the incidence of complications were analysed in both groups.

   At 24 months, the ranibizumab group had a mean improvement in BCVA of 2.8 ETDRS letters, and the PRP group showed a mean improvement of 0.2 ETDRS letters. In patients with DME, the difference in letter gain in favour of the ranibizumab group was +3.0. After two years of study, NV regression occurred in 35% of patients in the ranibizumab group and 30% in the PRP group. However, there was a significant difference in the rate of complications. In the ranibizumab group, DME was less frequent (9% versus 28%), a smaller percentage of patients required a vitrectomy (4% versus 15%), and visual field defects were significantly smaller. There were no significant differences between groups in terms of the incidence of systemic complications. The authors conclude that treatment with ranibizumab in PDR may be an alternative to classic panretinal photocoagulation.

   Of particular interest is the analysis of the Protocol S study results at five years[59]. In subsequent years (the third, fourth and fifth years), the mean number of injections in patients without DME was only three per year. After five years of study, there was no significant difference in BCVA between the ranibizumab and PRP groups: both groups

gained around three ETDRS letters. A significant difference was noted in visual field limitation – the ranibizumab group still had significantly less deficit. Retinal detachment was more common in the PRP group (15% versus 6%). DME was also more common in the PRP group (38% versus 22%).

It should be noted that not all patients remained in the study until its end (as many as ⅓ of patients did not complete the five-year follow-up period – the so-called LTFU group (LTFU – lost to follow up). Among the patients who did not undergo regular follow-ups complications such as retinal detachment or extensive NVD were significantly more common in the ranibizumab group (retinal detachment in 33%, NVD in 40%). In the PRP group, these complications occurred in a minority of patients (retinal detachment in 2.2%, NVD in 9%).

Similar results concerning LTFU patients were also reported by Obeid A et al.[60]. Serious PDR complications are much more frequent in LTFU patients treated with anti-VEGF monotherapy than those undergoing PRP monotherapy.

2. **The CLARITY Study**
   In 2017, Sivaprasad et al. conducted an analogous comparison of the use of aflibercept and PRP with proliferative diabetic retinopathy[61]. Patients treated with aflibercept at 52 weeks gained four ETDRS letters more than patients treated with PRP alone. In the aflibercept group, there was less intravitreal hemorrhage (9% versus 18%) and less frequent need for vitrectomy (1% versus 6%). It should be emphasized that these are the study results at 52 weeks only, and for the time being, we are unable to assess the long-term efficacy of aflibercept in the treatment of PDR.

3. **The PROTEUS study**[62]
   This study compared the regression of neovascularization in patients with HR PDR treated with PRP only with a group of patients treated with the combination therapy: PRP plus ranibizumab at a dose of 0.5 mg. The combination therapy group received three monthly injections of ranibizumab and PRP. The results were assessed after twelve months. A significantly better regression of NV was achieved in the group subjected to the combination therapy (complete regression of NV in 43.9% of eyes in the group subjected to the combination therapy versus 25% in the group of PRP monotherapy).

As can be seen from the presented studies, regular anti-VEGF therapy may be effective in treating PDR, rather than ad hoc management. However, it should be borne in mind that in the case of using intravitreal injections only, we cannot determine the end of such therapy. The DRCR.net study shows that injection frequency drops markedly in the second year of treatment, especially in patients without DME. However, we do not know if it is possible to achieve complete regression of NV when only anti-VEGF therapy is used. Some studies show that the severity of diabetic retinopathy decreases in response to anti-VEGF injections[63, 64]. According to other researchers, anti-VEGF therapy also improves vascular perfusion[65, 66].

Not everyone agrees with this thesis. Some studies using angio-OCT show that anti-VEGF therapy does not improve retinal perfusion[67]. According to some researchers, the lack of improvement in retinal blood supply means that the basic risk factor for the development of neovascularization is not eliminated. This, in turn, must result in the need to continue anti-VEGF therapy. Research on retinal vascular perfusion in the course of anti-VEGF therapy should be continued, especially with the availability of new diagnostic methods.

It is worth noting that panretinal photocoagulation, despite complications such as visual field loss or the risk of ME development, effectively regresses pathological vessels. Moreover, it usually does not need to be repeated many times, while anti-VEGF therapy does. The results of the Protocol S study after five years

show that not all patients can tolerate the inconvenience of frequent intravitreal injections (the LTFU group). PRP seems to be a better solution for this group as it prevents the development of dramatic complications without the need for numerous procedures.

The economic analysis of the costs of the treatment is also important. In this regard, PRP should be described as a cheap method, especially when compared with the financial burden associated with anti-VEGF therapy.

The cost-effectiveness analysis carried out by the DRCR.net group showed that ranibizumab monotherapy in patients with PDR and DME is the most reasonable option when treating the better eye[68]. Such cost-effectiveness was not recorded for the eyes with PDR without DME. The use of panretinal photocoagulation in such situations is much cheaper and more economically effective.

It should be emphasized that further large clinical trials are being conducted on anti-VEGF therapy in PDR. The aim of the PRIDE for PDR study is to compare the efficacy and safety of intravitreal ranibizumab alone with the effects of the combined therapy: ranibizumab plus PRP, and PRP alone. The results will be assessed after twelve months in regard to neovascular regression, final BCVA, reduction in the severity of retinopathy and change in CRT.

The Protocol W study of DRCR.net, on the other hand, aims to investigate aflibercept therapy in eyes that are at risk of developing DME and/or PDR. Assessment is planned two and four years after initiating intravitreal therapy and focuses primarily on the development of neovascularization and DME.

The effect of anti-VEGF therapy on the severity of diabetic retinopathy

Studies on the effectiveness of various anti-VEGF agents in DME treatment were also analysed in terms of the progression or regression of retinopathy itself (the so-called post hoc analysis). For this purpose, the Diabetic Retinopathy Severity Scale (DRSS) developed by ETDRS was used[69]. Below is presented the DRSS scale used in clinical trials (for example, RISE/RIDE). The numbers provided correspond to specific symptoms defined by the ETDRS. The reader can find them in the available ophthalmic literature.

DRSS grades	
DRSS 10, 12	no DR
DRSS 14, 15, 20	DR questionable
DRSS 35	mild NPDR
DRSS 43	moderate NPDR
DRSS 47	moderately severe NPDR
DRSS 53	severe NPDR
DRSS 61	mild PDR
DRSS 65	moderate PDR
DRSS 71 and 75	HR PDR
DRSS 81 and 85	advanced PDR

An analysis of DRSS change in patients treated for DME with ranibizumab (RISE/RIDE studies)[70] showed a marked improvement on the DRSS scale in most patients. Moreover, with patients who had these forms of retinopathy and who were treated with ranibizumab, the risk of developing neovascularization was three times lower than in the group that received sham injections[71, 72].

The analyses of the long-term effects of DME treatment with aflibercept in the VIVID and VISTA studies (analysis after 148 weeks) have shown similar results[73]. In both studies, at least a two-step improvement on the DRSS scale was noted in a significantly higher proportion of aflibercept-treated patients than patients receiving only laser treatment (for example 44.3% or 47.8% versus 17.4% in the VIVID study).

Interesting results on the regression of retinopathy during DME treatment with various intravitreal drugs (ranibizumab, aflibercept, bevacizumab) are presented in DRCR.net Protocol T[74, 63]. Regression of non-proliferative retinopathy was observed in all three groups. After two years of study, there were no significant differences between the effects of these drugs in

this respect (the percentage of patients with regression in DRSS: aflibercept 24.8%, ranibizumab 31%, bevacizumab 22.1%). A more apparent improvement was observed in patients with severe NPDR. In the case of the regression of proliferative retinopathy, the analysis showed the superiority of aflibercept over the other two drugs (regression in 75.9% for aflibercept, 55.2% for ranibizumab and 31.4% for bevacizumab).

The results of the five-year DRSS regression monitoring for ranibizumab alone (Protocol I of the DRCR.net group) are similar[75]. NPDR regression was noted in 32% of eyes and PDR in 23% of eyes after five years of treatment.

As can be seen from the presented results, intravitreal anti-VEGF therapy reduces the severity of retinopathy also in non-proliferative retinopathy, especially in its advanced stage. The question of whether or not to include anti-VEGF therapy in the treatment regimen of severe NPDR has subsequently arisen. Resolving this issue requires further research, which is, in fact, already underway.

For example, the results of the PANORAMA study have just been published[76]. The research aimed to compare the efficacy of intravitreal aflibercept applied with variable regimens with sham injections in moderately severe to severe NPDR. Results at 24 weeks show that patients treated with aflibercept achieved a significant improvement in the severity of retinopathy (at least 2-step improvement on DRSS scale: 58.4% of patients in the aflibercept group versus 6.0% in the sham group). This tendency was maintained through weeks 52 and 100. Moreover, by week 100, fewer eyes treated with aflibercept versus sham injections developed vision-threatening complications and/or center-involved DME.

The effect of intravitreal steroid therapy on the progression of diabetic retinopathy

Analysis of the impact of intravitreal steroid therapy on the progression of diabetic retinopathy is somewhat rare. The effects of administering intravitreal steroids in conjunction with PRP to prevent the complications of panretinal photocoagulation have been investigated more frequently (as discussed earlier). Nevertheless, most studies of such combination therapy report its effectiveness: patients with PDR who received intravitreal triamcinolone before or after panretinal photocoagulation had better visual acuity and a lower value of central retinal thickness[77, 78, 79, 80, 81]. Only single studies, including Mirshahi et al., do not show such a relationship[82]. Such results may suggest that intravitreal steroid therapy has a positive effect on the regression of retinopathy, as confirmed, for example, by the analysis of Bressler et al.[80]. However, it should be borne in mind that the cited studies also apply to patients with concomitant DME, which makes it difficult to assess the effect of triamcinolone on inhibiting the progression of retinopathy itself. In addition, known complications following the intravitreal administration of steroids (e.g. cataracts, increases in intraocular pressure) limit their regular use, which would be necessary to achieve a permanent regression effect of retinopathy. Since anti-VEGF agents became popular, they have been the main choice in combination therapy with PRP in treating proliferative diabetic retinopathy. Intravitreal steroids remain a form of treatment in pseudophakic patients with PDR and DME. It should also be emphasized that intravitreal steroids in combination therapy are second-line drugs used when anti-VEGF drugs are ineffective and in the treatment of patients with contraindications for anti-VEGF drugs.

Treatment options for diabetic retinopathy – a summary

Strategies for DR management

1. Absence of retinopathy – observation, follow-up visits every 1–2 years.
2. Mild and moderate NPDR:
   a. DME absent – observation and follow-up visits twice a year,
   b. DME present – DME treatment, follow-up visits depending on the treatment used.

3. Severe NPDR:
   a. DME absent
      - monitoring every 3–4 months; close observation,
      - PRP permissible in selected cases (depending on the concomitant risk factors mentioned above);
   b. DME present – treatment of DME according to the current recommendations (see Chapter 8: *Diabetic maculopathy (diabetic macular edema) – diagnosis and treatment*, pp. 113–168); monitoring depending on the treatment modality applied; PRP to be considered in parallel in selected cases.
4. Initial PDR (non-HR-PDR):
   a. DME absent – PRP or anti-VEGF, depending on the patient's age, compliance, and the preferences of the attending physician,
   b. DME present – anti-VEGF therapy as the main form of treatment; possibly concurrent PRP (e.g. low-density PRP).
5. HR PDR:
   a. DME absent – usually PRP, sometimes combined with anti-VEGF, possible posterior segment surgery,
   b. DME present – usually anti-VEGF with PRP, possible posterior segment surgery.

According to the current state of knowledge, it seems that combining PRP and anti-VEGF therapy is the most reasonable solution for the treatment of PDR. Patients with PDR and DME, and patients with early or more advanced PDR without significant vitreoretinal traction, are good candidates for combination therapy: PRP plus intravitreal injections. Intravitreal injections in monotherapy may be considered when treating young people with initial PDR, as such an approach saves the visual field and have better functional effects. In order for this therapy to be effective, good patient compliance is essential: adapting to frequent follow-up consultations and intravitreal injections of the drug. In general, the decision is made individually, taking into account the severity of retinopathy, the patient's general condition and his or her preferences. It should be remembered that despite the consequences, i.e. narrowing of the visual field, PRP remains a cheap and effective form of treatment for proliferative diabetic retinopathy. The treatment selecting process should always include considering surgical procedures (PPV), especially for advanced cases of PDR with present or impending vitreoretinal traction.

Controversial issues to be solved

1. PRP in severe non-proliferative retinopathy – precise recommendations are needed.
2. PRP intensity in the context of the metabolic theory of laser photocoagulation – is low-intensity PRP sufficient to obtain the desired effect.
3. PRP in initial proliferative diabetic retinopathy in the context of anti-VEGF therapy – when to start treatment with anti-VEGF monotherapy.
4. SMPLT in PDR – does this therapy make sense, and, if so, in what cases?
5. Anti-VEGF monotherapy in PDR– whether and when to use it.
6. Anti-VEGF therapy in severe NPDR – whether and how to use it to improve DRSS.

Simplified recommendations of management of diabetic retinopathy taking into account the above-mentioned therapeutic options are presented in the Appendix, pp. 244–246.

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Chapter 10: Posterior pars plana vitrectomy in diabetic retinopathy

General remarks

Surgical treatment in the posterior segment of the eye, or pars plana vitrectomy (PPV), is used to treat complications associated with the course of diabetic retinopathy (DR), primarily in its advanced, proliferative stage (PDR). Our understanding of the effects of PPV treatment is constantly evolving, which is largely related to the development of surgical techniques and the introduction of technological innovations in the equipment used to perform this procedure.

The purpose of this chapter is to present the guidelines for PPV in the treatment of a patient with DR. Explanations on the technical details of the procedure itself can be found in other publications devoted to vitreoretinal surgery.

The basic principles of vitrectomy

The essence of vitreoretinal surgery is to create access to the posterior segment of the eyeball, remove the vitreous body and perform surgical procedures related to the pathology of the retina and vitreous body present there. Robert Machemer developed the foundations of the modern technique of vitrectomy in the 1970s[1]. The most important step was the invention of the closed system vitrectomy setup, including a cutting-aspirating device (vitrector) and simultaneous infusion, which allowed adequate intraocular pressure to be maintained during the surgical procedure. Over the course of several decades, enormous technological advances have been made in the equipment for this surgery. Thanks to them, today we use sutureless techniques, advanced cutting systems, comfortable systems of lighting and the visualization of the fundus.

The surgery is usually performed under local anesthesia, sometimes with intravenous sedation. The primary form of anesthesia is blockage of the ciliary ganglion with a retrobulbar injection of 2% lidocaine or 0.5% bupivacaine. Sometimes, periocular injections and topical anesthesia are also used. In some cases, general anesthesia is necessary. This most often applies to children, restless patients, or situations where a long surgery time is expected.

With proliferative diabetic retinopathy, anti-VEGF injections are often administered several days before the planned surgery. The use of such therapy reduces the risk and intensity of intraoperative bleeding and the incidence of postoperative intravitreal hemorrhage[2, 3, 4].

The surgical procedure begins with preparing three ports in the sclera: a port for fluid infusion, a port for a light source, and a port through which instruments – forceps, scissors, vitrectors, etc. – are inserted into the eyeball. First, an incision is made through which the fluid infusion is introduced; then the other two ports are made. The ports are located 3.5–4 mm from the limbus of the cornea, at the flat portion of the ciliary body – pars plana – (see Chapter 3: *Anatomical aspects of diabetic retinopathy*, p. 46) devoid of the sensory retina. The sizes of the ports used today are 20, 23, 25 and 27 gauge (G). The 20G size ports are used very rarely. Smaller diameters are used more often, the advantage of which is that the conjunctiva is self-sealing and does not need to be repaired.

When using small diameter ports, it is not necessary to use scleral sutures. Incisions are made directly through the conjunctiva and sclera, using trocars consisting of a sharp awl and a cannula (Fig. 1).

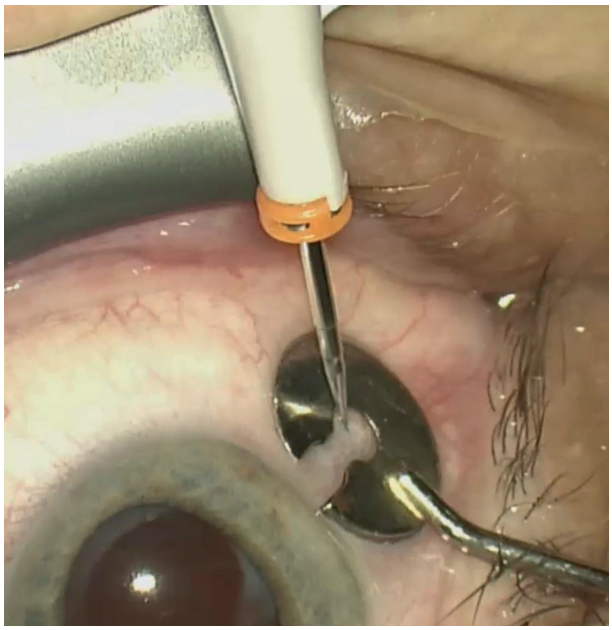

Figure 1. Making ports in the eyeball with trocars.

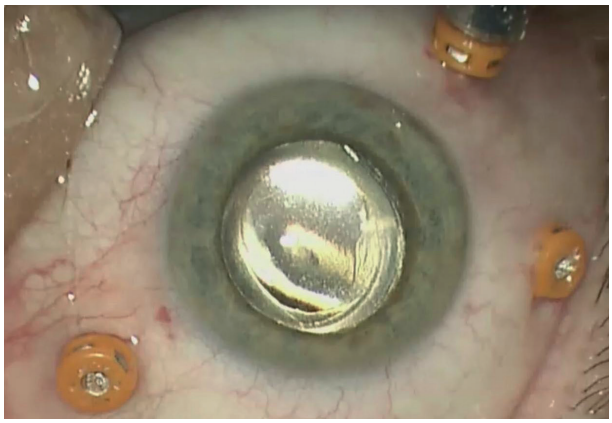

Figure 2. Image of an eye prepared for vitrectomy. A port with fluid infusion is visible at the top. The endoillumination and surgical instruments are introduced through the other two ports.

After the incision is made, the cutting stylet is removed, and the remaining cannula serves as a port for introducing instruments into the eyeball. The correct port layout is shown in Figure 2.

During the procedure, posterior detachment of the vitreous body and its removal at the base are performed. This is followed by various procedures (depending on the type of disease), such as removing hemorrhage or fibrovascular proliferations, peeling of the internal limiting membrane (ILM), endolaser photocoagulation, etc. The procedure ends with injecting air, perfluorocarbon gas or silicone oil into the eyeball. The trocars are then removed. There is usually no need for sutures at the trocar site in the case of 23, 25 and 27G vitrectomies.

The objectives of vitrectomy in DR

- elimination of vitreous opacity: non-absorbing vitreous hemorrhage, fibrovascular and fibrous proliferation, fibrin deposits after resorbed intravitreal hemorrhage,
- elimination of the vitreoretinal traction associated with the presence of fibrovascular and/or epiretinal membrane proliferation, or with increased vitreomacular adhesion (VMA),
- enabling peripheral panretinal photocoagulation,
- achieving retinal attachment (in case of its tractional detachment),
- removing the posterior vitreous cortex or inner limiting membrane in refractory diabetic macular edema (DME).

The principles of qualification for vitrectomy

Basic guidelines regarding the eligibility of patients for PPV were based on clinical trials of the Early Treatment Diabetic Retinopathy Study (ETDRS) and the Diabetic Retinopathy Vitrectomy Study (DRVS) groups in the 1980s and 1990s[5, 6, 7, 8, 9]. I will cite these guidelines later in this chapter, but it should be kept in mind that many years have passed since the results of those studies were published, and recommendations for PPV are constantly evolving. Therefore, qualification for this surgery can be based on the results of more recent clinical studies, even if they are not large randomized trials. The progress of the vitreoretinal surgical technique has resulted in fewer complications and lower surgical risk.

As a result, patients are qualified for PPV much more frequently than 20–30 years ago.

Diagnostic tests performed to qualify patients for pars plana vitrectomy

Fundus examination

The examination should be performed carefully, checking for areas of traction, tears and holes on the retinal periphery, local areas of retinal detachment, the extent of hypoperfusion, the presence of preretinal and intravitreal hemorrhages, and the presence of pathologies of vitreoretinal interface in the macula. A panfundoscope is useful for evaluating the far retinal periphery. The presence of advanced fibrovascular membranes suggests an intravitreal injection with an anti-VEGF agent should be administered shortly before the planned PPV procedure to reduce intraoperative bleeding.

Slit lamp examination

This allows the assessment of iris rubeosis and neovascularization (NV) of the angle (gonioscopy), which are retinal hypoxia symptoms. Detecting significant retinal ischemia with the coexistence of other symptoms of PDR prompts the decision to proceed with surgical treatment. Additionally, a biomicroscopic examination reveals the presence and density of cataract, which could make it challenging to perform PPV, and therefore facilitates the planning of combined surgery or prior cataract surgery.

Ocular ultrasound examination

This is particularly helpful in diagnosing retinal pathology in the absence of a clear view of the fundus (due to vitreous hemorrhage, cataract). It allows us to monitor the potential development of retinal traction and its detachment in such situations. In addition, it allows visualization of vitreoretinal tractions on the retinal periphery.

Optical coherence tomography (OCT) of the macula

This enables the assessment of macular edema, primarily in terms of the presence of vitreoretinal traction, increased adhesion of the vitreous cortex and the presence of the epiretinal membrane (Fig. 3). It reveals the morphology of the edema, including, for example, the presence of large cysts that pose a risk of developing a macular hole. It detects the holes in the macula and allows the assessment of their extent (impending, partial thickness or full thickness).

Fluorescein angiography

Fluorescein angiography, including UWF (ultra-wide field) systems, allows the assessment of peripheral retinal perfusion and the presence of undetected areas of NV. The identification of significant areas of hypoperfusion may accelerate the decision to perform PPV.

The basic indications for PPV in the treatment of DR and its complications will be discussed below.

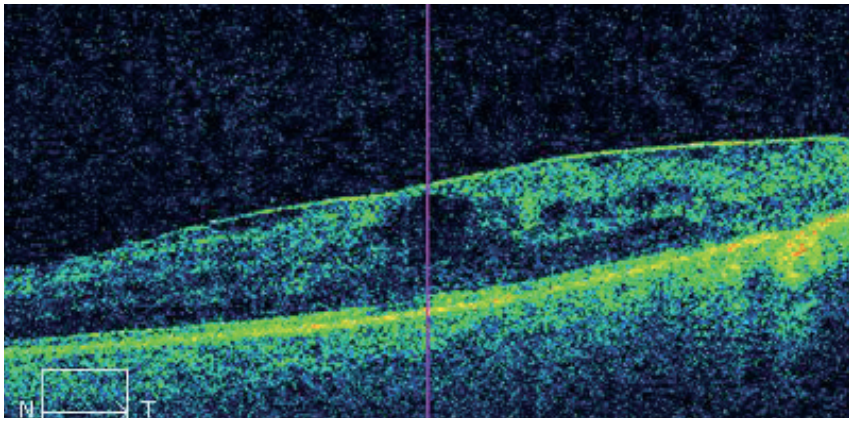

Figure 3. Diabetic macular edema with the presence of epiretinal membrane.

The management of non-resorbing vitreous hemorrhage or preretinal hemorrhage

Vitreous hemorrhage (VH) can occur in two locations: into the vitreous or between the retina and the posterior vitreous border (preretinal hemorrhage (subhyaloid hemorrhage, SH). Hemorrhage may derive both from normal retinal vessels and neovascularization. In most cases, however, the occurrence of VH indicates the presence of active retinal neovascularization. The consequence of hemorrhage is usually a significant decrease in visual acuity and, in the long term, clouding of the vitreous body.

Simple vitreous hemorrhage is hemorrhage without other vitreoretinal pathology. Usually, it does not require urgent surgical treatment as it often resorbs spontaneously within a few weeks. In the case of simple vitreous hemorrhage without significant proliferation, it is possible to wait for its resorption and, after gaining a view into the fundus, perform or expand panretinal panphotocoagulation (PRP).

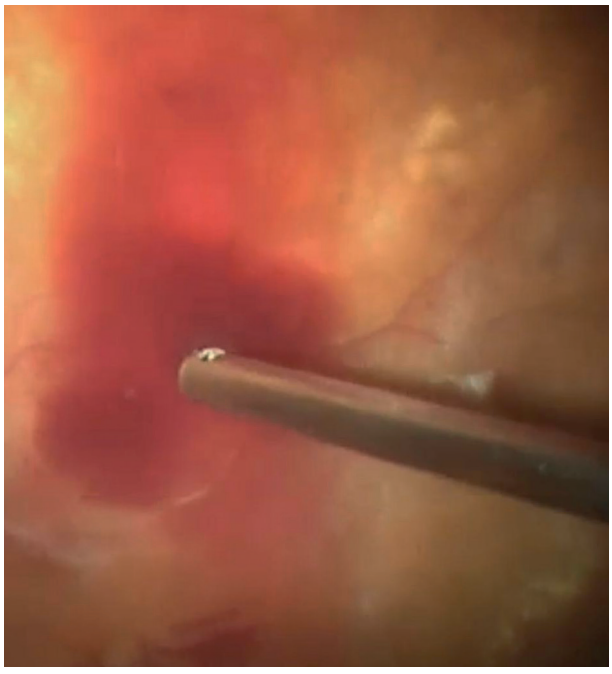

Figure 4. The removal of vitreous hemorrhage in proliferative diabetic retinopathy.

If VH does not completely obscure the view of the fundus, complementary laser therapy may be performed while waiting for the complete resorption of the hemorrhage.

In reports no. 2[5] and no. 5[6], the DRVS group compared the effects of early vitrectomy and vitrectomy deferred for one year in the treatment of vitreous hemorrhage. This large randomized trial showed significantly better functional effects of early vitrectomy in individuals with type 1 diabetes (DM1), who were usually young and had more advanced retinopathy. In patients with type 2 diabetes (DM2), the effects of early PPV were not significantly better than deferred PPV.

It is now believed that vitreous hemorrhage in the course of aggressive PDR in patients with DM1 requires prompt surgical intervention. In the absence of the view of the fundus, a failure to control the progression of retinopathy may lead to the progression of fibrovascular proliferation, significant traction, retinal tears, and eventually retinal detachment. Therefore, delaying surgical treatment is senseless, and usually, the decision for vitrectomy is taken one month after the occurrence of non-resorbing hemorrhage (Fig. 4).

An issue discussed in the medical literature is planning treatment for vitreous hemorrhage in other cases, such as PDR in patients with DM2. According to the available data, early vitrectomy also provides good functional results in this group of patients[10]. Both the Royal College of Ophthalmologists (RCO) and the American Academy of Ophthalmology (AAO) recommend PPV in patients with DM2 with non-resorbing vitreous hemorrhage up to three months after its onset[11, 12]. This is especially true for patients with recurrent vitreous hemorrhages despite previous retinal laser therapy. The Polish Ophthalmological Society (PTO) guidelines recommend urgent vitrectomy one month after the occurrence of non-resorbing vitreous hemorrhage in virtually every group of patients[13]. This approach is consistent with the current opinions of most vitreoretinal surgeons[14].

Vitreous hemorrhage may also occur after panretinal photocoagulation, usually due to shrinkage of fibrovascular tissue by scarring after laser therapy and subsequent bleeding from damaged vessels. When almost full PRP has already been performed, the patient should be observed and monitored with ultrasound examination. In the absence of spontaneous resorption of the hemorrhage, surgery may be scheduled one or two months after the onset of the hemorrhage[15]. However, if a hemorrhage occurs after laser therapy with a small number of laser spots, it should be treated as a sign of active PDR and treated according to the recommended schedule, i.e. surgery should be planned early (see above).

A patient with vitreous hemorrhage requires constant and regular monitoring due to the risk of developing secondary retinal detachment and/or secondary glaucoma. Follow-up examinations should include a fundus examination, ocular ultrasound, and assessment of the iris and the iridocorneal angle in the slit lamp. Ultrasound examination reveals potential retinal pathologies in the absence of a view into the fundus, and the detection of iris and/or angle neovascularization indicates advanced ischemia and accelerates the decision to perform surgical treatment.

VH following PPV is usually mild and most often undergoes spontaneous resorption. Nevertheless, it is always necessary to perform an ocular ultrasound examination and exclude retinal pathologies. A decision that a subsequent surgical procedure is necessary should be made after a month of observation in expectance of spontaneous resorption of the hemorrhage[15].

In the case of dense preretinal hemorrhage, blood builds up between the retina and the posterior vitreous border, i.e. in a limited space. This situation occurs when the vitreous body is incompletely detached. The posterior border of the vitreous provides an excellent scaffolding for fibrovascular proliferation, so the prolonged presence of preretinal hemorrhage increases risk for rapid progression of these proliferations.

Non-absorbing preretinal hemorrhage should be treated surgically, according to the same principles as intravitreal hemorrhage, often in conjunction with anti-VEGF therapy. Studies are available that show better functional results in patients with preretinal hemorrhage undergoing vitrectomy within four weeks of its onset – compared to patients undergoing deferred vitrectomy[16]. The AAO recommends PPV in subhyaloid hemorrhage one month after its onset[12].

In the medical literature on SH, we can also find reports on the beneficial effects of vitreolysis of the posterior vitreous cortex using the Nd:YAG laser[17, 18, 19]. The procedure drains blood into the vitreous chamber to facilitate its resorption. Nowadays, this procedure is not used – instead, vitreoretinal surgeons tend to opt for surgical treatment that eliminates the potential causes of hemorrhage: vitreoretinal traction and neovascularization.

Intravitreal injections of anti-VEGF agents are frequently administered a few days before vitrectomy in non-resorbing VH. Numerous studies have shown that adding this procedure to vitrectomy prevents the development of secondary/recurrent hemorrhages into the vitreous body[4, 20, 21], although not all authors agree with this thesis[22, 23].

In the management of vitreous hemorrhage, the principle of waiting for spontaneous resorption for six months was a standard for years. In the light of clinical studies and advances in vitrectomy techniques, such an approach is not justified. In most cases, early vitrectomy produces better functional results than postponing it. The type of diabetes, the severity of retinopathy, and the patient's age should always be considered when deciding to treat VH.

The use of anti-VEGF injections as the main method of treatment of vitreous hemorrhage in diabetic retinopathy is an interesting issue. In the study by Parikh et al. during a one-year follow-up of patients with vitre-

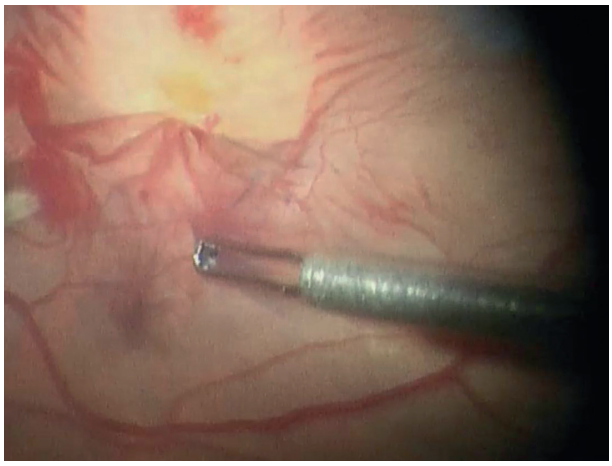

Figure 5. Peeling of the internal limiting membrane.

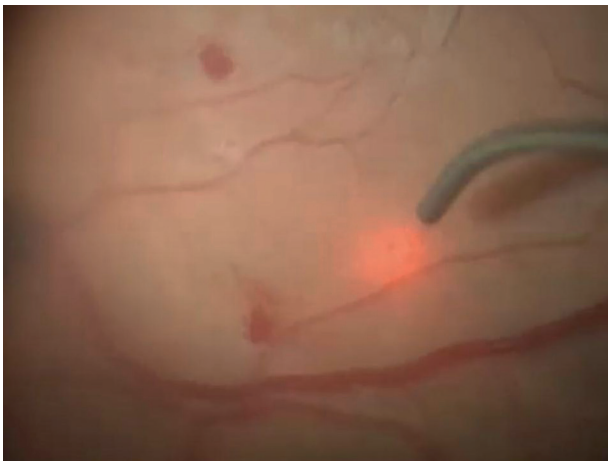

Figure 6. Endophotocoagulation of the retina.

ous hemorrhage in PDR, 31.6% could be successfully treated with bevacizumab injections alone, 49.5% required PRP, and 18.9% needed vitrectomy[24]. The use of bevacizumab may accelerate the resorption of VH in patients who already had full PRP applied, but does not prevent recurrent bleeding and does not ensure full resorption of VH in all patients (28% had residual bleeding at the end of the study[25]).

Anti-VEGF therapy cannot replace surgical treatment, but its application shortly after the onset of VH may accelerate resorption and allow visualization of the fundus, and, consequently, enable decisions to be made regarding further therapy (PRP, vitrectomy; see Chapter 9: *Diabetic retinopathy management*, p. 189).

Tractional and rhegmatogenous retinal detachment in diabetic retinopathy

Shrinking fibrovascular membranes may cause tractional retinal detachment, which is usually an indication that surgical treatment is necessary. This is especially the case when the extent of the traction involves the macula[26]. Peripheral traction with local retinal detachment outside the fovea can be monitored without surgical intervention. However, surgery is necessary if the traction progresses.

Occasionally, significant traction also leads to retinal tears, penetration of the vitreous beneath the sensory retina and, as a consequence, to rhegmatogenous retinal detachment. Therefore, a mixed mechanism for the development of retinal detachment in DR patients can also be observed. Patients with simultaneous tractional and rhegmatogenous retinal detachment are at risk of severe and rapid vision loss and should be operated on urgently. It is worth remembering that increased traction especially affects younger diabetic patients, in whom the vitreous body strongly adheres to the retina, and its posterior surface provides a good scaffold for the development and progression of vascular proliferations[26].

The decision to perform a vitrectomy should be preceded by a careful examination of the fundus, in particular the extent and location of the vitreoretinal traction, the presence of tears and breaks in the peripheral retina and the involvement of the fovea (a panfundoscope should be used to assess the retinal periphery). In patients with PDR and local traction, a change in retinal architecture from concave to convex indicates the formation of a retinal tear and the development of a rhegmatogenous retinal detachment. Ultrasound is recommended for examining peripheral traction and OCT for traction in the macular area.

In tractional retinal detachment or detachment of mixed etiology, posterior vitrectomy should include such procedures as removing the vitreous cortex and its posterior border, ILM peeling (Fig. 5), removal of fibrovascular proliferation, drainage of subretinal fluid, securing the retinal tears, endophotocoagulation[27] (Fig. 6). It is worth mentioning that the use of anti-VEGF drugs alone in PDR patients with vitreoretinal traction entails the risk of rapid progression of the disease to retinal detachment[28, 29]. This form of treatment may sometimes cause shrinkage of the fibrovascular tissue, intensification of traction, formation of retinal tears and retinal detachment. Therefore, anti-VEGF agents should only be administered in such patients in addition to scheduled surgical treatment.

The following situations are indications for immediate surgical treatment in the case of present or imminent tractional retinal detachment in PDR:

- macular involvement,
- fast progression of traction, even without macular involvement,
- retinal detachment of mixed etiology: tractional and rhegmatogenous,
- the presence of neovascularization of the iris (an indication for preoperative anti-VEGF therapy).

Advanced fibrovascular proliferation without retinal detachment

In some patients, most often young people with DM1, PDR progresses rapidly with intense growth of fibrovascular tissue, despite intense retinal photocoagulation. Such patients are candidates for surgical treatment (Figs. 7–8). The DRVS group in a large randomized trial showed the advantage of early vitrectomy over laser photocoagulation for such cases[7, 8]. Among patients undergoing PPV within three months of diagnosis of aggressive retinopathy, 44% achieved good visual acuity (BCVA 6/12 and more), assessed four years after surgery. In the group treated with laser therapy, the percentage of people with such

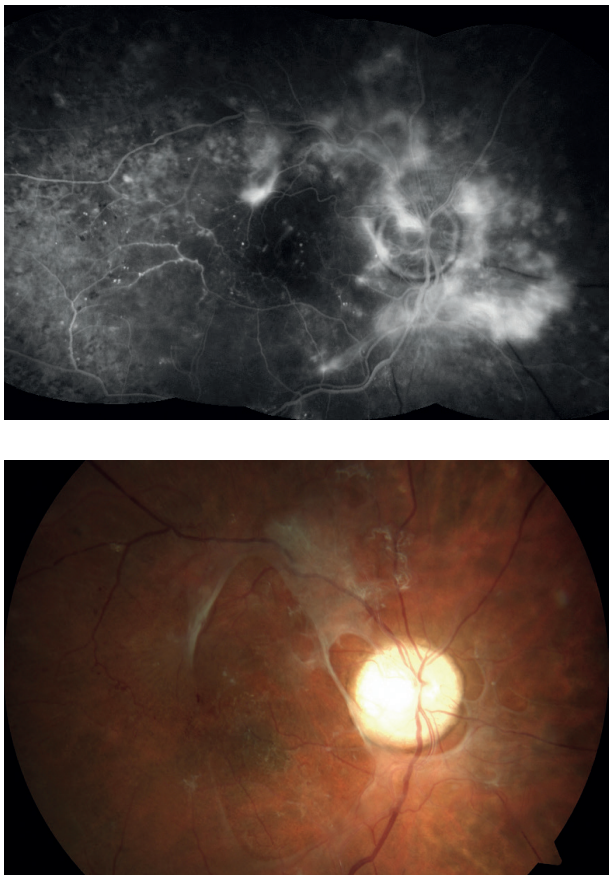

Figure 7. Significant fibrous proliferation in the posterior pole with traction in the macula. The patient is eligible for vitrectomy.

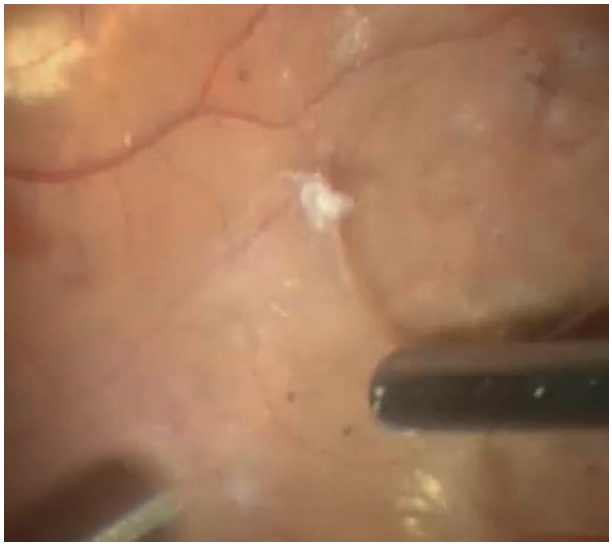

Figure 8. Removal of fibrovascular proliferations in the course of proliferative retinopathy.

good BCVA was only 28%. Subsequent studies by other authors confirmed the effectiveness of early vitrectomy in the treatment of PDR[30, 31, 32].

Vitrectomy for diabetic macular edema

In patients with DR, the posterior vitreous cortex becomes denser, which is a potential source of pathology of the vitreoretinal interface in the macular region[33]. Possible disorders include macular edema with increased vitreomacular adhesion (VMA) and traction (VMT), a partial- or full thickness macular hole secondary to macular edema, and epiretinal membrane (ERM).

The eligibility of DME patients for vitrectomy is still subject to debate by experienced vitreoretinal surgeons. Initially, posterior vitrectomy in DME was reserved for the previously mentioned cases with macular vitreoretinal interface pathologies[34, 35, 36]. Improvement in vision was obtained following most such surgeries, although cases of vision loss were also noted. A large study of DRCR.net (Protocol D) showed a BCVA improvement of 10 or more ETDRS letters in 38% of patients with DME and vitreoretinal traction treated with PPV. On the other hand, 22% of patients in this group had a deterioration in BCVA of 10 or more ETDRS letters. The anatomical results were good: the achieved central retinal thickness (CTR) was reduced by 160 μm on average, and in 68% of cases, the reduction in retinal edema was at least 50%[36]. Nowadays, PPV (most often with ILM peeling) is also tested in DME cases without vitreoretinal traction[37, 38]. Studies show that DME is less common in patients with posterior vitreous detachment (PVD)[39]. The effects of DME treatment are also better in patients who developed spontaneous PVD[40].

The mechanism behind the efficacy of PPV in the treatment of DME cases without traction is not fully understood. Several theories have been proposed. PPV may mechanically eliminate subclinical adhesion of the vitreous body, improve retinal oxygenation and eliminate proinflammatory and proedematous mediators accumulated in the vitreous[41, 42]. According to most reports, uncomplicated vitrectomy in these cases results in good anatomical outcomes, improving the condition of the inner and the outer retinal layers[43, 44]. However, morphological effects are not always reflected in improved visual acuity[45, 46]. It should be emphasized that the results regarding the improvement of BCVA after PPV in DME without traction varied widely between studies.

Most reports present a series of clinical cases, but as yet, there are no large randomized trials[47, 48, 49]. A meta-analysis by Jackson et al. of five randomized clinical trials on PPV in DME showed no statistically

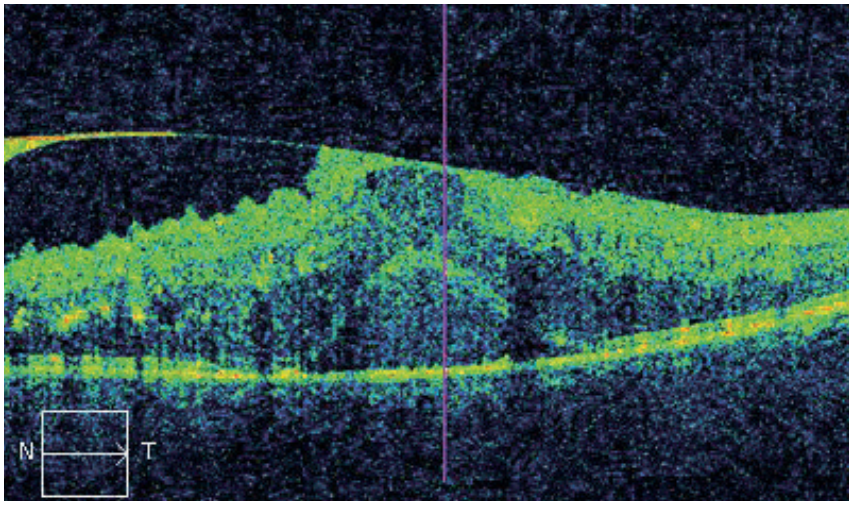

Figure 9. The SD-OCT scan shows a significant degree of diabetic macular edema with increased posterior vitreous adhesion and traction.

significant improvement in BCVA in favour of surgically treated patients compared with patients treated with laser photocoagulation or just observed[50]. In addition, the anatomical effect of the procedure was short-term. It should be remembered that surgical treatment always involves risks – in Jackson's meta-analysis, a retinal tear occurred in 7.1% of patients. The limited availability of such a procedure should also be taken into account, especially in terms of the number of potential patients.

It seems that posterior vitrectomy may be a good solution in selected cases of DME resistant to treatment with other methods (intravitreal injections, laser therapy), especially in the case of the coexistence of various pathologies at the vitreoretinal interface (epiretinal membranes, traction). Further randomized clinical trials are required to confirm the efficacy of PPV in non-tractional DME.

EURETINA recommends PPV for tractional DME[51]. According to these recommendations, PPV in non-tractional DME may be considered in the absence of a satisfactory response to other therapies.

Nowadays, we definitely start considering surgical treatment in diabetic retinopathy at an earlier stage than we did just a few years ago. The development of the surgical technique and equipment technology resulted in better and more predictable outcomes of PPV. Posterior vitrectomy can therefore also have a preventive effect – when visible symptoms on the fundus suggest rapid progression of retinopathy. Steel lists the following current indications for early vitrectomy in diabetic retinopathy[52]:

- rapidly progressive neovascularization with any VH or traction (PPV with laser endophotocoagulation and/or anti-VEGF therapy),
- any risk of developing tractional retinal detachment,
- in any situation of macular involvement visible in SD-OCT (Fig. 9).

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Chapter 11: Ophthalmic care for special diabetic patients: children, adolescents and pregnant women

The care of diabetic patients in any country of the world presents therapeutic and organizational challenges. Each country has its own system of care for such patients, usually involving an entire multidisciplinary medical team. One problem is that patients with diabetes (DM) do not always fit into standard therapeutic algorithms or screening systems and require a separate treatment regimen. This chapter is devoted to the treatment of the following groups of DM patients: children, adolescents and pregnant women.

Diabetic retinopathy in children and adolescents

Epidemiology

In any ophthalmic care system for diabetic patients and in diabetic retinopathy (DR) screening, it is important to optimize the costs of this care in terms of the recommended frequency of follow-up and the recommended diagnostic tests. In the case of children and adolescents, most of whom have type 1 diabetes (DM1), the important facts are associated with the occurrence of DR after the diabetes diagnosis.

Retinopathy in young patients does not develop immediately after the diagnosis of DM. Massin et al. studied a group of 504 children (aged 11–17) with DM1 who were participating in a summer camp in France. Colour photographs of the fundus taken in all of them revealed the presence of DR in 4.6%. In the age group of 10–13 years, the prevalence of DR was only 1%, in the age group 14–15 years, it was 5.8%, and in the group of adolescents 16–18 years – 17.7%[1]. In turn, Donaghue et al. studied young DM1 patients six years after their DM diagnosis. Diabetic retinopathy was found in 8% of children under the age of 11, 12% of pre-pubertal children, 25% of adolescents and 19% of pubertal adolescents[2].

In turn, Maguire et al. studied a group of 1,000 children and adolescents with DM1 who underwent annual ophthalmic monitoring. At the beginning of the study, some form of DR was found in 20% of patients[3]. Interestingly, in the following years, in the group of children under the age of eleven, DR regressed in 80%, and progression was not observed in any case. In the older group – over eleven years – DR regression occurred in 36% of cases and progression in 13%. None of the children developed proliferative retinopathy (PDR), and none required retinal laser photocoagulation.

In 2015, Geloneck et al. studied 370 children up to the age of eighteen with DM1 or DM2[4]. Diabetic retinopathy was not diagnosed in any of the children. The authors suggest regular ophthalmic examinations in children over the age of fifteen or after five years of developing diabetes, whichever occurs first.

As can be seen from the above data, the risk of children developing severe retinopathy is not high, and before the age of eleven, it is practically zero.

Risk factors for the development of diabetic retinopathy in children and adolescents

Like in adult patients, the risk of diabetic retinopathy in children increases with the duration of diabetes. Donaghue et al. estimate that the risk of developing DR increases by 28% for every prepubertal year of DM, and by 36% for each postpubertal year of DR[5]. Puberty is particularly important for the possible progression/onset of DR in children and adolescents. Natural resistance to insulin develops with age, and

metabolic control during adolescence is usually much poorer. The risk of developing DR is 30% higher in each year post menarche compared with pre-pubertal years[6].

Donaghue argues that the years before puberty are protective in the context of DR development[5]. According to the author's research, diabetic retinopathy appears significantly later (by 2–4 years) in patients diagnosed with DM before the age of five than in patients diagnosed with DM after the age of five.

Systemic treatment and risk factor control

The Diabetes Control and Complications Trial group conducted a study on 195 adolescent patients with DM, analysing the effectiveness of systemic treatment. According to the authors, intensive diabetes treatment reduces the risk of progression of mild retinopathy by 53% compared to conventional insulin therapy[7]. The extension arm of the study showed very beneficial long-term effects of such treatment. The risk of developing DR in subsequent years was much lower in patients undergoing intensive insulin therapy[8].

Young patients with poorly controlled diabetes are a particular problem. The American Academy of Pediatrics (AAP) believes that patients with DM1 for over ten years and glycated hemoglobin (HbA1c) values above 10 mg% may develop advanced retinopathy very quickly and should undergo frequent ophthalmic evaluation[9]. A large study in Sweden showed that HbA1c values below 7.6% may delay PDR development up to 20 years[10].

The relationship between high blood pressure and DR incidence is not straightforward. In the available studies, however, the authors state that young patients with DR have higher blood pressure than patients without DR[1, 11]. Some studies also show that high BMI may be a risk factor for DR development in children[12].

Screening regimens

Considering the cost rationalization of the diabetes care system, it is necessary to develop an effective DR screening system for younger patients. While the application of a strict monitoring system is unlikely to be questioned in adults diagnosed with retinopathy and adequately classified, in young patients it does not have to be restrictive. Firstly, monitoring very young people with DM does not appear to provide any ophthalmic information, since they do not develop retinopathy. Secondly, until adolescence there is practically no recorded retinopathy progression to the borderline stages of DR classification (threshold disease)[13]. It is known that puberty is the moment when rapid progression of DR can occur, so we need to determine the point in time when a young patient's regular ophthalmological evaluation should begin.

Practical recommendations for the ophthalmic management of children and adolescents with DM

- annual monitoring starting from the age of 9–10, especially after five years of developing diabetes,
- intensive diabetes care,
- thorough ophthalmological monitoring during adolescence, with the frequency depending on the presence of retinopathy, its severity, and glycemic control.

Currently, there is no single rigid regimen for DR screening in children and adolescents. The American Academy of Ophthalmology (AAO) recommends annual ophthalmic examination five years after the diagnosis of DM[14]. The American Diabetes Association recommends regular ophthalmological monitoring 3–5 years after the diagnosis of DM and from the time the patient is ten years old[15]. The AAP recommends annual follow-up 3–5 years after the diagnosis of diabetes and after the patient reaches the age of nine[9]. On the other hand, the International Society for Pediatric and Adolescent Diabetes recommends an annual follow-up in patients over eleven years of age if the duration of DM is more than two years, or annual follow-up after nine years of age if the duration of diabetes is more than five years[16].

Ophthalmic treatment for children and adolescents with diabetic retinopathy

Local ophthalmic treatment is usually unnecessary in young DM patients because they rarely develop retinopathy requiring intervention. However, adolescents in puberty may develop advanced retinopathy requiring local therapy. Laser treatment is then administered according to the generally accepted principles discussed earlier (see Chapter 9: *Diabetic retinopathy management*, pp. 177–188). Naturally, patient cooperation can be a problem, especially at younger age.

In the event of significant diabetic macular edema (DME), which is very rare, intravitreal therapy may be considered; however, it should be borne in mind that there is limited data on the use of intravitreal agents in children and adolescents and the Summary of Product Characteristics (SmPC) should be consulted. In the case of aflibercept, the SmPC does not allow the drug to be administered to children and adolescents. We find the same information in the SmPC of Ozurdex. On the other hand, while the SmPC of ranibizumab states that the safety of this drug in children and adolescents has not been confirmed, it refers to the results of the MINERVA study in which ranibizumab was used in adolescent patients (12–17 years old) and no complications were found[17]. We know from practice that anti-VEGF therapy is quite commonly used in children with such diseases as retinopathy of prematurity, Coats' disease or angioid streaks[18, 19, 20, 21]. Logic dictates that this form of treatment should not be abandoned in patients with DME below the age of 18, and it seems rational to choose a drug without clearly defined contraindications for administration in children, i.e. off-label ranibizumab or bevacizumab.

Diabetic retinopathy in pregnant women

Epidemiology and risk factors

DM patients of childbearing potential are advised to plan their pregnancy. According to recommendations, the best age to get pregnant is before the age of 30 in most cases. Pregnancy may cause DR progression in some patients regardless of other risk factors[22, 23]. The mechanism of this progression is not fully understood, but it is undoubtedly caused by the growth factors present in the blood.

Rahman reports the progression of retinopathy during pregnancy in 24% of DM1 patients[24]. A similar percentage is reported by Vestgaard et al. (27%) and Egan (25.9%) in a large multi-center study[25, 26].

In addition to pregnancy, there are other additional risk factors that influence the progression of DR in pregnant patients. An important factor is the severity of retinopathy at the beginning of pregnancy[27]. Generally, if a patient does not show any evidence of retinopathy prior to pregnancy, approximately 10% of cases will progress to some form of retinopathy. Only 0.2% of such patients develop PDR. In turn, in patients with non-proliferative retinopathy (NPDR) at conception, we observe the progression of retinopathy during pregnancy in up to 50% of cases. The advancement of NPDR usually improves in the third trimester of pregnancy and after delivery. In 5–30% of cases, there is a progression of NPDR to PDR. The risk of such progression is greater if the patient has developed severe NPDR prior to pregnancy. In other words, the severity of retinopathy at the beginning of pregnancy is a significant risk factor for its progression during pregnancy[27, 28]. During this period, proliferative retinopathy may worsen in 50–60% of cases. Diabetes duration is a risk factor for the worsening of PDR and progression of NPDR to PDR[28]. However, it seems that this risk factor is of less importance than the stage of DR at the beginning of pregnancy.

Performing retinal laser treatment reduces the risk of PDR progression by up to 50%. It has been shown that when the proliferative changes have completely regressed before pregnancy, they do not recur during pregnancy[24, 29].

Another important risk factor for the progression of DR during pregnancy is poor metabolic control of diabetes

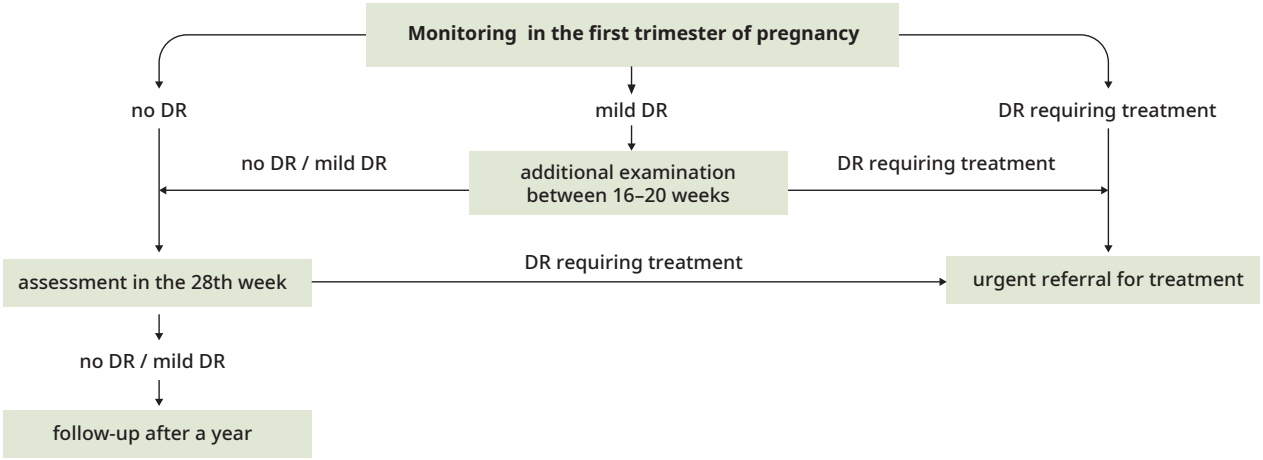

Figure 1. Ophthalmic monitoring in patients with diabetes in pregnancy according to NICE[31].

at conception. On the other hand, rapid normalization of metabolic parameters during pregnancy may cause progression of retinopathy, so it has to be achieved with the close monitoring of the patient.

In a study by Egan et al.[26], one of the major additional risk factors identified for DR progression was a significant reduction in HbA1c between the first and third trimesters of pregnancy. These reports are consistent with the earlier Diabetes in Early Pregnancy Study[24]. Patients who had poor metabolic control of their diabetes at the beginning of pregnancy, but achieved improvement in the following trimesters, showed the greatest progression of DR[26, 27, 30].

An important risk factor for the progression of DR in pregnancy, consistently mentioned in both older and newer studies, is arterial hypertension[23, 26, 27]. Maintaining correct blood pressure during pregnancy is critical to controlling retinopathy itself.

Ophthalmological monitoring before and during pregnancy

The British National Institute for Health and Care Excellence (NICE) recommends that women with DM who plan to get pregnant should have their retina examined and photographed. If local therapy is necessary, it is recommended that the intensive optimization of blood glucose levels should be postponed until ophthalmic treatment is completed[31]. Detailed NICE ophthalmological recommendations for pregnant patients are presented below.

Recommendations for the ophthalmic control during pregnancy of patients with DM – NICE recommendations[31]:

- retinal assessment with digital imaging (the pupils dilated only with tropicamide) at the first antenatal clinic appointment (unless an examination has already been performed in the last three months),
- additional retinal assessment in the 28th week of pregnancy,
- if retinopathy is revealed during the first visit, additional examination between 16–20 weeks,
- close monitoring of women with pre-proliferative or more advanced retinopathy for six months after delivery,
- the mere presence of diabetic retinopathy is not a contraindication to vaginal birth.

Figure 1 presents a diagram of the above recommendations.

The AAO recommends ophthalmic examination in the first trimester and subsequent examinations depending on the severity of DR: in the case of mild NPDR every 3–12 months, in the case of severe NPDR every 1–3 months[32].

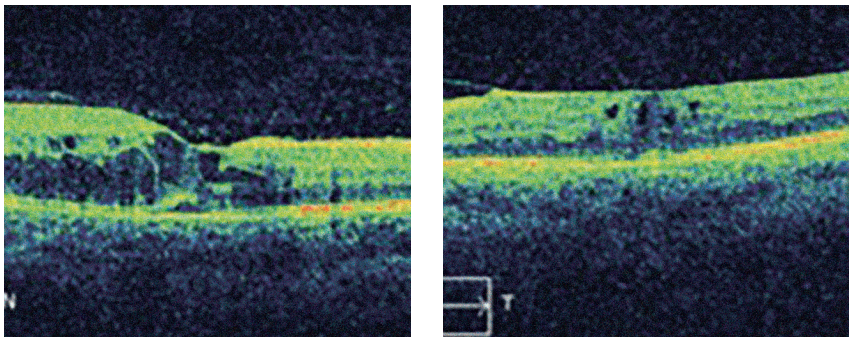

Figure 2. Diabetic macular edema in the right and left eye two months before delivery.

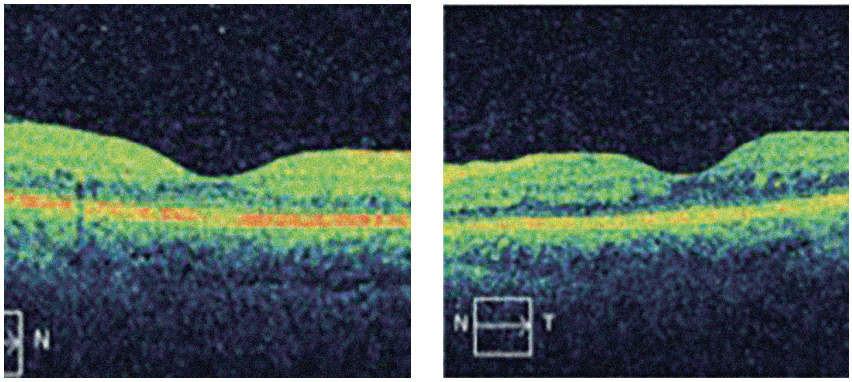

Figure 3. Spontaneous regression of diabetic macular edema in both eyes one month after delivery.

Gestational diabetes (GDM) is not associated with the risk of developing retinopathy, and such cases do not require ophthalmic monitoring during pregnancy.

Ophthalmic treatment in pregnancy

As mentioned earlier, for a woman with DR, the optimal standard of care is to have the condition stabilized prior to pregnancy. Therefore, laser treatment procedures (primarily panretinal photocoagulation in PDR) should be performed before conception. However, if for some reason such therapy has not taken place, and the local condition requires it, laser photocoagulation should be performed during pregnancy – waiting until after delivery is not advisable.

Diabetic macular edema may develop and/or worsen during pregnancy. The risk of developing DME affects mainly women with proteinuria and hypertension. In a large percentage of postpartum cases, macular edema regresses spontaneously[26, 33, 34] (Figs. 2–3). Therefore, the most common management of DME in pregnant patients is waiting for delivery and spontaneous remission of edema, possibly starting treatment after delivery. The available methods of DME therapy, primarily intravitreal injections of anti-VEGF agents and steroids, carry the risk of teratogenicity due to their mechanism of action. So far, there are few reports on the use of these agents in pregnancy[35, 36, 37], so it is difficult to rely on clinical studies in this area. According to the SmPCs, the use of ranibizumab, aflibercept or dexamethasone during pregnancy is not recommended unless the potential benefit outweighs the possible risk to the fetus. In practice, the risk of administering these drugs to pregnant patients is very rarely taken, and if medication is absolutely necessary, then steroid drugs are selected.

Practical recommendations for the ophthalmic management of patients with DM in the context of pregnancy

- planning conception,
- stabilization of the local condition before pregnancy (laser treatment),
- regular ophthalmic examinations according to the NICE or AAO regimen,
- if necessary, immediate laser treatment during pregnancy.

The presence of a stable DR is not an indication for delivery by caesarean section[38]. However, in the presence of active PDR, caesarean section should be considered[39].

Summary

The management of patients with DR requires standardization. Failure to apply specific therapeutic algorithms results in uncontrolled disease progression in patients and, consequently, higher treatment costs and burdens for the healthcare system. Certain diabetic patients, such as children, adolescents and pregnant women, also require an individual medical approach and a separate procedures according to specific algorithms. There is a need to implement such management in everyday medical practice.

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Chapter 12: Ophthalmic conditions associated with diabetic retinopathy

Cataract

Diabetic retinopathy and cataract

Diabetes mellitus (DM) is a risk factor for cataract development. In the diabetic population, cataracts occur more frequently and earlier than in the general population[1, 2, 3, 4]. In younger diabetics, cataracts develop more frequently in insulin-treated patients, while in older patients, the proportion of cataracts is similar for insulin-dependent and non-insulin-dependent DM[5]. Gruslund et al. showed that in the population of patients with type 1 diabetes (DM1), cataracts occur on average 20 years earlier than in the non-diabetic population[6]. In a study conducted by Harding et al., diabetes was the cause of 11% of all diagnosed cataracts[7]. It is estimated that several to several dozen percent of all cataract surgeries performed in the world involve patients with diabetes[8]. In the USA, this number is as high as 40%, or 22.3% if only outpatient operations are counted[9, 10].

Cortical cataracts are typical for diabetes, and their occurrence is often independent of sugar level fluctuations[11, 12]. Posterior subcortical cataracts are usually associated with poor glycemic control[13, 14].

The coexistence of cataract and diabetic retinopathy (DR) has therapeutic implications, depending on the severity of these two diseases and glycemic control. When advanced cataract and DR coexist, the goal of cataract surgery is not only to improve visual acuity, but also to enable treatment of the retinopathy itself. Even if it is not very advanced, a cortical cataract might make it impossible to perform effective laser treatment of the retina. This situation is an indication for prompt cataract surgery, especially in the case of proliferative diabetic retinopathy (PDR).

The coexistence of cataract and DR is not uncommon. A large study of cataract surgery patients conducted in Malaysia indicated that 37.1% of them had diabetes, and 10.7% had diabetic retinopathy[15]. In a retrospective analysis from Auckland, New Zealand, these proportions were 31% and 8%[16].

The exacerbation of diabetic retinopathy after cataract surgery

Each surgical procedure, including cataract surgery, induces inflammatory processes. Inflammatory mediators also reach the posterior segment of the eyeball and can theoretically influence the course of retinopathy. Liu et al. investigated the thickness of the retina after uncomplicated cataract surgery in diabetic patients in a group without retinopathy and in a group with mild and moderate non-proliferative diabetic retinopathy (NPDR)[17]. In the NPDR group, the central retinal thickness was significantly increased in the first, third, and sixth months after surgery as compared to the group without retinopathy. Similar results have been reported by Stunf et al.[18].

The progression of retinopathy after cataract surgery is frequently analysed in the medical literature, although not all studies have confirmed such a scenario. Reports of DR progression after cataract surgery were more often related to the technique of intracapsular and extracapsular extraction than phacoemulsification[19, 20, 21, 22]. Due to the development of this surgical technique, the use of a small incision, and a shorter procedure time, the percentage of complications related to the surgery itself has significantly decreased. Currently, the prevailing opinion is that uncomplicated cataract surgery performed with phacoemulsification technique does not significantly worsen mild and moderate retinopathy[23, 24, 25].

However, although few in number, some studies show such deterioration related to the procedure itself. Their authors report that the exacerbation of retinopathy affects about 15–30% of patients[26, 27, 28, 29]. The risk of progression is greater in more severe retinopathy and retinopathy eligible for laser photocoagulation, and in patients with poor glycemic control[30, 31, 32].

The deterioration may also include the onset or exacerbation of diabetic macular edema (DME). To some extent, this is related to the potential development of cystoid macular edema (CME), which is one of the complications associated with the surgical treatment of any cataract. (Sometimes this clinical entity is referred to as pseudophakic macular edema). Nowadays, its incidence is estimated at 0.1–2.35%[33]. Patients with diabetes are at greater risk of developing such edema than those with non-diabetic cataracts.

Kim reports the incidence of CME up to three months after cataract surgery in diabetic patients to be at 22%. This study assessed CME using optical coherence tomography (OCT) as the main diagnostic method[34]. In turn, in a study of DM2 patients, Samanta et al. found CME in 47% of patients without retinopathy and 55% of patients with retinopathy within the eight weeks after cataract surgery[35]. Eriksson et al. demonstrated the presence of significant CME, defined as the loss of at least five letters on the ETDRS chart, in 6% of non-diabetic patients and 12% of diabetic patients up to six weeks after cataract surgery[36].

After analysing 81,984 eyes, the United Kingdom Pseudophakic Macular Edema Study Group reported an increased risk of pseudophakic macular edema in diabetic patients, even without retinopathy. For diabetics with retinopathy, the risk of occurrence of DME after surgery was even greater and increased with the severity of the retinopathy[37]. The American group DRCR.net also confirmed the risk of CME development after cataract surgery in diabetic patients[38]. Similarly to the exacerbation of diabetic retinopathy, the occurrence of CME after cataract surgery in diabetes is also associated with poor glycemic control, insulin dependency, the severity of retinopathy, and the course of surgery (greater duration and the amount of ultrasound used)[39]. Therefore, it is advisable that only experienced surgeons perform cataract surgery in diabetic patients.

CME prevention is a very important element in the preparation and management of a DM patient. According to a large meta-analysis of data from the medical literature, the most effective topical medication (eye-drops) used for that purpose in diabetic patients is a combination of nonsteroidal anti-inflammatory drugs (NSAID) and corticosteroids[40]. The administration of NSAID drops begins 1–3 days before the procedure. The Polish Ophthalmological Society (PTO) recommends the use of topical NSAID drugs for at least four weeks, topical corticosteroids for 2–4 weeks, and topical antibiotic drops for 7–14 days after surgery with DM patients. The time to administer the drops may be extended in selected high-risk cases, including DR. Among the NSAIDs used after cataract surgery on diabetic patients, the PTO recommends nepafenac due to its good penetration to the posterior segment of the eyeball[41]. In diabetic patients, Nepafenac is recommended 3 times daily for 60 days after the surgery.

Managing diabetic retinopathy with cataract (based on the Royal College of Ophthalmologists)[42]

1. The best possible control of DM before surgery.
2. Performing adequate retinal laser photocoagulation (PRP) before surgery in patients with PDR, if visualization of the fundus is possible.
3. Prompt continuation of laser treatment after cataract surgery in patients with PDR who did not manage to undergo full PRP before surgery.
4. Treating DME before surgery, if possible.
5. Strict monitoring of DR and DME for several months after the procedure: examination of the fundus, spectral optical coherence tomography (SD-OCT) of the macula.

6. Prevention of postoperative CME: topical NSAIDs and corticosteroids. Usually, non-steroidal anti-inflammatory drugs are used from 1–3 days before surgery to 4–6 weeks after surgery. Topical steroids are usually recommended 2–4 weeks after surgery.
7. Periocular or intravitreal therapy with steroids or intraocular anti-VEGF drugs after surgery in the case of persistent/deteriorating CME/DME.

Cataract treatment outcome in patients with diabetic retinopathy

Studies report improved visual acuity in patients with DR after cataract surgery. A large study conducted in several South American countries showed an improvement in all diabetic patients who had cataract removed – from an average of 0.82 logMAR to 0.14 logMAR (from 0.15 to 0.7 on Snellen chart)[43]. An analysis of cataract treatment effects in DR patients undergoing retinal laser photocoagulation was performed by ETDRS one yearafter cataract surgery[44]. Improvement in visual acuity by at least two lines on the ETDRS chart was demonstrated in 64.3% of patients undergoing early laser therapy and 59.3% of patients undergoing deferred laser therapy. Treatment outcomes were better in patients with mild to moderate NPDR, 53% of whom achieved BCVA of 20/40 or a better score. In the group with severe NPDR and worse, only 23% achieved such visual gain. In a study by Krepler et al. BCVA was improved by 85% of patients with mild and moderate NPDR, 71% of whom had visual acuity better than 0.5 Snellen[23]. The difference between the effects of cataract treatment in the group of patients with mild NPDR and severe diabetic retinopathy has also been confirmed in later studies[45].

It should be emphasized that although the main goal of cataract surgery is to improve vision, it should also be considered in patients in whom the main goal of cataract removal is to create conditions for the treatment of diabetic retinopathy. There are patients who do not notice a significant improvement in visual acuity after surgery, but cataract removal will enable the continuation of retinopathy treatment and will make it possible to maintain their current vision or improve it in the future.

Technical aspects of surgery and postoperative follow-up in diabetic patients with cataract[9]

1. Surgical technique. In the case of incipient and moderately advanced diabetic cataracts, the most common are cortical and subcapsular opacifications, with soft lens nucleus. Surgical treatment of such cataracts can be problematic for less experienced surgeons. The technique of nucleus chopping is usually not successful in such situations. Often, both the cortical and epinucleus masses adhere quite tightly to the lens capsule and take longer to remove. On the other hand, in the case of mature cataracts in DM patients, intraoperative problems concern the removal of the nucleus itself. Such a cataract is rubbery in consistency, which makes it difficult to divide. Procedures are usually time-consuming and may generate intraoperative complications, such as lens subluxation or posterior capsule rupture.
2. Dilation of the pupil. Poor mydriasis is not uncommon in patients with diabetes. Difficulty in achieving full pupil dilation sometimes results in the need for iris retractors.
3. Greater risk of conjunctival and iris bleeding. DM patients may have blood clotting disorders and prolonged bleeding times. This means that even simple procedures on the conjunctiva can be a source of significant bleeding – hematomas and edema may appear. Additionally, the cases involving neovascularization of the iris, the risk of bleeding into the anterior chamber of the eye increases, which may make the procedure more difficult.
4. Posterior capsular opacification (PCO). According to some studies, PCO after cataract surgery is more common in patients with DM than in patients without DM. Most authors believe that the difference in the incidence of PCO in patients with DM and without DM is significant in the period from one year to one and a half after surgery, but it is not

noted several weeks after surgery and several years after surgery[46, 47, 48]. Some DM patients therefore require posterior capsulotomy with an Nd:YAG laser, usually one year after cataract surgery.

5. Risk of ocular inflammation. Intraocular inflammation is a rare complication occurring in approximately 0.02–0.04% of all cataract surgery cases[49, 50]. Diabetes mellitus increases the risk of such a complication[51]. Among patients with endophthalmitis after cataract surgery, approximately ¼ are diabetics[48, 49, 52]. It is believed that poor glycemic control is a risk factor for the development of endophthalmitis, but since this complication is very rare, there is a lack of extensive research. Perioperative prevention of endophthalmitis is particularly important in diabetic patients, especially the intraoperative administration of cefuroxime[53, 54].

Summary

- Cataracts occur earlier and more frequently in people with diabetes than in the general population.
- After cataract surgery, diabetic retinopathy may be exacerbated, and such cases should be closely monitored.
- For preventing cystoid macular edema after cataract surgery, topical NSAID drugs are usually used for 4–6 weeks, and topical steroids for 2–4 weeks.

Glaucoma

Diabetic retinopathy and glaucoma

Primary open-angle glaucoma (POAG) is one of the most frequently treated ophthalmic diseases. The relationship between the incidence of POAG and diabetes is unclear. A large number of publications show that diabetes is a risk factor for the development of POAG[55, 56, 57, 58], but there are also studies that do not confirm this relationship[59]. The Ocular Hypertension Study Group has even shown that diabetes protects against the risk of developing POAG[60]. Currently, no clear correlation can be found between diabetes and the occurrence of POAG. If POAG is diagnosed in a patient with diabetes, treatment is carried out according to generally accepted principles of treating this clinical entity.

Secondary neovascular glaucoma (NVG) is of greatest interest to the ophthalmologist and diabetologist in charge of a patient with diabetic retinopathy.

The source of NVG is hypoxia of the intermediate and distal periphery of the retina and, consequently, the production of vascular endothelial growth factor (VEGF) – as well as other vasoproliferative factors – by the retina and ciliary body. These particles pass into the vitreous, and then into the aqueous humor. Through the aqueous humor, neovascularization is stimulated in the iris (NVI) and in the iridocorneal angle (NVA). The consequence of neovascularization in these locations is bleeding, the formation of synechiae and scarring at the angle and, as a result, obstruction of the outflow of aqueous humor from the anterior chamber. The pressure in the eyeball usually increases significantly, which poses a direct threat of vision loss.

It has been demonstrated that a high concentration of VEGF in the aqueous humor is closely related to the occurrence of anterior segment neovascularization, and this fact has therapeutic consequences, i.e. for the effectiveness of retinal laser therapy and anti-VEGF therapy in the treatment of this clinical entity[61].

Anatomically, NVI is associated with the formation of a myofibroblastic membrane on its anterior surface, which contracts, causing ectropion of the iris margin with exposure of pigment epithelium and the formation of synechiae in the iridocorneal angle (NVA)[62]. The newly formed vessels are located under the membrane. Neovascularization typically tends to affect the anterior surface of the iris (Fig. 1), but there are cases of vessel growth on its posterior surface, towards the surface of the ciliary body, and in the lumen of the pupil – onto the lens[63]. In such situations, hemorrhage into the anterior chamber is not uncommon.

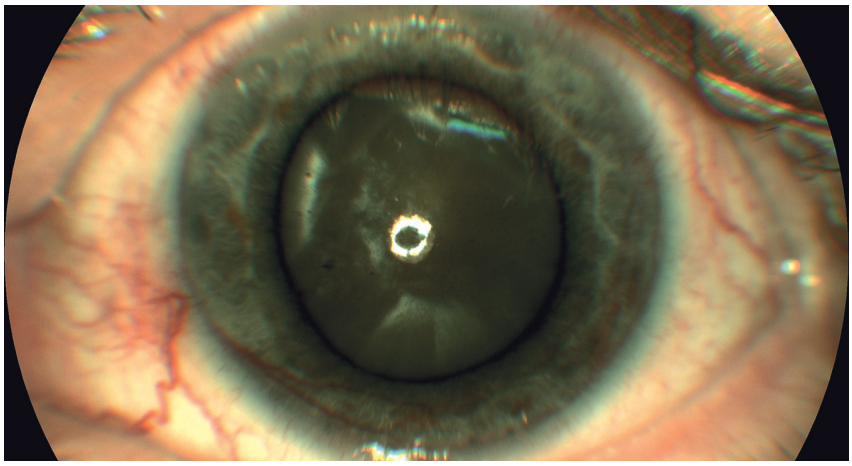

Figure 1. Rubeosis iridis in neovascular glaucoma.

Neovascularization of the iris itself does not necessarily cause neovascular glaucoma, but its occurrence entails a significant risk of developing this disease and requires prompt therapeutic intervention.

The incidence of NVI and NVA

The incidence of NVI depends on the severity of the diabetic retinopathy. NVI most commonly affects patients with PDR, but it also occurs in a certain percentage of patients with NPDR[64, 65]. NVI in NPDR usually concerns severe non-proliferative lesions, but the effects of retinal hypoxia seen in the anterior segment may sometimes appear even in mild retinopathy (although they do not cause secondary glaucoma in most cases). Bandello et al. analysed the sensitivity of anterior segment fluoroangiography to assess NVI in diabetic patients. Of the patients with known advanced neovascularization of the iris and/or of the angle, all had proliferative or pre-proliferative retinopathy, while of those with initial NVI, 58% had either NPDR or no retinopathy, and 42% had either PDR or pre-proliferative retinopathy[66].

Hamanaka et al. analysed the relationship between the size of areas of peripheral retinal ischemia and the incidence of NVA in proliferative diabetic retinopathy[67]. The strongest risk factor for NVA was the lack of perfusion of more than 50% of the far and mid retinal periphery. Other studies also confirm the key role of ischemia of the far retinal periphery in the pathogenesis of neovascularization of the anterior segment of the eye[68, 69].

Additional risk factors for NVI development in DR patients include previous posterior vitrectomy and cataract surgery, as both procedures create conditions for easier VEGF circulation and facilitate their penetration into the aqueous humor[70, 71, 72]. However, not all researchers consider these risk factors significant, especially in the age of modern surgical techniques[73]. Additionally, the peri- or intraoperative addition of anti-VEGF therapy to posterior vitrectomy significantly reduces the risk of developing NVI and NVG after surgery[74, 75, 76].

The percentage of patients with NVI in the diabetic population as determined by slit lamp examination is not very high. The Diabetic Retinopathy Study (DRS) group reports that patients with NVI in the PDR group constitute only 2.3%[77]. Funatsu et al. estimate the percentage of patients with NVI at 1.5% in the entire population of patients with DM2[78].

Course of the disease

Usually, in the first stage of neovascularization of the iris, pathological vessels are formed at the pupil margin. Neovascularization of the angle and in the peripheral sectors of the iris usually occurs later[79] (Fig. 2). This situation differs from ischemia in the course of central retinal vein occlusion, where not infrequently

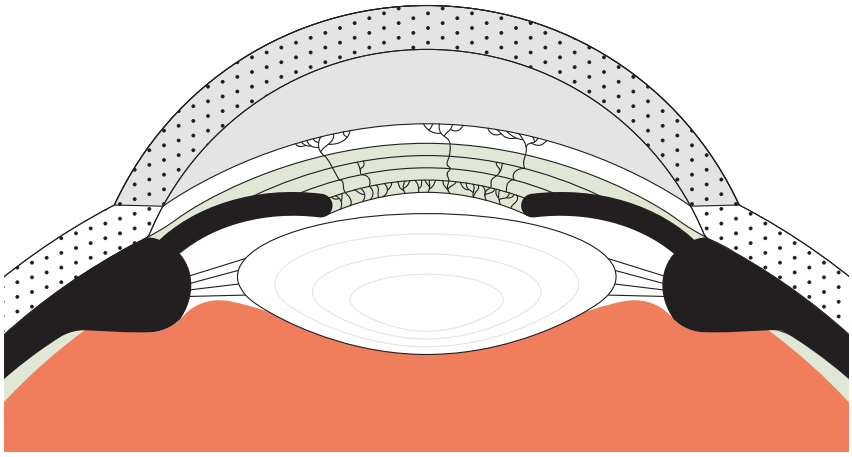

Figure 2. Iris and iridocorneal angle (NVA) neovascularization. Visible progression of vascular neovascularization from the pupil margin to the iridocorneal angle.

(12%) NVA appears before neovascularization of the iris itself or without this neovascularization and shows rapid progression to secondary glaucoma[80].

A rare complication observed after posterior vitrectomy is fibrovascular proliferation on the anterior surface of the vitreous, more commonly seen in the past[81, 82]. The complication was most common in young people with DM1 and severely ischemic advanced retinopathy. Fibrovascular proliferation extended from the peripheral part of the retina to the posterior surface of the iris and lens. As a consequence, this led to frequent hemorrhages into the vitreous and anterior chamber, lens dislocation and detachment of the ciliary body. Thanks to better care for diabetic patients and advances in the surgical technique, this complication is rare nowadays.

Ophthalmic examination for suspected secondary glaucoma in diabetic retinopathy

1. Intraocular pressure measurement. This is the basis for the diagnosis of secondary glaucoma. It should be performed routinely with ophthalmic patients who have diabetes mellitus, especially when NVG is suspected and for monitoring of treatment effects.
2. Slit lamp examination of the iris without dilatation of the pupil. Often in the diagnosis of DR, ophthalmologists focus on examining the fundus with a dilated pupil, without carefully looking at the undilated iris. It has to be emphasized, that any possible NVI must be evaluated before administering the pupil dilating drops. NVI is a good marker of retinal ischemia, and its detection is a vital factor in qualifying a patient for PRP and/or anti-VEGF therapy besides retinopathy severity[83, 84].

During the examination, NVI should be distinguished from the dilated iris vessels in the course of inflammation or vascular anomalies. Light irises are associated with easier diagnosis process, while brown irises are more challenging and sometimes require supplementary anterior segment angiography.

3. Anterior segment fluorescein angiography. This test facilitates the diagnosis of NVI and is more sensitive to iris neovascularization than a conventional slit-lamp examination, especially in the case of dark irises. Additionally, by performing an anterior segment angiography, NVI can be diagnosed before it is visible in a simple slit-lamp examination[85]. Identifying NVI in a diabetic patient with mature cataract that does not allow fundus examination influence therapeutic management, e.g. planning anti-VEGF and/or PRP therapy soon after surgery.
4. Gonioscopy. This procedure involves NVA evaluation. In DR, gonioscopy is usually not necessary to diagnose NVI, because neovascularization of the iris in DR occurs earlier than NVA. The presence of NVA indicates significant retinal ischemia.

Table 1: Diagnosis and management according to the stage of NVG[86].

NVG stage	Symptoms	Treatment options
1	NVI and/or NVA present, open angle and no IOP increase	• prompt PRP alone or with anti-VEGF intravitreally or intracamerally • if it is not possible to obtain a clear view of the fundus – removal of the cause: PPV with endophotocoagulation, cataract removal
2	NVI and/or NVA present, open angle, increased IOP	• control of IOP with topical medications • in the case of pain and inflammatory reaction: topical steroid drops and cycloplegics • PRP, anti-VEGF intravitreally or intracamerally • if it is not possible to obtain a clear view of the fundus, treatment as in stage 1 • in the case of insufficient IOP control – further procedures: surgical and cyclodestructive
3	NVI and/or NVA present, synechiae in the angle, angle partially closed, increased IOP	• mostly surgical treatment, often combined with PRP and anti-VEGF • cyclodestructive procedures (the choice of treatment depends on the eye's potential to maintain vision)

NVG – neovascular glaucoma, NVI – neovascularization of the iris, NVA – neovascularization of the angle, IOP – intraocular pressure, PRP – panretinal panphotocoagulation, PPV – pars plana vitrectomy

Treatment of NVG and NVI

The treatment strategy for NVG and the management of NVI depend on the cause of neovascularization and the stage of the disease (Table 1). The principle of therapy at its early stage is to respond appropriately to the pathophysiology of the disease. For example, the diagnosis of retinal ischemia on funduscopic examination and fluorescein angiography determines the course of further treatment. In addition, it is helpful to determine the stage of the disease by slit lamp examination and gonioscopy[86].

The diagnosis of NVI means that therapy must begin immediately, even in the absence of increased intraocular pressure. The main goal of treatment after diagnosis of NVI is to prevent the development of neovascularization in the iridocorneal angle. The mere presence of NVI without increases in intraocular pressure is not a source of pain. Symptoms, primarily painful reactions, appear when secondary glaucoma develops.

Treatment methods for NVG and NVI

1. Panretinal photocoagulation. Intensive laser therapy of the hypoxic retinal periphery destroys large areas of the RPE and photoreceptors, which consume about ⅔ of the oxygen utilized by the retina. As a consequence, the oxygen demand of the retina decreases and the perfusion of the surviving retinal layers improves. VEGF production decreases, and vascular growth regresses[87, 88, 89]. The effect depends on the extent of the panretinal photocoagulation (the size of the area undergoing PRP) and does not occur immediately[90].
2. Anti-VEGF therapy. Administration of VEGF inhibitors into the vitreous and/or anterior chamber

inhibits vascular growth and may lead to its regression from the anterior segment[91, 92]. Wang et al. have shown that intravitreal administration of ranibizumab to patients with NVG significantly – but temporarily – lowers elevated aqueous humor VEGF-A levels[93]. Anti-VEGF therapy is used in conjunction with PRP – for example, treatment may begin with anti-VEGF agents[94]. It should be remembered that the use of anti-VEGF agents in NVG is auxiliary and cannot replace panretinal photocoagulation and/or surgical treatment[95].

Pharmacological treatment

In the event of increases in intraocular pressure, antiglaucoma medications should be used to lower IOP and relieve pain. In the treatment of NVG, usually beta-blockers, alpha-2 agonists and carbonic anhydrase inhibitors are used. Prescribing prostaglandins should rather be avoided, due to the risk of exacerbating the inflammatory reaction. Myotics such as pilocarpine are similarly contraindicated since they exacerbate the inflammatory process and may lead to the formation of posterior synechiae. In some situations, atropine drops can be applied to reduce pain through cycloplegia and improve outflow via the uveoscleral pathway. If IOP is not stabilized after the application of drops, oral carbonic anhydrase inhibitors can be used. The use of those drugs is not a causal treatment, so the patient should undergo laser therapy and/or anti-VEGF therapy in parallel. PRP and anti-VEGF therapies are used to treat both NVI and NVG. When intraocular pressure peaks are not controlled with those procedures, glaucoma surgery should be performed.

Surgical treatment

Surgical treatment is scheduled when the previously described treatment methods are ineffective, i.e. when there is advanced anterior neovascularization and synechiae in the iridocorneal angle. The aim of surgical treatment is to reduce intraocular pressure by facilitating the outflow of aqueous humor from the anterior chamber of the eye or reducing its production. This section presents the principles of surgical treatment of neovascular glaucoma. Detailed descriptions of surgical techniques can be found in specialized manuals.

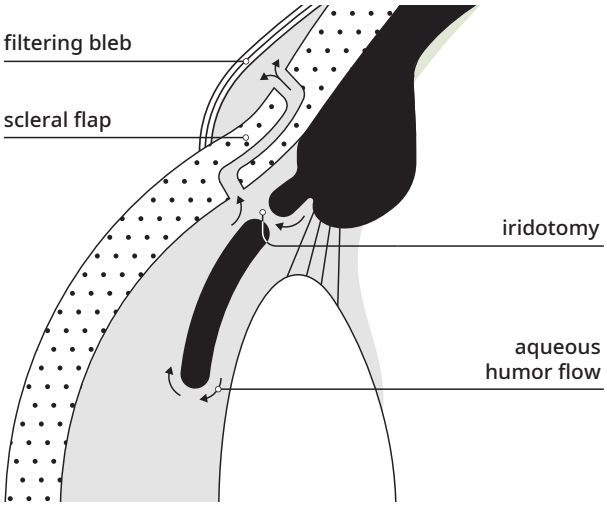

Figure 3. Diagram of aqueous humor flow after trabeculectomy. The aqueous humor flows from the posterior and anterior chambers through the surgically created ostium to the subconjunctival space (filtering bleb), where it is resorbed into the episcleral and conjunctival veins.

1. Trabeculectomy (Fig. 3–4). This procedure is used to treat NVG, but the outcomes are poorer than in other types of glaucoma[96]. The purpose of trabeculectomy is to create an ostium between the anterior chamber and the subconjunctival space. The pathway to the anterior chamber is made underneath a layered scleral flap. The aqueous humor is drained under the conjunctiva and into the conjunctival and episcleral veins. Trabeculectomy, especially in NVG, is performed with the use of antimetabolites that prevent fibrosis of the filtering bleb[97]. Additionally, preoperative administration of anti-VEGF agents may improve the long-term effects of this procedure[98, 99, 100]. Modern modification of trabeculectomy involves the additional use of filtering implants, for example, the Ex-PRESS device (Fig. 5–6).
2. Treatments with the use of artificial drainage implants. There are many models of such devices with

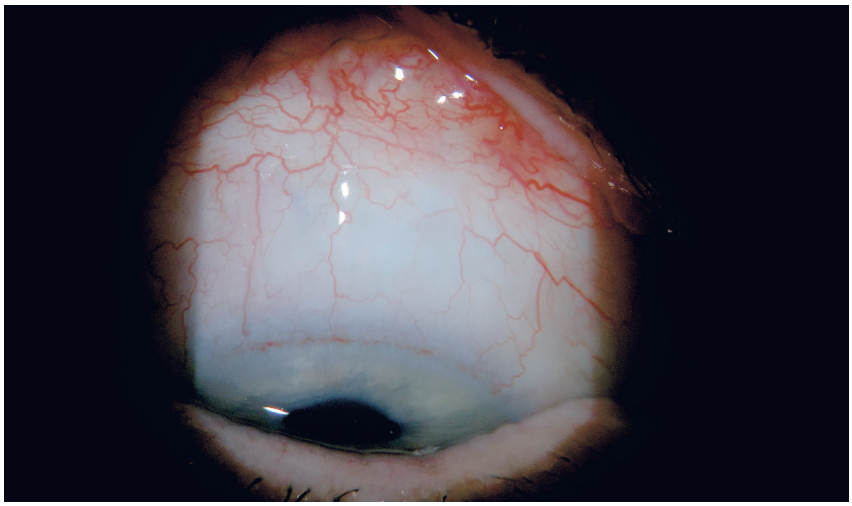

Figure 4. Conjunctival filtering bleb after trabeculectomy.

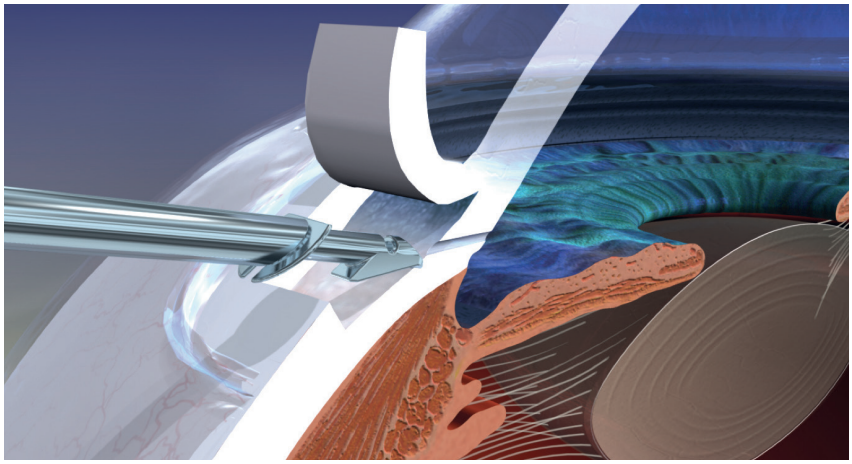

Figure 5. Implantation of the Ex-PRESS device using the injector.

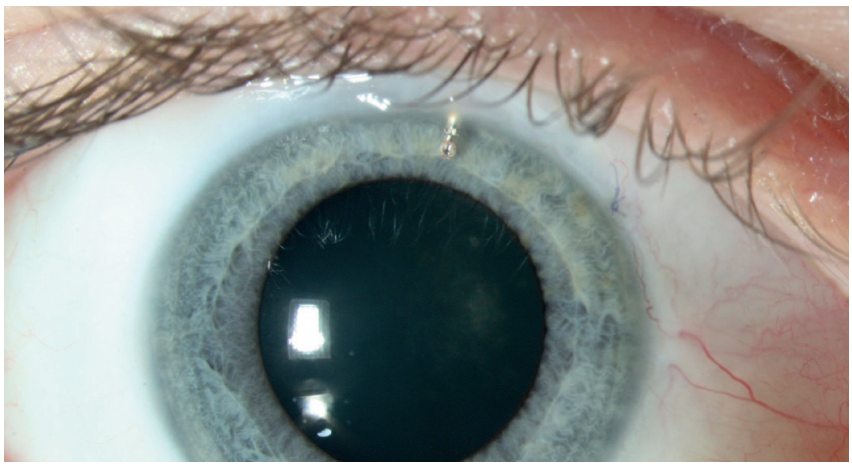

Figure 6. The tip of the Ex-PRESS implant in the anterior chamber.

eponymous names commemorating their inventors, for example Ahmed (Fig. 7), Molteno, Krupin and Baerveldt. The idea behind the drainage device is to drain the aqueous humor via an implant directly from the anterior chamber to the subconjunctival space. The implant consists of a drainage tube inserted into the anterior chamber from the side of the sclera, and a plate (a reservoir for outflowing aqueous humor), fixed subconjunctivally to the sclera. Some implants (e.g. Ahmed's or Krupin's) are

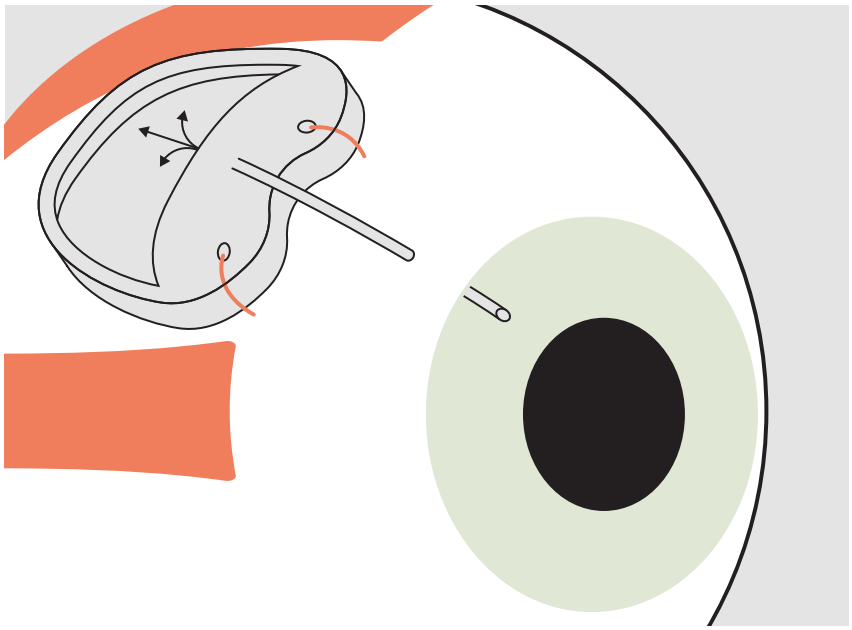

Figure 7. Ahmed's valve. The tip of the device is visible in the anterior chamber. The remaining part is located under the conjunctiva.

additionally equipped with a valve that prevents excessive drainage of aqueous humor and postoperative hypotony. Often the procedures are combined with anti-VEGF therapy, which, according to some authors, improves the prognosis for the effectiveness of the procedure and leads to better functional effects (BCVA)[101, 102, 103].

3. Cyclodestruction. These procedures are aimed at lowering IOP by partially destroying the ciliary body. Nowadays, diode laser transscleral cyclophotocoagulation (TSCPC) is most often performed. The procedure has been successfully used in advanced NVG resistant to other forms of treatment[104, 105]. Some authors even report comparable treatment effects with TSCPC and Ahmed's valve[106]. TSCPC can also be combined with cyclocryodestruction of the ciliary body[107]. Cryotherapy of the ciliary body in the course of glaucoma resistant to treatment with other methods was often used before diode lasers and drainage implants appeared on the market[108, 109]. However, such treatments were very painful and less precise. Nowadays, TSCPC is the preferred cyclodestructive treatment in NVG[110]. Additionally, transscleral cyclophotocoagulation with micropulse lasers with a wavelength of 810 nm are available. This laser application allows for a more precise procedure and is not associated with significant complications. Therefore, it does not have to be used only in very advanced forms of glaucoma with an uncertain prognosis[111, 112, 113]. Recently, reports on the use of endocyclophotocoagulation in the treatment of NVG have been published, but they discuss combined therapies – with vitrectomy and panretinal photocoagulation[111].

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Chapter 13: Principles of diabetic retinopathy screening and monitoring

Introduction

As highlighted in the Chapter 1: *Epidemiology of diabetes, diabetic retinopathy and diabetic macular edema* (pp. 23–27), diabetic retinopathy (DR) is one of the most common causes of legal blindness worldwide, and especially in developed countries. The social and socioeconomic consequences of retinopathy that is treated too late are very serious, so there is a need and necessity to develop a system for the early detection and treatment of both diabetes (DM) and diabetic retinopathy. In turn, diagnosed DR requires a specific monitoring regimen and unambiguous guidelines for the therapeutic process.

The purpose of screening is to diagnose DR in its early stages. The ideal model for such tests is the ability to detect lesions before they cause visual impairment (before diabetic macular edema (DME) occurs) and before neovascularization develops (proliferative diabetic retinopathy (PDR))[1].

The World Health Organization (WHO) defined the rules for conducting screening tests in 1968[2]. Such tests should concern diseases which pose a social problem, particularly with regard to their treatment. It should be carried out as per the accepted protocols of diagnosis and therapy for a given disease.

According to WHO, screening tests should have specific features, such as simplicity, safety and ease of interpretation (allowing a straightforward distinction between healthy and sick individuals). Furthermore, they should be economically effective, since they need to involve large populations. Additionally, ensuring suitable facilities for conducting such tests should not be problematic.

Ophthalmic screening in diabetes

Diabetes mellitus and diabetic retinopathy are subject to screening principles. The basics of ophthalmic DM screening were developed at the international conference in Saint Vincent in 1989[3]. The declaration made at the conclusion of the conference set out the goal of ophthalmic DM screening: to reduce DR-related blindness by ⅓ in the subsequent five years.

There are basically two methods of screening for DR:

1. direct screening,
2. photographic screening.

Direct screening is an examination performed by an ophthalmologist which involves performing basic procedures, in particular a stereoscopic fundus examination with the dilated pupil and a visual acuity test. Fundus photography can also be performed. The examination ends with classifying a specific type of retinopathy and determining further treatment/monitoring for each patient. Direct screening is based on the equipment found in most ophthalmic clinics, so it does not require large investments. The most common problem is providing access to qualified personnel.

In photographic screening, a trained technician takes an image of the fundus, which is then analysed by a specialist, who usually is not an ophthalmologist. The gold standard is the seven-field imaging of the retina recommended by the Early Treatment Diabetic Retinopathy Study (ETDRS) (see Chapter 4: *Diagnostic techniques for diabetic retinopathy*, p. 59, and Chapter 6: *Classifications of diabetic retinopathy*, pp. 95–106), but such an examination is time-consuming and inconvenient for the patient. Therefore, for the screening purposes, images usually include two retinal fields:

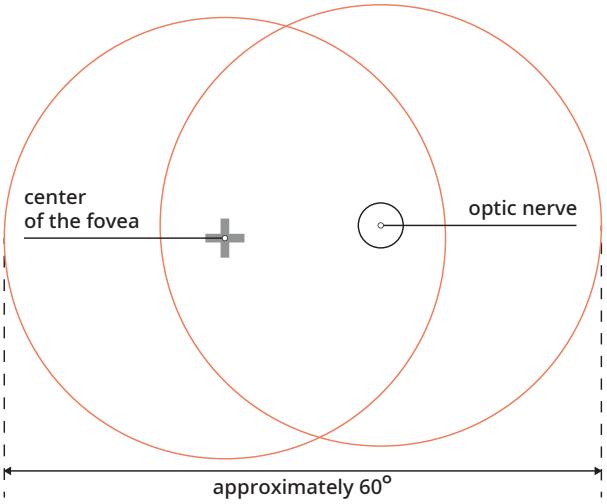

Figure 1. Photographic screening as used in England and Wales: two fields with a width of 45-degrees, centred on the fovea and the center of the optic nerve.

the central field and the field centred on the optic nerve disc. Sometimes the examination is performed by photographing three, four or five fields of the retina[4]. Fundus cameras used for examinations sometimes enable taking images without dilating the pupil. However, better image quality and a greater range of the photographed retina can be obtained with mydriasis. It is also possible to take a single image of the retina with wide-angle fundus cameras, but such equipment is very expensive, which is an obstacle to its widespread use (see Chapter 4: *Diagnostic techniques for diabetic retinopathy*, pp. 64–67).

A solid foundation for photo screening has been established in the UK, where screening is provided by the national healthcare system. The ophthalmic care system in the UK is based on a relatively small number of ophthalmologists, who are most often also involved in ophthalmic surgery. The non-surgical part of eye care largely remains in the hands of optometrists and nursing staff. Consequently, ophthalmologists burdened with performing other medical procedures, cannot perform ophthalmic diabetic screening. A multitude of specialists (usually technicians or optometrists) have been trained and certified to evaluate fundus photographs and identify the advancement of DR. Their main task is to refer the patient to an ophthalmologist in the event of detection or suspicion of retinopathy requiring intervention or evaluation by a specialist. If mild or no retinopathy is detected, the patient is scheduled for follow-up examinations. In this system, the role of ophthalmologists is to provide specialized examinations and treatment for the patients referred to them, and organize the screening system at the local level.

National photographic screening programs have been introduced in England, Wales, Scotland and Northern Ireland[5, 6, 7, 8]. While maintaining the same basic principles, the programs in individual countries slightly differ from each other. The differences relate to the number of photographed retinal fields and the methods of pupil dilation. For example, in England and Wales, two retinal fields with a 45-degree radius are photographed. One image is centred on the optic nerve disc, the other – on the macula center (Fig. 1). In Scotland, one central retinal field of a 45-degree radius is screened.

Taking good-quality images of the fundus requires a visit to a specialized clinic or clinic equipped with appropriate photographic equipment. This situation generates a very large number of visits to medical centers, which are primarily involved in treatment processes. As a result of ageing populations and rising standards of medical care in highly developed countries, medical centers are overburdened with work and cannot always implement preventive programs effectively. Hence, there is ongoing search for solutions that would reduce the number of necessary visits to specialist ophthalmology clinics.

Using smartphones to take fundus images seems to be a sound idea. Their use is widespread and the cameras built into mobile devices are of high quality. Using smartphones to take pictures of the fundus would eliminate the need for patients to visit a medical clinic with specialized equipment. Photographs could be taken at

general practitioners', in mobile clinics or local social centers, or even at the patient's home with the help of family or friends. Probably in most cases, such a procedure would not need to involve a physician or trained personnel. Smartphone attachments that enable the examination of the fundus have come on the medical market, for example, D-Eye (Italy; Fig. 2), DigiSight Paxos Scope (USA), Remedio Fundus on Phone (India; Fig. 3), Welch Allyn Panoptic with iExaminer (USA). The clinical evaluation of the usefulness of fundus images obtained from smartphones for DR screening is satisfactory, as has been confirmed by clinical studies[9, 10, 11].

Figure 2. D-Eye – an example of an ophthalmoscope on a smartphone.

Photo screening is also the basis of 'telescreening', i.e. a form of organizing screening tests during which test results are sent remotely via the Internet and assessed in another center. In the case of DR, this applies to fundus images obtained during screening tests in the offices of a family doctor, at a diabetic clinic, or at the patient's home. Subsequently, it is necessary to classify the specific type of retinopathy that the patient has. The classification is performed by a physician or, more often, by trained staff. Although such screening systems usually do not engage doctors much, they still require intensive training of other medical personnel, which generates high costs. One possible solution to these staff shortages may be involving artificial intelligence (AI) systems in the DR screening process. Development works of such systems have been ongoing for several years.

Figure 3. The Fundus on Phone ophthalmoscope attachment produced by the Indian company Remidio.

Artificial intelligence in diabetic retinopathy

The most common use of AI in DR screening is the automated analysis of fundus photographs taken by medical staff or technicians or even by the patient themselves. The purpose of such screening is to detect lesions and to classify them into one of several categories, such as no lesions and mild lesions (requiring no treatment), moderate or threshold lesions (requiring evaluation by an ophthalmologist) and vision-threatening lesions (requiring urgent consultation and treatment).

An effective system of this type should have high sensitivity and specificity. The former guarantees reliable and early retinopathy detection, which is the reason for screening. On the other hand, high specificity allows for the effective exclusion of healthy people from further diagnostic tests. There are several systems available on the medical market for the automated assessment of fundus photographs, including IDx-DR, which is certified by the Food and Drug Administration (FDA). Other systems are still being tested: Retmarker DR, EyeArt (mainly the USA and Canada), Google (tested in the USA and India), SERI-NUS (Singapore), Bosch DR, Retinalyze[12]. Most of these systems have a high sensitivity of DR detection (usually above 90%), but there are still problems with specificity, which in turn necessitates further monitoring by qualified personnel[13]. Interestingly, the first studies have been conducted on AI in DR screening using photos obtained from smartphones[14, 15]. The results justify some optimism – the tested systems show a high level of specificity and sensitivity, making them likely to become common in screening tests.

It should be emphasized that AI is not yet reliable enough to replace other forms of screening, although it may already play an auxiliary role[16]. For example, Portugal has a screening system in which a computer program pre-selects fundus images, extracting those in which retinopathy is more advanced. Qualified professionals assess only selected images[17]. In the future, we can expect that the automatic evaluation of fundus photography will be the main form of screening worldwide.

In Poland, Professor Andrzej Grzybowski is the precursor of research into artificial intelligence in DR screening[18]. In 2018, he began working on an automatic screening program that checks diabetic patients for DR. The AI-based DR system (IDx Technologies Inc., Coralville, IA, USA) assesses fundus images taken with a non-mydriatic fundus camera (two images with a 45-degree radius, one focused in the center, the other on the optic nerve) operated by a nurse. The results fall into three categories: more than mild retinopathy not detected, more than mild retinopathy detected or vision-threatening retinopathy detected. The first results had a system sensitivity of 94% and a specificity of 95%. Research on the use of AI in DR screening is currently being carried out in several centers in Poland, which gives grounds for hope that a financially feasible system of DR screening will be introduced in this country.

The frequency of screening for patients without retinopathy

Children and adults with type 1 diabetes

Diabetic retinopathy rarely develops before adolescence, so it is not necessary to screen all diabetic children on a regular basis (see Chapter 11*: Ophthalmic care for special diabetic patients: children, adolescents and pregnant women*, pp. 209–210). There are two aspects to consider when initiating ophthalmic screening in diabetic patients: their age and the duration of their diabetes. Most ophthalmic organizations do not recommend regular ophthalmic examinations for diabetic children before the age of ten. The American Academy of Ophthalmology (AAO) recommends DM1 patients should have their first ophthalmic examination five years after their diabetes diagnosis. In the absence of retinopathy, follow-up examinations are recommended once

a year[19]. The same procedure is recommended by the Polish Diabetes Society (PTD), although it also allows screening tests after two years if no changes in the fundus are found during this time[20].

The American Diabetes Association recommends initiating screening tests 3–5 years after diabetes mellitus is diagnosed and/or when the patient is ten years old[21]. On the other hand, the American Academy of Pediatrics (AAP) recommends the first ophthalmic examination 3–5 years after the diagnosis of diabetes if the patient is nine years of age or older. The International Society for Pediatric and Adolescent Diabetes (ISPAD) makes similar recommendations: ophthalmic examinations as of the age of ten or adolescence, whichever occurs earlier – 2–5 years after the diagnosis[22].

Apart from the situations described above, it can be assumed that screening for retinopathy should be performed annually in DM1 patients, and if there are risk factors for its development – more frequently.

Patients with type 2 diabetes

The AAO recommends the first ophthalmic examination for DM2 patients at the time of diagnosis. In the absence of DR, subsequent follow-up examinations should be performed once a year[9]. Identical recommendations are provided by the British National Institute for Health and Care Excellence (NICE)[23]. The International Council of Ophthalmology recommends follow-up examinations in patients without DR every 1–2 years[24]. The PTD allows funduscopic examination in patients without DR and with good control of type 2 diabetes even after three years[20].

Pregnant women

The AAO recommends ophthalmic examinations for pregnant diabetic women shortly after conception and in the first trimester of pregnancy. After that, the frequency of follow-up consultations depends on the presence of retinopathy. If it is not detected, follow-up is scheduled after 3 to 12 months.

On the other hand, the British Royal College of Ophthalmologists (RCO) recommends the first ophthalmic examination at the same time as the first obstetric consultation during pregnancy. In the absence of retinopathy, a follow-up examination should be performed in the 28th week of pregnancy[25]. Detailed recommendations from NICE are presented in Chapter 11*: Ophthalmic care for special diabetic patients: children, adolescents and pregnant women*, pp. 212–213. The PTD recommends ophthalmic examinations in pregnancy every 1–3 months, depending on the presence and severity of fundus lesions[19]. Gestational diabetes mellitus (GDM) does not require ophthalmic examination.

The frequency of monitoring for patients with diabetic retinopathy

Most diabetes and ophthalmology societies publish recommendations on their websites for a follow-up plan for DR patients. Insufficient monitoring of a patient with advanced and/or uncontrolled diabetes may lead to irreversible lesions in the eye and deprive the patient of the chance to maintain good vision. The section below contains the recommendations published by the RCO, AAO, PTD[25, 19, 20].

Royal College of Ophthalmologists

The RCO's recommendations for the frequency of ophthalmic follow-up examinations for diabetic patients are based on the severity of the diabetic retinopathy.

1. Mild to moderate non-proliferative diabetic retinopathy:
   a. annual monitoring (national screening programs),
   b. glycemic control should be optimized.
2. Severe non-proliferative diabetic retinopathy (preproliferative) (NPDR):
   a. monitoring every 4–6 months, depending on the severity,
   b. examination by an ophthalmologist (slit-lamp examination, fundus photography),
   c. in some situations, especially with suspected

retinal ischemia, fluorescein angiography is recommended,

d. in the event of progression towards PDR, panretinal photocoagulation (PRP) should be considered,
e. PRP for severe NPDR is to be considered especially in the following situations:
   - with elderly DM2 patients,
   - difficulty in obtaining a clear view into the fundus,
   - prior to cataract surgery,
   - with monocular patients if the blindness of the other eye is due to PDR,
   - if patient compliance is poor (irregular follow-up visits).

3. Proliferative diabetic retinopathy:
   a. fluorescein angiography to assess the extent of ischemia,
   b. PRP within two weeks of diagnosis.
4. Advanced proliferative diabetic retinopathy:
   a. early vitrectomy,
   b. auxiliary anti-VEGF.
5. Patients with diabetic macular edema:
   a. follow-up 3–4 months after laser photocoagulation,
   b. regular monitoring of patients during anti-VEGF therapy according to regimen dependent on the drug used (see Chapter 8: *Diabetic maculopathy (diabetic macular edema) – diagnosis and treatment*, pp. 152–156),
   c. regular examinations of retinal morphology using spectral domain optical coherence tomography (SD-OCT) and control of intraocular pressure (IOP) in patients after intravitreal steroid therapy.

American Academy of Ophthalmology

The AAO recommendations and the management and monitoring regimen depend on the type of retinopathy, the presence of macular edema and its clinical significance.

1. Patients without retinopathy:
   a. DM1: first examination five years after diagnosis, then a follow-up once a year,
   b. DM2: first examination at diagnosis, then a follow-up once a year.
2. Pregnant patients:
   a. the first examination prior to pregnancy (pregnancy planning) or shortly after conception and the next one in the first trimester,
   b. in the absence of retinopathy, or with mild and moderate retinopathy, monitoring every 3–12 months,
   c. in severe or more advanced DR, monitoring every 1–3 months.
3. Mild non-proliferative diabetic retinopathy:
   a. in the absence of DME, an ophthalmic examination once a year,
   b. in the presence of non-center-involved diabetic macular edema (NCI DME), ophthalmic examinations every 3–6 months; focal/GRID photocoagulation may be considered (evaluation usually 3 months after laser treatment),
   c. in the presence of center-involved diabetic macular edema (CI DME):
      - monitoring every month,
      - possible treatment: usually anti-VEGF therapy; rarely – focal or GRID laser.
4. Moderate diabetic retinopathy:
   a. in the absence of DME, ophthalmic examinations every 6–12 months, or more frequently if there is a risk of progression to severe NPDR,
   b. in the presence of NCI DME, follow-up every 3–6 months; focal/GRID retinal photocoagulation may be considered (evaluation usually 3 months after laser treatment),
   c. in the presence of CI DME:
      - monitoring every month,
      - possible treatment: usually anti-VEGF therapy; rarely focal or GRID laser.
5. Severe non-proliferative diabetic retinopathy:
   a. in the absence of DME, follow-up every 3–4 months,
   b. in the presence of NCI DME:
      - monitoring every 2–4 months,
      - PRP may be considered, focal/GRID retinal

photocoagulation may be considered (evaluation usually 3 months after laser treatment),

c. in the presence of CI DME:
   - monitoring every month,
   - PRP may be considered
   - possible treatment: usually anti-VEGF therapy; rarely focal or GRID laser.

6. Non-high-risk proliferative diabetic retinopathy:
   a. in the absence of DME:
      - monitoring every 3–4 months,
      - PRP may be considered,
   b. in the presence of NCI DME:
      - monitoring every 2–4 months,
      - PRP may be considered, focal/GRID retinal photocoagulation may be considered (evaluation 3 months after laser treatment),
   c. in the presence of CI DME:
      - monitoring every month,
      - PRP may be considered,
      - possible treatment: usually anti-VEGF therapy; less frequently focal or GRID laser.
7. High-risk proliferative retinopathy:
   a. in the absence of DME:
      - monitoring every 2–4 months,
      - PRP is recommended,
      - anti-VEGF therapy is possible,
   b. in the presence of NCI DME:
      - monitoring every 2–4 months,
      - PRP is recommended,
      - focal/GRID retinal photocoagulation may be considered (evaluation 3 months after laser treatment),
      - sometimes anti-VEGF therapy,
   c. in the presence of CI DME:
      - monitoring every month,
      - PRP is recommended,
      - usually – anti-VEGF therapy, less frequently – retinal laser treatment.

The Polish Diabetes Society

Much like the RCO and AAO, the Polish Diabetes Society establishes the frequency of screening and control based on the severity of the retinopathy and the duration of the diabetes. The society points out that in the absence of retinopathy (and with good glycemic control), a follow-up ophthalmic examination can be scheduled after as long as two years (and even three years in the case of DM2 without any lesions in the fundus).

1. First examination:
   a. DM1 – in the first five years after diagnosis,
   b. DM2 – as soon as possible after diagnosis.

   Then monitoring examinations according to the following regimen/plan.
2. Patients without retinopathy – ophthalmoscopic examination every 1–2 years (or even every three years – see the comment above).
3. Mild and moderate non-proliferative diabetic retinopathy – examination every 6–12 months.
4. Severe non-proliferative diabetic retinopathy:
   a. monitoring at least every 3–6 months,
   b. laser treatment is possible.
5. Proliferative diabetic retinopathy – urgent laser treatment or other ophthalmic surgery, such as posterior vitrectomy.
6. Diabetic macular edema:
   a. non-foveal: laser therapy,
   b. foveal: anti-VEGF therapy and/or laser treatment.
7. Evaluation after ophthalmic procedures:
   a. after laser treatment – one month after the procedure,
   b. after vitrectomy – depending on the condition of the eye.
8. Women:
   a. planning pregnancy – if necessary, retinal laser treatment before pregnancy,
   b. during pregnancy – depending on the eye condition – evaluation every 1–3 months.
9. Patients with uncontrolled diabetes, hypertension, proteinuria – evaluation every 1–6 months depending on the severity of DR.

As can be seen, the recommendations of various medical societies regarding the follow-up of patients with

diabetic retinopathy differ only slightly. It is important to follow the core principles of DR monitoring based on up-to-date medical knowledge.

- In DM1, diabetic retinopathy rarely develops within the first five years after the disease onset and even more rarely before the age of nine, so ophthalmic monitoring of young children with short-term diabetes is pointless. It is different for the puberty period, when monitoring should be regular.
- Patients without retinopathy may be monitored annually or less frequently (cases with good glycemic control).
- Patients with mild to moderate retinopathy without DME should be monitored 1–2 times a year.
- Advanced non-proliferative retinopathy requires evaluation at least three times a year.
- Panretinal photocoagulation is necessary in most cases of proliferative diabetic retinopathy. Anti-VEGF therapy can be used as an auxiliary treatment in such cases. Anti-VEGF monotherapy may be used in selected cases of initial PDR, or with concomitant DME.
- Clinically significant diabetic macular edema (CSME) should be monitored and treated at all stages of diabetic retinopathy. CSME requires frequent monitoring (monthly at the beginning of treatment), especially with anti-VEGF therapy, intravitreal steroid therapy and/or laser treatment.
- Patients with systemic complications of diabetes, such as nephropathy or hypertension, as well as patients with poorly controlled glycemia should be monitored more frequently, regardless of the condition of their retina (every 1–6 months according to the PDT).

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Appendix. Definitions and algorithms for the management of diabetic retinopathy

List of abbreviations used in the appendix

BCVA – best-corrected visual acuity
CI DME – center-involved diabetic macular edema
CSME – clinically significant macular edema
DA – disc area: the area of the optic nerve disc
DM – diabetes (Lat. *diabetes mellitus*)
DM1 – type 1 diabetes
DM2 – type 2 diabetes
DME – diabetic macular edema
DMI – diabetic macular ischemia
DR – diabetic retinopathy
EZ – ellipsoid zone, formerly referred to as a junction of inner and outer photoreceptor segments (IS and OS)
FAZ – the foveal avascular zone
HR PDR – high-risk proliferative diabetic retinopathy
IRMA – intraretinal microvascular abnormalities
IS – internal segments of the photoreceptors
NCI DME – non-center-involved diabetic macular edema
NPDR – non-proliferative diabetic retinopathy
NV – neovascularization
NVA – neovascularization of the angle
NVD – neovascularization at the disc
NVE – neovascularization elsewhere
NVG – neovascular glaucoma
NVI – neovascularization of the iris
OCT – optical coherence tomography
OCTA – OCT angiography
OS – outer segments of photoreceptors
PDR – proliferative diabetic retinopathy
PPV – pars plana vitrectomy
PRN – as required (Lat. pro re nata)
PRP – panretinal photocoagulation
SMPLT – subthreshold micropulse laser treatment
SRF – subretinal fluid
VEGF – vascular endothelial growth factor
VMA – vitreomacular adhesion

Sources used in the appendix

The following list is a synthesis of the recommendations of some of the most important ophthalmology and diabetes societies in Poland and around the world: the Polish Ophthalmological Society (PTO), the Polish Diabetes Association (PTD), the American Academy of Ophthalmology (AAO), the American Diabetes Association (ADA), the Royal College of Ophthalmologists (RCO) and the European Society of Retina Specialists EURETINA. It was developed on the basis of the following sources:

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6. Wytyczne postępowania w terapii cukrzycowe-

Table 1. Simplified classification of diabetic retinopathy.

Disease severity level	Findings observed upon dilated ophthalmoscopy
No apparent retinopathy	no abnormalities
Mild NPDR	microaneurysms only
Moderate NPDR	more lesions than just microaneurysms but less than severe NPDR
Severe NPDR	US definition: any of the following and no signs of PDR (4:2:1 rule) • severe intraretinal hemorrhages and microaneurysms in each of four quadrants • definite venous beading in two or more quadrants • moderate IRMA in one or more quadrants International definition: any of the following and no signs of PDR • more than 20 intraretinal hemorrhages in each of the four quadrants • definite venous beading in two or more quadrants • prominent IRMA in one or more quadrants
PDR	one or both of the following • neovascularization • vitreous/preretinal hemorrhage

NPDR – nonproliferative diabetic retinopathy, PDR – proliferative diabetic retinopathy, IRMA – intraretinal microvascular abnormalities

go obrzęku plamki (Guidelines for the management of diabetic macular edema), 2017 (www.pto.com.pl).
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The definition of high-risk diabetic proliferative retinopathy (HR PDR) and clinically significant macular edema (CSME)

1. Definition of high-risk proliferative diabetic retinopathy (HR PDR):
   a. neovascularization on or within 1 DD of the optic disc (NVD) with an area ¼ to ⅓ DA,
   b. NVD with preretinal or vitreous hemorrhage,
   c. neovascularization elsewhere (NVE) with an area of > ½ DA and with preretinal or vitreous hemorrhage.

Table 2. Classification of diabetic macular edema (DME).

Disease severity level	Indirect ophthalmoscopy fundus image
DME apparently absent	apparent absence of retinal thickening and hard exudates in the posterior pole
DME apparently present	apparent thickening of the retina or hard exudates in the posterior pole
Mild DME	retinal thickening or hard exudates in the posterior pole but distant from the macular center
Moderate DME	retinal thickening or hard exudates approaching the center of the macula, but not involving the center
Severe DME	retinal thickening or hard exudates in the macular center

2. Definition of clinically significant macular edema (CSME):
   a. retinal thickening 500 μm or less from the macular center, or
   b. hard exudates at a distance of 500 μm or less from the macular center, if accompanied by retinal thickening, or
   c. retinal thickening with an area of ≥ 1 DA, where any portion of thickening is within 1 DD or less from the macular center.

Table 1 presents a simplified classification of diabetic retinopathy and Table 2 presents a classification of diabetic macular edema.

The purpose and frequency of diagnostic tests

1. Fluorescein angiography – purpose:
   a. to determine the type of retinopathy (non-proliferative, proliferative),
   b. to locate the areas of hypoperfusion, mainly on the periphery of the retina,
   c. to diagnose ischemic maculopathy (DMI),
   d. to locate hard-to-find areas of neovascularization (NV), mainly NVE in the far retinal periphery, and initial NVD.
2. Since fluorescein angiography is an invasive procedure, it should only be performed in specific situations:
   a. at the beginning of the diagnostic and therapeutic process in DME,
   b. before planned focal macular laser treatment,
   c. to define unexplained deterioration of vision and other diagnostic difficulties at the beginning of and during the treatment process.

   It should not be used as a routine ophthalmic inspection and screening tool.
3. Retinal optical coherence tomography (OCT) and angio-OCT (OCTA) – purpose:
   a. the diagnosis and classification of DME,
   b. assessment of the DME architecture (subretinal fluid (SRF), intraretinal fluid, traction, extend of damage to the ellipsoid zone (EZ)),
   c. monitoring the effectiveness of treatment in the case of:
   - intravitreal anti-VEGF therapy or steroid therapy – performed at each follow-up visit,
   - laser treatment (photocoagulation and/or subthreshold micropulse laser) – usually 1–3 months after the session,
   - surgical treatment of lesions in the macular area (vitreoretinal traction, epiretinal membranes, DME refractory to other forms of treatment),

d. OCTA – primarily to assess the surface and shape of the FAZ, especially the capillary drop-out areas.

Principles of screening and ophthalmic monitoring for patients with diabetes mellitus (DM)

1. Children:
   a. first examination five years after the onset of diabetes (according to AAO, PTD),
   b. ophthalmological examination 3–5 years after the onset of diabetes and once the child is nine years old (according to AAP).
2. Older children and adults with DM1: screening for DR routinely once a year. In the absence of DR and with good glycemic control, monitoring visits can be scheduled every 2 years.
3. Adults with DM2: the first ophthalmic examination immediately after diagnosis of DM. Then, in the absence of DR, evaluation every 1–2 years (depending on glycemic control); in the absence of fundus lesions, the PTD allows evaluation every 3 years.
4. Pregnant women:
   a. pregnancy planning:
      • stabilization of glycaemia and the local condition before pregnancy,
      • ophthalmic examination before pregnancy,
      • if necessary, retinal laser treatment before pregnancy,
   b. the first ophthalmic examination after conception and/or at the beginning of the first trimester,
   c. the frequency of subsequent examinations depends on the severity of retinopathy.
5. The monitoring regimen for patients with DM depends on the severity of retinopathy (according to RCO, AAO, PTD):
   a. mild and moderate non-proliferative diabetic retinopathy – 1–2 times a year (if DME is absent),
   b. severe non-proliferative retinopathy – at least three times a year (if DME is absent); in some situations, panretinal photocoagulation (PRP) may be considered,
   c. any DME associated retinopathy – the frequency of follow-up depends on the location of the edema, the severity of the retinopathy, and the treatment used (see Table 3); at the initiation of treatment with intravitreal injections of anti-VEGF agents, monitoring is performed monthly (loading dose), and subsequently the frequency depends on the administered agent and duration of treatment; if there is a stabilization of BCVA and retinal morphology, it is possible to extend the intervals between follow-up examinations,
   d. proliferative diabetic retinopathy – follow-up depends on DR status, the coexistence of DME, and the type of treatment – PRP, anti-VEGF, PPV (see Table 3).

Treatment guidelines and the management of diabetic retinopathy

1. Eligibility for pars plana vitrectomy (PPV) and scheduling for vitrectomy in DR (according to PTO, AAO):
   a. non-resorbing or/and recurrent vitreous hemorrhage and preretinal hemorrhage – immediate surgery (a maximum one-month observation period while awaiting spontaneous resorption; in the case of mild hemorrhage in patients with DM2, the waiting period for hemorrhage resorption can be up to three months (AAO)); anti-VEGF injection a few days before the surgical procedure,
   b. non-resorbing hemorrhage for four weeks after PPV – immediate surgery,
   c. tractional, rhegmatogenous or mixed-mechanism retinal detachment – an urgent surgical procedure (PPV) should be scheduled in the event of a retinal tear or mixed mechanism, and whenever the macula is at risk;
   d. advanced fibrovascular proliferation, if there is a potential for improvement of vision and/

or the risk of retinal detachment and/or macular involvement – immediate surgery,

e. epiretinal membranes, macular traction, vitreomacular adhesion (VMA), especially in the presence of DME – elective surgery,

f. significant DME refractory to other therapies – elective PPV surgery may be considered.

2. The management of advanced proliferative retinopathy (according to PTO, RCO, AAO):
   a. with neovascularization of the angle (NVA) and neovascularization of the iris (NVI) but without neovascular glaucoma (NVG):
      - in the case of a clear view of the fundus– urgent PRP,
      - auxiliary anti-VEGF,
   b. with neovascular glaucoma (NVG):
      - in the case of a clear view of the fundus – PRP,
      - intravitreal anti-VEGF therapy,
      - surgical procedures: transscleral cyclophotocoagulation, cyclocryotherapy, trabeculectomy, drainage implants,
      - blind eyes after NVG – pain control, mainly with the help of topical atropine and steroids and IOP-lowering drugs,
   c. vitreous hemorrhage and dense preretinal hemorrhage – the procedure described in the above paragraph (qualification for vitrectomy),
   d. advanced fibrovascular proliferation – early vitrectomy,
   e. retinal detachment:
      - rhegmatogenous, mixed mechanism: tractional-rhegmatogenous – urgent surgery,
      - tractional – the procedure depends on the severity of the traction, macular involvement and dynamics of the disease – usually also urgent.
3. Indications for PRP:
   a. mild and moderate non-proliferative diabetic retinopathy (NPDR) – no indications for PRP,
   b. severe NPDR – PRP may be considered with severe NPDR and early PDR, in the following situations (according to the RCO):
      - older adults with DM2,
      - when it is difficult to obtain a clear view into the fundus,
      - before a planned cataract surgery,
      - in the better eye, when the other has lost sight due to PDR,
      - in the event of difficulties with regular monitoring,
   c. proliferative retinopathy less advanced than HR PDR – PRP can be performed if there are coexistent risk factors that could lead to progression of retinopathy,
   d. HR PDR – PRP is strongly recommended
   e. indications for supplementing PRP and possibly starting auxillary anti-VEGF treatment:
      - no regression of NV,
      - progression of NV,
      - new vitreous hemorrhage,
      - new foci of NV.

The treatment of diabetic macular edema – possible options

1. DME not involving the fovea:
   a. classical laser photocoagulation of clearly visible microaneurysm clusters (vasogenic subform of DME) – according to ETDRS recommendations,
   b. classic laser photocoagulation for edema smaller than 300 μm (EURETINA),
   c. subthreshold micropulse laser,
   d. anti-VEGF therapy,
   e. observation alone is possible with BCVA > 20/32 and close monitoring (AAO).
2. DME involving the fovea:
   a. observation:
      - at BCVA ≥ 20/25 (AAO),
      - optional with good BCVA (for example > 0.63), if the microaneurysms are close to the fovea and the patient does not want to undergo intravitreal injection procedures (according to the RCO),
   - with low BCVA (0.05 or less) and long-term edema, if significant foveal ischemia is present

and there is no potential for improvement with anti-VEGF therapy (RCO),

b. anti-VEGF therapy (ranibizumab, aflibercept and bevacizumab – off-label):
   - ranibizumab – loading dose: injections every month until maximum visual acuity is reached, then injections in PRN (pro re nata) or treat-and-extend mode (depending on the SD-OCT and BCVA results),
   - aflibercept – in the first year: the loading dose of five injections every month, then injections every two months; usually PRN or treat-and-extend re-injections starting from the second year of treatment,
   - bevacizumab – usually the same regimen as for ranibizumab,

c. intravitreal steroid therapy:
   - pseudophakic patients are preferred,
   - dexamethasone (Ozurdex) – re-injections every six months (according to the SmPC); clinical practice shows that the time interval between injections may be shorter (real-life studies),
   - triamcinolone acetate (Kenalog, Vitreal S) – re-injections every three months (according to the PTO),

d. subthreshold micropulse laser therapy:
   - usually with smaller edema below 400 μm and with patients with good visual acuity (EURETINA),
   - if anti-VEGF therapy is unavailable, or if the patient does not consent to this treatment,
   - it can be repeated many times (intervals between sessions from six weeks to three months).

3. Central DME resistant to other therapies:
   a. long-term, after laser treatment: a slow-release fluocinolone implant (36 months),
   b. posterior vitrectomy,
   c. classic laser photocoagulation as emergency therapy.
4. Posterior vitrectomy in DME:
   a. vitreomacular traction, epiretinal membrane, significant vitreomacular adhesion,
   b. lack of response to other therapies.

Intravitreal therapy with DR and DME

According to current recommendations, the first-line drugs are anti-VEGF agents; intravitreal steroids are used in case of lack of response to anti-VEGF treatment and as the first line if there are contraindications to anti-VEGF agents.

Table 3 presents the treatment and monitoring algorithms for DR, depending on the severity of retinopathy and the presence and location of DME.

Appendix. Definitions and algorithms for the management of diabetic retinopathy

Table 3. Management of diabetic retinopathy (based on AAO recommendations, including some PTD and RCO recommendations).

Retinopathy severity	DME present	Frequency of monitoring	PRP	Focal laser treatment/ GRID/SMPLT	Intravitreal anti-VEGF therapy
Mild	no	every 12 months	no	no	no
	yes	• for CI DME: every month at the beginning of the intravitreal therapy • for NCI DME: every 3–6 months (3 months after laser treatment)	no	sometimes: with NCI DME, when intravitreal injections are not available	yes – with CI DME
Moderate	no	every 6–12 months	no	no	no
	yes	• for CI DME: every month at the beginning of the intravitreal therapy • for NCI DME: every 3–6 months (3 months after laser treatment)	no	occasionally: with NCI DME, when intravitreal injections are not available	yes – with CI DME
Severe	no	every 3–4 months	sometimes with co-existing risk factors	no	no
	yes	• for CI DME: every month at the beginning of the intravitreal therapy • for NCI DME: 2–4 months (3 months after laser treatment)	sometimes with co-existing risk factors	sometimes: with NCI DME, when intravitreal injections are not available	yes – with CI DME
Non HR PDR	no	every 2–4 months	usually yes	no	sometimes in combination therapy with PRP, or in monotherapy instead of PRP

Retinopathy severity	DME present	Frequency of monitoring	PRP	Focal laser treatment/ GRID/SMPLT	Intravitreal anti-VEGF therapy
	yes	• for CI DME: every month at the beginning of the intravitreal therapy • for NCI DME: 2–4 months (3 months after laser treatment)	usually yes	sometimes: with NCI DME, when intravitreal injections are not available	yes
HR PDR	no	every 2–4 months	yes	no	sometimes in combination therapy with PRP, or in monotherapy instead of PRP
	yes	• with CI DME: every month at the beginning of intravitreal therapy • for NCI DME: 2–4 months (3 months after laser treatment)	yes	sometimes: at NCI DME, when injections are not available	yes

Comments:
In the case of CI DME and BCVA ≥ 20/25, treatment should be postponed until the BCVA score decreases. In the case of NCI DME with BCVA > 20/32 and close monitoring, observation and treatment delay may be considered. For severe NPDR without DME, the efficacy of anti-VEGF (regression of retinopathy) therapy is under investigation.

AAO – American Academy of Ophthalmology, PTD – Polish Diabetes Society, RCO – Royal College of Ophthalmologists, CI DME – center-involved diabetic macular edema, DME – diabetic macular edema, NCI DME – non-center-involved diabetic macular edema, PRP – panretinal photocoagulation

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