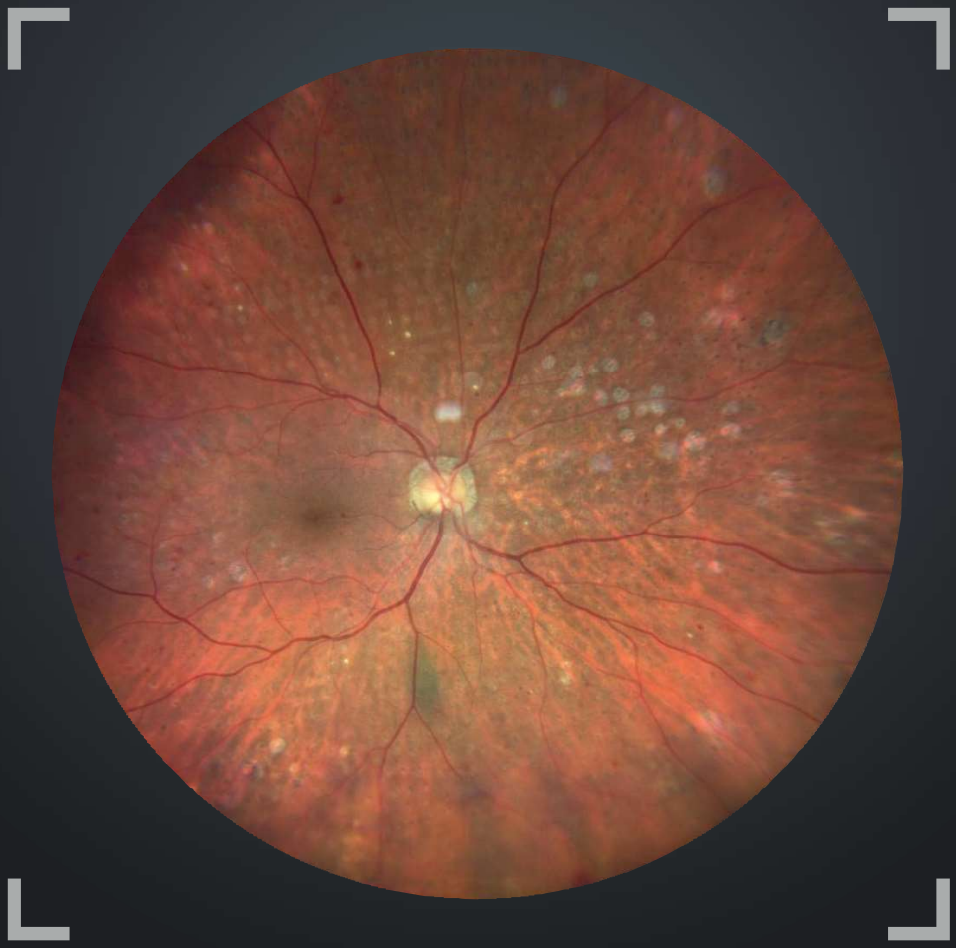
Diabetic Retinopathy

Maciej Gawęcki



Théa
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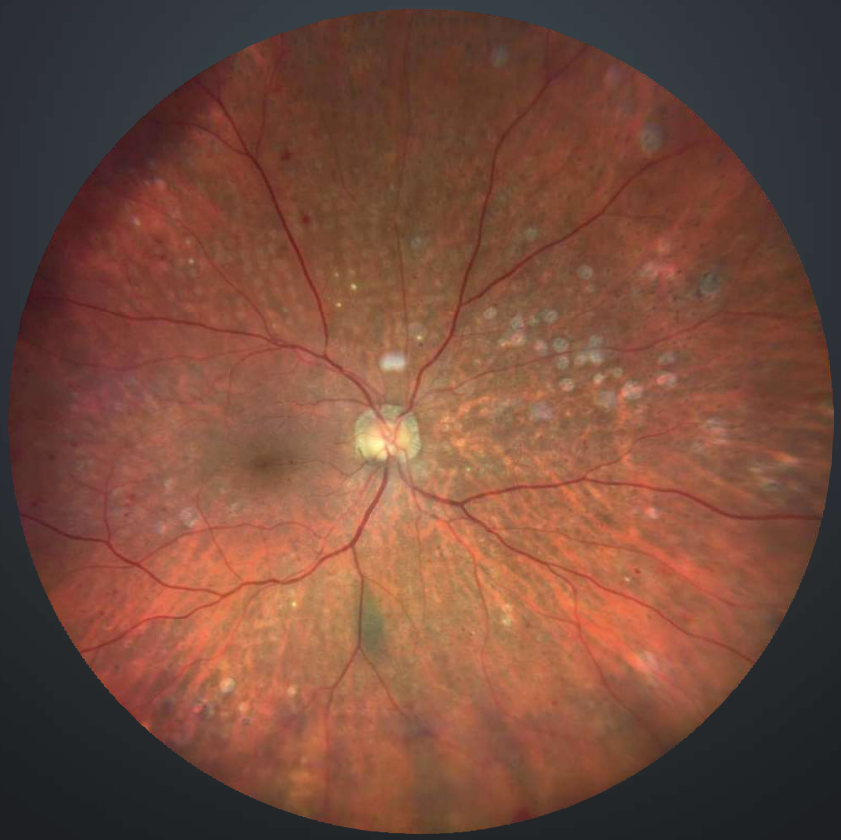

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Maciej Gawęcki

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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