Retina Lasers in Ophthalmology

Clinical Insights and Advancements

Andrzej Grzybowski
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ISBN 978-3-031-25778-0 ISBN 978-3-031-25779-7 (eBook)
https://doi.org/10.1007/978-3-031-25779-7

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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Abbreviations

PRP	panretinal photocoagulation
RPC	retinal photocoagulation
SML	subthreshold micropulse laser
LIRD	laser-induced retinal damage

Others, pretty obvious

ABD	Adamantiades-Behcet disease
AAO	American Academy of Ophthalmology
ACE	angiotensin converting enzyme
AMD	age related macular degeneration
APS	antiphospholipid syndrome
AVMD	adult onset vitelliform macular dystrophy
BCVA	best corrected visual acuity
BRVO	branch retinal vein occlusion
BVMD	Best vitelliform macular dystrophy
CCF	carotid cavernous fistula
CNV	choroidal neovascularization
CRVO	central retinal vein occlusion
CS	contrast sensitivity
CSCR	central serous chorioretinopathy
CST	central subfoveal thickness
CW	continuous wave
DC	duty cycle
DCP	deep capillary plexus
DME	diabetic macular edema
DR	diabetic retinopathy
DRCR net	Diabetic Retinopathy Clinical Research network

DRIL	disorganization of inner retinal layers
DRS	Diabetic Retinopathy Study
DSM	dome shaped macula
ECA	external carotid artery
ED	Eales' disease
EDI -OCT	enhanced depth of imaging OCT
EpM	end-point management
EOG	electrooculography
ERG	electroretinography
ERM	epiretinal membrane
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FAF	fundus autofluorescence
FAZ	foveal avascular zone
FCE	focal choroidal excavation
FEVR	familial exudative vitreoretinopathy
HVS	hiperviscosity syndromes
ICA	internal carotid artery
ICGA	indocyanine green angiography
ILM	internal limiting membrane
IOP	intraocular pressure
IOTB	intraocular tuberculosis
IP	incontinentia pigmenti
IRV	idiopathic retinal vasculitis
IRVAN	aneurysms and neuroretinitis
IVA	intravitreal aflibercept
IVB	intravitreal bevacizumab
IVR	intravitreal ranibizumab
LFTU	lost to follow-up
MAPASS	Manchester Pascal Study
ME	macular edema
MNV	macular neovascularization
MRI	magnetic resonance imaging
nAMD	neovascular age related macular degeneration
ND	Norrie disease
NPDR	non-proliferative diabetic retinopathy
NPSR	non-proliferative sickle cell retinopathy
NV	neovascularization
NVD	neovascularization at disc
NVE	neovascularization elsewhere
OCT	optical coherence tomography
OCTA	OCT angiography
ODP	optic disc pit
OIS	ocular ischemic syndrome
PCV	polypoidal choroidal vasculopathy

PDR	proliferative diabetic retinopathy
PDT	photodynamic therapy
PED	pigment epithelial detachment
PEHC	peripheral exudative hemorrhagic chorioretinopathy
PHR	proliferative hypertension retinopathy
PNV	pachychoroid neovasculopathy
PPE	peripapillary pigment epitheliopathy
PPS	peripapillary pachychoroid syndrome
PPV	pars plana vitrectomy
PRN	pro re nata – as needed
PSR	proliferative sickle cell retinopathy
RCO	Royal College of Ophthalmologists
RPE	retinal pigment epithelium
RR	radiation retinopathy
RVO	retinal vein occlusion
SAH	systemic arterial hypertension
SCP	superficial capillary plexus
SCD	sickle cell disease
SCR	sickle cell retinopathy
SD – OCT	spectral domain optical coherence tomography
SFCT	subfoveal choroidal thickness
SLE	systemic lupus erythematosus
SRD	serous retinal detachment
SRF	subretinal fluid
SRT	selective retinal therapy
SS-OCT	swept source OCT
TR	therapeutic range
TRD	tractional retinal detachment
UWF	ultra-wide field
VEGF	vascular endothelial growth factor
VH	vitreous hemorrhage
VKH	Vogt-Koyanagi -Harada

Chapter 1
Book Introduction

Andrzej Grzybowski, Jeffrey K. Luttrull, and Igor Kozak

After its introduction into ophthalmology in the 1960s, retinal photocoagulation (RPC) was firmly established as the standard of care for retinal laser treatment by the Early Treatment of Diabetic Retinopathy Study (ETDRS 1985) and Macular Photocoagulation Study Group reports (1986). Note that this was some 40 years ago. Remarkably, despite the relatively ancient (in modern technological terms) origins of RPC, it remains the standard of care for retinal laser treatment and particularly the treatment of complications of DR according to *AAO preferred practice patterns.* Such stasis should be of concern to everyone. How many other interventions in ophthalmology continue essentially unchanged since 1985? Where have intracapsular cataract surgery, aphakic spectacles and open-sky vitrectomy gone? This persistence in the ophthalmic armamentarium is not because of the superiority of RPC to other treatment approaches that have developed since that time, or the lack of progress. It is because the rise of drug therapy and influence of the pharmaceutical industry have diverted professional attention and virtually all funding for clinical trials away from retinal laser treatment, to drug therapies [1]. This focus has been amplified by the fact that researchers tend to follow established trends rather than pursue novel research. This affects both the availability of funding and peer acceptance. Consider research in the 1990's, when virtually every research grant and paper

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_1

was judged by its relevance to acquired immune deficiency. It is more acceptable to fail following the crowd than by taking a different approach or pursuing a new direction alone; failure pursuing popular research is unfortunate, failure pursuing novel research may be considered foolish and even unscientific [2].

The shift of attention away from laser to drug therapy has had a great impact on both basic research and clinical practice. The lack of trial funding for laser treatment has created the impression that retinal laser treatment has not progressed since RPC and is thus no longer relevant in the drug era. Despite this impression, there is ample evidence to the contrary. Unfortunately, this evidence gets little attention. This may be because retinal laser treatment does not produce revenue for the companies that sponsor over 95% of all clinical trials in medicine and ophthalmology, produce revenue for numerous practitioner investigators for recruiting and treating patients in the many large industry funded clinical trials, and financially support all major ophthalmic journals and professional societies alike. Thus, data for retinal laser treatment since the 1980s has relied on small clinical trials, retrospective studies, and real-world data studies that can be done at far lower cost than large RCTs. One result is that advances in laser treatment are dismissed as lacking sufficient data and large RCTs, despite highly consistent results from numerous sources. Despite neglect of laser treatment, studies show that retinal laser treatment continues to be indispensable. In this light, we will review the historical data on RPC for DR, and attempt to move the discussion forward by noting advances in our understanding an application of retinal laser treatment since 1985. Older, increasingly obsolete treatments will always have an advantage in evidence over newer, better treatments, simply by virtue of a larger library of data accumulated over the years. If the weight of accumulated evidence is all that guides us, there will be no progress. In this book we review the historical standards but will also attempt to show where progress is being made, and where more needs to be made.

We hope to show that modern retinal laser therapy, defined as that which is effective while being reliably sublethal to the RPE and thus clinically harmless, has no rival—drug or other laser approach—in its usefulness. Conventional RPC applications were limited very narrowly to treatment of diabetic retinopathy, central serous chorioretinopathy, retinal vein occlusions and ablative treatment of choroidal neovascularization. Modern retinal laser treatment improves the management of such traditional laser treatment indications without harming the retina, but also might increase the utility of retinal laser treatment to include neuroprotective, preventive, and therapeutic treatment of all the major causes of irreversible visual loss, the chronic progressive retinopathies, including dry age-related macular degeneration and open angle glaucoma. The indications for RPC were those things that could be destroyed. The indications for modern retinal laser therapy are those things can benefit from improvement and restoration. This is a longer list. We hope you will agree that such progresses warrants both more attention and great optimism for the future of retinal laser therapy.

References

1. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2017;(2). https://doi.org/10.1002/14651858.MR000033.pub3. Art. No.: MR000033.
2. Amiri AR, Kanesalingam K, Cro S, Casey AT. Does source of funding and conflict of interest influence the outcome and quality of spinal research? Spine J. 2014;14(2):308–14. https://doi.org/10.1016/j.spinee.2013.10.047. Epub 2013 Nov 12 PMID: 24231776.

Chapter 2
History of Lasers in Ophthalmology

Andrzej Grzybowski

The history of medicine is full of controversy over the priority of inventions. There are two such controversies in the history of lasers. The first concerns the idea of photocoagulation, the second—the concept of laser.

The Idea of Photocoagulation

Early observations and first attempts

The idea of photocoagulation consists of several observations that have been known for a long time. First, it is the idea of the so-called burning glass, i.e. that the sun's rays can be focused with a lens to ignite or burn an object.

Burning Glass

This technology of using lenses to start fires for various purposes has been known since antiquity, as reported by many Greek and Roman writers [1]. For example, the use of glass vases filled with water to create a heat intense enough to ignite clothing, as well as convex lenses that were used to cauterize wounds was described by Pliny the Elder [2]. This concept was also used in very popular plays of Aristophanes, what shows that this knowledge was quite common and easy available [3]. The most

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_2

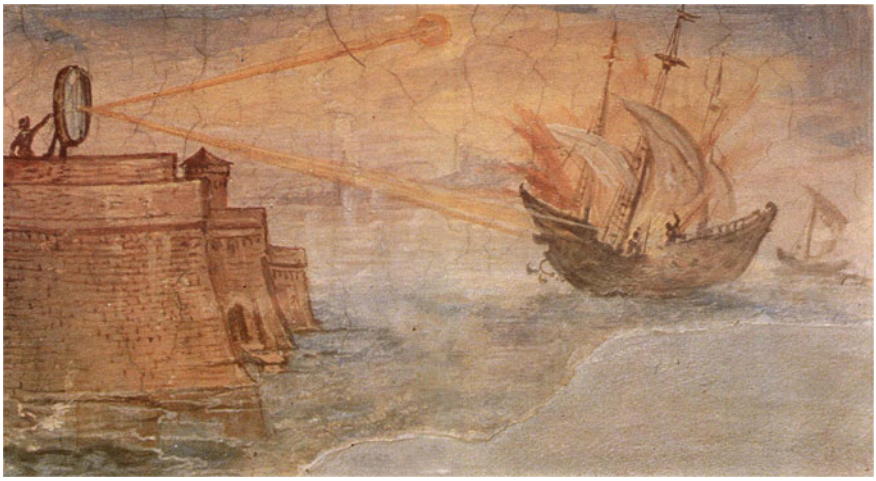


Fig. 2.1 Wall painting from the Uffizi Gallery, Stanzino delle Matematiche, in Florence, Italy, showing the Greek mathematician Archimedes' mirror being used to burn Roman military ships. Painted in 1600. *Source* https://commons.wikimedia.org/wiki/File:Archimedes-Mirror_by_Giulio_Parigi.jpg

famous, although never confirmed, is the story that during the siege of Syracuse in 212 BC, when the city was besieged by Marcus Claudius Marcellus of the Roman Republic, Archimedes devised a burning glass that was used to set fire to Roman warships (Figs. 2.1, 2.2 and 2.3).The Roman fleet was supposedly incinerated, though eventually the city was taken and Archimedes was murdered [3, 4]. This legend probably led to the future interest and research on burning glasses and lenses, by both Christian and Islamic world, including Ibn Sahl in his *On Burning Mirrors and Lenses* (tenth century), [5] Alhazen in his *Book of Optics* (1021), and many others. Both Joseph Priestley and Antoine Lavoisier used burning lenses in their experiments [6] (Fig. 2.4).

Solar Blindness

The second issue related to the concept of photocoagulation was the understanding that the light might be deleterious to human tissues. The dangerous of the light to the eye following the observation of a solar eclipse was known since antiquity. For example, in Plato's Phaedo Socrates admonished that one must take care not to look directly at the sun during an eclipse but to view the sun's reflection in water or some other such medium: „*…there is a danger in looking at the sun during an eclipse, unless the precaution is taken of looking only at the image reflected in the water, or in a glass. (…) Socrates proceeded: —I thought that as I had failed in the contemplation of true existence, I ought to be careful that I did not lose the eye of my soul; as people*

Fig. 2.2 Engraving from the title page of *Opticae Thesaurus*, a Latin edition of Ibn al-Haytham's *Book of Optics*. Among other things it shows how Archimedes allegedly set Roman ships on fire with parabolic mirrors during the Siege of Syracuse. *Source* https://commons.wikimedia.org/wiki/File:Thesaurus_opticus_Titelblatt.jpg

may injure their bodily eye by observing and gazing on the sun during an eclipse, unless they take the precaution of only looking at the image reflected in the water, or in some similar medium" [7].

Galen describes that blindness can be produced by gazing at the sun without blinking, especially during sun eclipse.

„*Indeed, if anyone wished to gaze full at the sun without blinking, he would quickly destroy his sight, and at the time of an eclipse many who wish to gain a more accurate understanding of the phenomenon and so look intently at the sun have blinded themselves completely without realizing what they were doing. And how bad for the eyes it is to walk through the snow you may learn by trying it yourself, if you do not believe Xenophon*" [8].

Galileo is known to have injured his eyes by observation of the sun with his telescope [9]. The first description of a central scotoma following a solar burn of the retina was reported by Theophilus Bonetus (1620–1689) [10]. One of the early clinical ophthalmoscopy descriptions comes from Coccius in 1853 [11], and in 1858 by Charcot who gave the description of photophthalmia and erythema produced by a small electric laboratory furnace [12]. Since than it was reported by many,

Fig. 2.3 Illustration depicting the sun's rays being focused to start a fire. Source Johann Amos Comenius. Orbis sensualium pictus. Nürnberg, 1658. https://en.wikipedia.org/wiki/Burning_glass#/media/File:OrbisPictus_b_162.jpg

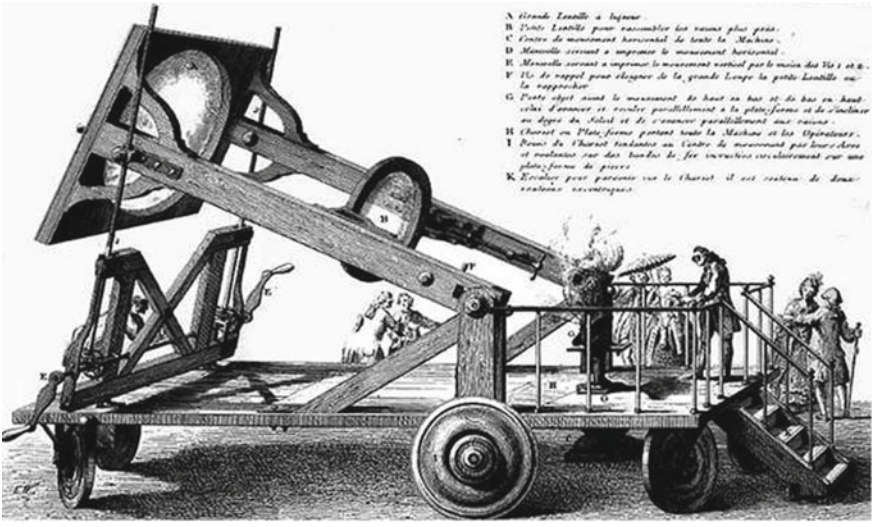


Fig. 2.4 Lavoisier with French Academy of Sciences' *lentilles ardentes*

with one of the largest series of 200 cases reported by Birch-Hirschfeld [13] and Blessig [14] after the eclipse in 1912. Interestingly, early experimental studies on the use of light energy to affect the retina started in the nineteenth century. Czerny in 1867 [15] and Deutschmann in 1882 [16] described their studies based on the use of mirrors and lens system to produce the retinal lesion in rabbits. Czerny found marked destruction of retinal elements in 10 to 15 s exposure with concentrated sun rays [15]. Deutschman reported that these changes could be noted in 1 s in the same manner [16]. In 1898 Herzog confirmed these results and reduced the exposure time to less than 1 s [17]. The introduction of the arc light in years 1879–1880 helped for more accurate and extensive study of ultra violet light which the electric arc supplies; and produced many cases of new entity „ophthalmia electrica". In 1893 Widmark reported to produce a retinal lesion with an arc light [18]. Verhoeff et al. published in 1916 an interesting study on pathological effects of radiant energy to the eye, including retinal burns conducted by carbon arc [19].

In 1927 Maggiore performed the first experimental photocoagulation of the human retina in eyes with malignant intraocular tumors by reflecting sunlight. He focused sunlight for 10 min into an eye that was to be enucleated because of a malignant tumor, and eyes were studied histologically and were found to show marked hyperemia and edema of the retinal structures [20]. In 1944, Cordes described macular burns in the military personnel who observed Japanese airplanes into the sun during the WWII [21].

Gerd Meyer-Schwickerath (1920–1992)

Meyer-Schwickerath developed the technique to obtain clinically useful results and is worldwide considered the father of retinal photocoagulation. In 1946 he, 26-year-old at that time, started his seminal work that led to the introduction of a light photocoagulation into clinical practice. It was due to his teacher Marchesani who requested his help with a medical student who was describing his own macular burn which he received while watching the sun eclipse of July 10, 1945 [22, 23]. His thesis was accepted at the University of Hamburg in 1947 [24] (Fig. 2.5).

It took him more than four years to translate the idea into the first instrument for clinical use. The first experimental device was based on a huge carbon arc from an old episcope. Although the experiments on rabbits were promising, the human results were disappointing. This led him to develop the next instrument that used the sun as the light source. This device made use of heliostate to compensate for the movement of the earth what otherwise would remove the sunlight out of the optical axis of the instrument (Fig. 2.6). The major limitation of this approach was that it could be used only on bright sunny days. In 1949, he started working on high-intensity arc, known also as Beck arc (Fig. 2.7), that he used between 1950–1956 in several hundreds of patients. In 1956, in collaboration with Dr. Hans Littmann from Zeiss they developed first commercially available device, Zeiss photocoagulator with xenon arc (Fig. 2.8). The first cases treated with photocoagulation were a peripheral horseshoe-shaped

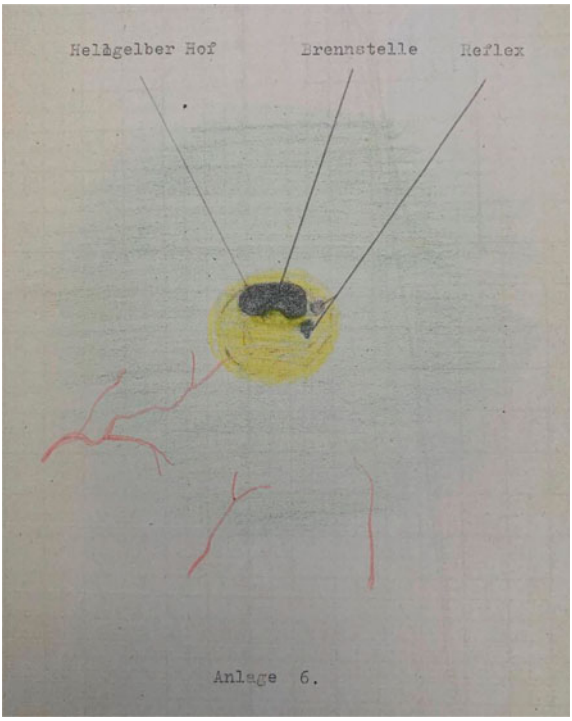


Fig. 2.5 The 1947 drawing of a "retinopathia solaris" that sparked Meyer-Schwickerath's idea of photocoagulation. (*Source* Hamm H. Zentralskotom nach Sonnenblendung. [dissertation]. University of Hamburg, Hamburg, Germany. 1947)

tear with no retinal detachment and a traumatic macular hole. He later developed treatment protocols for intraocular tumors, Eales disease, Coats disease, and von Hippel-Lindau angiomatosis [25–29].

He was also first to treat diabetic retinopathy with light coagulation between 1955 and 1959, but results were disappointing [30]. In 1964, Schott from Essen in Germany reported the convincing and positive results of treating 58 patients. He advocated the treatment in advanced background and early proliferative phase retinopathies. He proposed the number of up to 200 individual coagulations within 2–3 sessions. This gave the origin to panretinal coagulation [31]. In 1968, Meyer-Schwickerath and Schott, proposed that the signs and symptoms of diabetic retinopathy can be reversed if treatment if performed in the early stages and that photocoagulation in the early stages can prevent the late complications of proliferation, hemorrhage, and retinal detachment [30].

José Morón Salas (1918–2000)

What is much less-known that before Meyer-Schwickerath, Spanish ophthalmologist José Morón Salas (1918–2000) conducted similar experiments [32, 33]. In fact, he

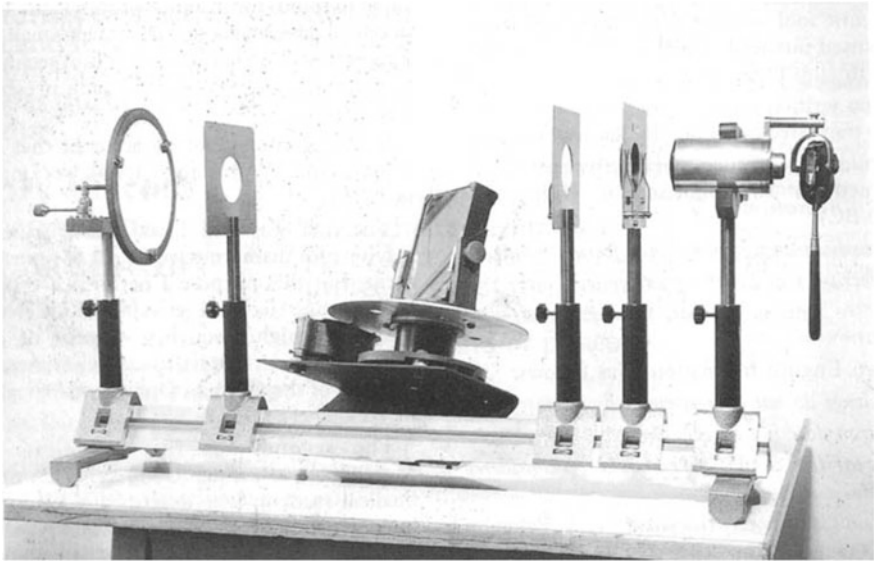


Fig. 2.6 Sunlight photocoagulator with heliostate

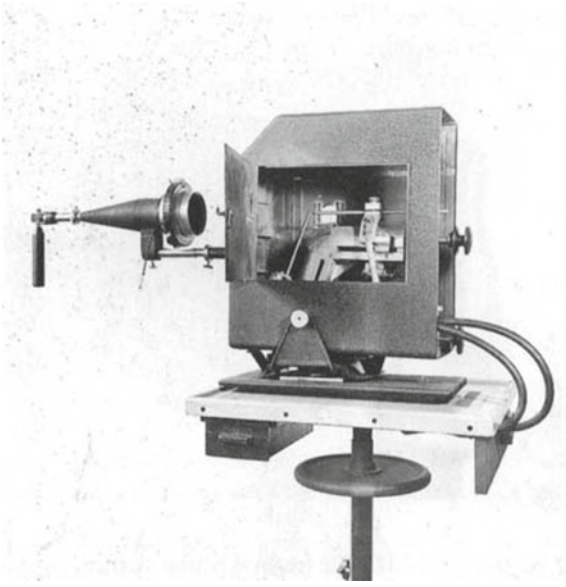


Fig. 2.7 Beck arc photocoagulator

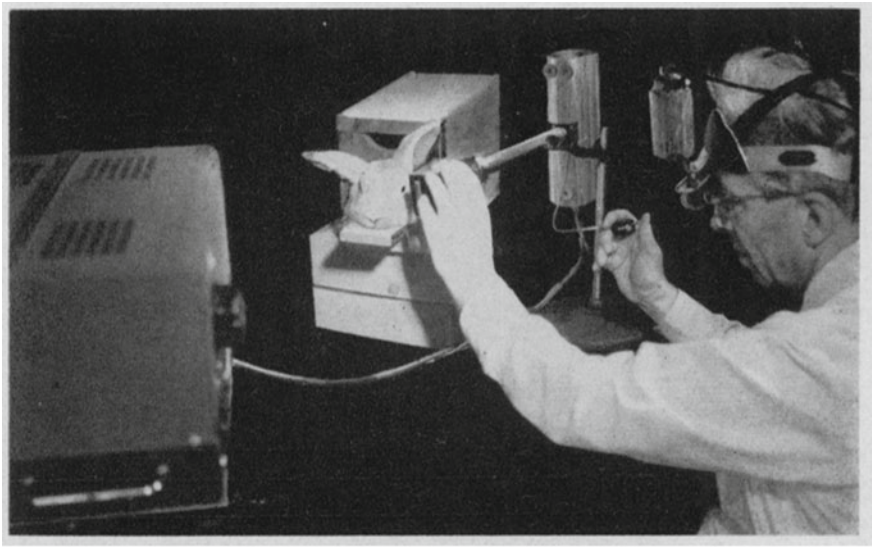


Fig. 2.8 Zeiss photocoagulator with xenon arc

was the author of the first known experience of therapeutic photocoagulation of retina, because he had previously used a similar technique in rabbit and human eyes in 1945 and 1946. These studies were described in his doctoral dissertation, which was defended in 1946, almost three years before Meyer-Schwickerath. He wrote: *"(…) scars produced by sunlight are very variable in intensity, depending on the stational variations, amount of sunlight, moment of the day, atmospheric changes, ophthalmoscopy lens position, (…) pupil size, refractive status of the patient, media transparency, retinal pigmentation, gaze direction, (…)"* [34]. Interestingly, Morón did not publish his results until 1950, when after reading the Meyer-Schwickerath´s reports he decided to share his experiences [35]. Due to the limitations derived from the sunlight variations, he searched for a different light source. All trials with lamps with filament were negative, and he tried with an arc lamp up to 15 amperes. In 1946, he practiced the procedure with an intense white light in four patients with retinal detachment. After pharmacological mydriasis, the patient kept his gaze in the same direction that of the light, Moron placed the voltaic arc in the place of the observer. The exposition time was 5 min. The results were unsatisfactory, the fixation was not good enough and patients complained with heating. Later, he tried the same procedure in two patients with retinal tear without retinal detachment, and the final lesion was not strong enough to close a retinal tear. Morón postulated that ideal conditions to treat a retinal tear with light photocoagulation, include the attached retina, not peripheral tear, dark fundus, clean ocular media, emmetropia and good mydriasis. He noted also that he had never treated a case with such a favorable condition, and remarked that Meyer-Schwickerath was luckier or more perseverant than him, getting what he was looking for, and resolving three retinal detachment cases with that technique.

Fig. 2.9 The Spanish ophthalmologist José Morón Salas (1918–2000) (right) with Dr. Antonio Olivella (left) and Prof. Meyer-Schwickerath (center) in the Retina Symposium celebrated in Sevilla in 1983

Interestingly, Meyer-Schwickerath mentioned in his first articles Morón as one of the precursors in the idea of photocoagulation [29] (Fig. 2.9).

Other Important Contributors

The first successful clinical application of photocoagulation in USA was performed in 1957 by Guerry, Wiesinger and Ham [36]. They photocoagulated a central von Hippel's hemangioma of 2–3 diameters in size with a light beam from an experimental instrument built for retinal burn studies in rabbits. This device employed a 24-inch carbon arc searchlight as light source with an ellipsoidal mirror for reduction of the solid cone of radiation. They reported only a faint macular scar after four years and improvement in visual acuity from 20/200 and large central scotoma to 20/70 with a small scotoma. The same authors presented their clinical and experimental experiences with light coagulation in several subsequent articles. This group, later with W. Geeraets, was very well-prepared for early light coagulation studies since they have worked earlier on the toxicity of light produced by atomic bomb to the eye structures [37–39]. Later, they become the leading groups in photocoagulation in USA [40–42]. In 1958 Guinan presented his observations from his visit to Bonn University to Mayer-Schwickerath [43], and Ten Doesschate reported a few cases

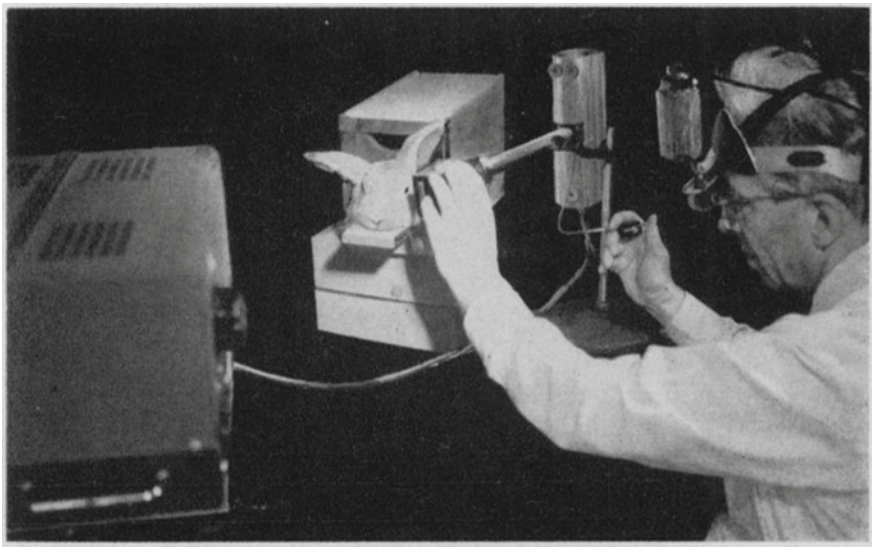


Fig. 2.10 Operator with binocular indirect ophthalmoscope exposing rabbit eye to light coagulation. *Source* Brockhurst RJ, Wolf E, Schepens CL. Light coagulation with indirect ophthalmoscopy. AMA Arch Ophthalmol. 1959 Apr;61(4):528–32

treated with photocoagulation, including choroidal melanoma, peripheral degenerations with retinal holes, flat retinal detachments with retinal holes [44]. In 1959, Heinzen, Ricci, Dubler and DuFour presented a report from 3 Swiss ophthalmology clinics on their experiences with light coagulation [45], and Brockhurst et al. reported on light coagulation with indirect ophthalmology [46] (Fig. 2.10).

In the following years, photocoagulation found application in the prevention and treatment of retinal detachment. One of the first to notice this was Meyer-Schwickerath. This was proposed in 1959 by Linnen, in 1960 by Boecke, Girard, Havener, Murreh, Pischel et al., Nowell et al., and Cibis [47–57]. In the same year, Heinzen published an extensive monograph on the prophylactic treatment of retinal detachment and presented critical discussion of indications and contraindications for the light coagulation for this purpose [58]. This time of enthusiasm and reserve towards the new treatment possibilities, introduced first by light coagulation, and later by lasers, is interestingly described in interview by American Academy of Ophthalmology Oral History Collections with DuPont Guerry III, MD and Dohrmann Kaspar Pischel, MD, two pioneers of these technologies in USA [59, 60].

The Complicated Beginnings of Laser

Max Planck in 1900 showed based on his studies on the radiancy of light that light is a form of electromagnetic radiation. Then, Albert Einstein in 1917 proposed the theory of stimulated emission in his work on *quantum theory of radiation.* This argued that light travels in units of energy called photons, and that most atoms exist in a standard ground energy stage, however, some occur at higher energy levels. Einstein postulated that by adding energy to atoms in a ground energy level they could be excited to a higher energy level. Then, when returning to their ground energy level, atoms emit the energy they acquired spontaneously in the form of photons or electromagnetic wave. In short, this concept led to the stimulated emission that was the fundament of laser development. In 1951, Charles Townes (1915–2015) (Fig. 2.11) conceived a new way to create intense, precise beams of coherent radiation, for which he invented the acronym *maser* (for Microwave Amplification by Stimulated Emission of Radiation). Townes in collaboration with James P. Gordon, and Herbert J. Zeiger built the first ammonia maser that used stimulated emission in a stream of energized ammonia molecules to produce amplification of microwaves at a frequency of about 24.0 gigahertz at Columbia University in New York in 1953. He also received the patent for "microwave oscillator" in 1957. In 1956, Gordon Gould (1920–2005) proposed using optical pumping to excite a maser, and discussed this idea with Townes, who advised him on how to obtain a patent on his innovation, and agreed to act as a witness. In 1957, Gould realized that an appropriate optical resonator can be made by using two mirrors in the form of a Fabry–Pérot interferometer what would produce a narrow, coherent, intense beam. He also coined the name of laser and many possible applications of such a device. Gould had his ideas witnessed and notarized. At the same time Arthur Schawlow and Charles Townes discovered the importance of the Fabry–Pérot cavity and called the resulting device an "optical maser". They submitted patent application for "masers and maser communication systems" in 1958, and it was issued in 1960. Gould recorded his analysis and suggested applications in a laboratory notebook under the heading "Some rough calculations on the feasibility of a LASER: Light Amplification by Stimulated Emission of Radiation"—the first recorded use of this acronym (Fig. 2.12). Gould's notebook was the first written prescription for preparing a potentially working laser. Then, the story gets much more complicated, because Gould did not patent nor publish his concept at that time. He believed incorrectly that he needed to build a working laser to do this, he left Columbia University without completing his doctoral degree and joined a private research company TRG (Technical Research Group) that obtained funding for his project from the Advanced Research Projects Agency. The government declared the project classified, which meant that a security clearance was required to work on it, and Gould due to his former participation in communist activities, was unable to obtain a clearance what greatly complicated his participation in the project and extended its duration [61–63].

In 1958 Schawlow and Townes, both later Nobel Prize awardees (Fig. 2.13), were the first to publish the theory of laser design and operation in their seminal 1958

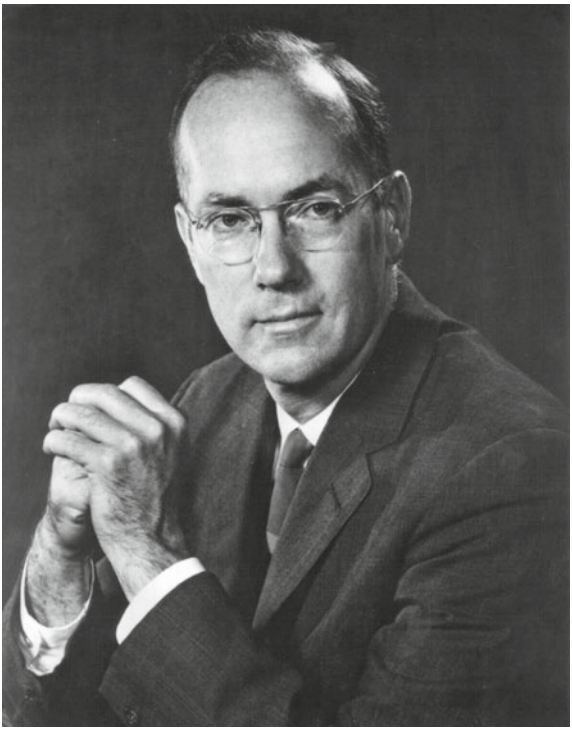
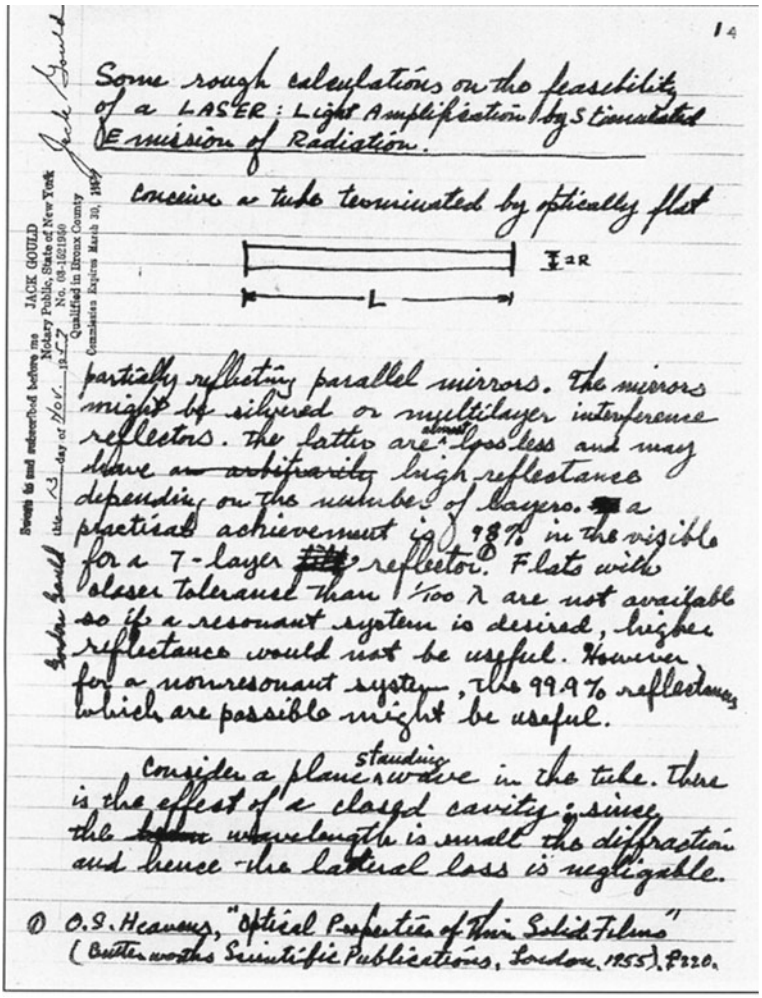


Fig. 2.11 Charles Townes (1915–2015). *Source* https://commons.wikimedia.org/wiki/File:Charles_Townes.jpg

paper on "optical masers" [64]. Townes along with Nikolay Basov and Alexander Prokhorov received the 1964 Nobel Prize in Physics "for fundamental work in the field of quantum electronics, which has led to the construction of oscillators and amplifiers based on the maser-laser principle". Schawlow shared the 1981 Nobel Prize in Physics with Nicolas Bloembergen and Kai Siegbahn for their contributions to the development of laser spectroscopy. On the other hand, Gould is often credited with the "invention" of the laser, due to his unpublished work that predated Schawlow and Townes by a few months. Due to the aforementioned difficulties, TRG and Gould was beaten in the race to build the first working laser by Theodore Maiman (1927–2000) (Fig. 2.14) at Hughes Research Laboratories, who made the first working laser in 1960. After reading the paper by Schawlow and Townes, Maiman turned to the development of a laser based on his own design with a synthetic ruby crystal. On May 16, 1960, his solid-state pink ruby laser emitted mankind's first coherent light, with rays all the same wavelength and fully in phase. Maiman documented his invention in *Nature* [65]. His piece consisted of two simple figures, fewer than 300 words, and the device itself looked surprising in its simplicity. It is known that Maiman had begun conceptualizing a solid-state laser design even before he undertook the maser project at Hughes. Moving the microwave frequency of masers up the electromagnetic spectrum 50,000-fold to the frequency of light would require finding a feasible lasing medium and excitation source and designing the system.


14

Some rough calculations on the feasibility of a LASER: Light Amplification by Stimulated Emission of Radiation.

Conceive a tube terminated by optically flat

2R

L

partially reflecting parallel mirrors. The mirrors might be silvered or multilayer interference reflectors. The latter are almost loss-less and may have an arbitrarily high reflectance depending on the number of layers. A practical achievement is 98% in the visible for a 7-layer reflector. Flats with closer tolerance than 1/100 λ are not available so if a resonant system is desired, higher reflectance would not be useful. However for a nonresonant system, the 99.9% reflectances which are possible might be useful.

Consider a plane standing wave in the tube. There is the effect of a closed cavity since the wavelength is small the diffraction and hence the lateral loss is negligable.

① O.S. Heavens, "Optical Properties of Thin Solid Films" (Butterworths Scientific Publications, London, 1955), P220.

Sworn to and subscribed before me this 13 day of Nov. 1957
JACK GOULD
Notary Public, State of New York
No. 60-1621500
Qualified in Bronx County
Commission Expires March 30, 1959

Jack Gould

Gordon Gould

Fig. 2.12 The first page of the notebook in which Gould coined the acronym LASER and described the essential elements for constructing one

This laser had a wavelength of 694.3 nm. At the same time, other research groups at IBM, Bell Labs, MIT, Westinghouse, Radio Corporation of America, and Columbia University, among others, were also pursuing projects to develop a laser. Maiman submitted patent application for "Ruby laser systems" in 1961, and it was issued in 1967 (Fig. 2.15).

Gould spent next 30 years fighting with the United States Patent and Trademark Office to obtain patents for the laser and related technologies, and with laser manufacturers in court to enforce the patents he subsequently did obtain. Finally, in 1985 Gould won his battle, was issued 48 patents, with the optical pumping, collisional

Fig. 2.13 Charles Townes receiving Noble Prize in 1964. *Source* https://m.facebook.com/nobelprize/photos/a.164901829102/10158808321239103/?type=3

Fig. 2.14 Theodore Maiman (1927–2007) *Source* https://en.wikipedia.org/wiki/Theodore_Maiman#/media/File:Maiman_with_the_first_laser.jpg

Fig. 2.15 Maiman with his laser in July 1960 https://en.wikipedia.org/wiki/Theodore_Maiman#/media/File:Theodore_Maiman_1960.jpg

pumping, and applications patents being the most important, including technologies covering most lasers used at the time, like the first operating laser, a ruby laser. The spread of lasers into many areas of technology meant that the patents were much more valuable than if Gould had won initially, and he made of them several million dollars. Gould was elected to the National Inventors Hall of Fame in 1991 for inventing optically pumped laser amplifier [66, 67].

In conclusion, credit for the invention of the laser is disputed, since Gould conceived the idea, Townes and Schawlow were the first to publish the theory and Maiman was the first to build a working laser.

Beginnings of Lasers in Ophthalmology

Maiman's laser introduced in 1960 opened the ophthalmic world doors to many new applications (Fig. 2.16). In 1961 Zaret started experimentations with ruby laser photocoagulation in the rabbit retina, and in 1962 Campbell and Zweng started using it in human treatment [68–72]. The experimental studies were continued by Kapany, Noyori, Geeraets and Ham, among few more [73–75] (Figs. 2.17 and 2.18). The

ruby laser was useful in sealing retinal holes, but not very helpful in the treatment of vascular disorders. Moreover, it was related with instability of the beam and inconvenient pulse duration. In 1961 Ali Javan, William Bennett and Donald Herriott of Bell Laboratories described a different kind of laser, using a mixture of helium and neon as the active medium and producing a continuous beam rather than a series of pulses [76]. Not long afterwards, a laser based on carbon dioxide was proposed. Gas lasers due to their ease of construction, efficiency, and versatility became, both scientifically and commercially a dominant technology in the next decades.

The blue-green argon laser was developed in the Edward Harkness Laboratories in the Columbia Presbyterian Medical Center in 1965, and the first study on humans was conducted by Francis A. L'Esperance in 1968 [71]. He reported that the argon ion laser produced a coherent, monochromatic blue-green beam of intense light energy that is 4.5 times more effectively absorbed by hemoglobin and vascular structures than xenon-arc radiation, and 7–8 times than ruby laser radiation; can be absorbed even more effectively in vascular lesions by the intravenous addition of sodium fluorescein, can deliver more continous wave (cw) power through the ocular medium and produce a greater cw power density at the retina than any other light source. Moreover, he showed that the blue-green beam had greater inherent energy per photon than any laser source considered for photocoagulation therapy, and that the argon laser produced radiation that was more highly absorbed per incident photon at the pigment epithelium than any existing photocoagulation system [71]. In 1969, over

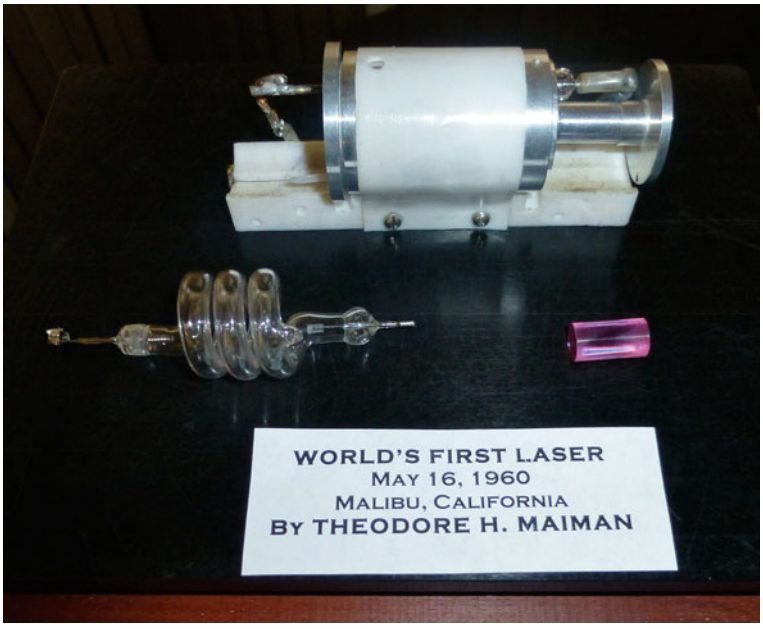


Fig. 2.16 World's first laser https://en.wikipedia.org/wiki/Theodore_Maiman#/media/File:World's_first_laser_out_of_case.jpg

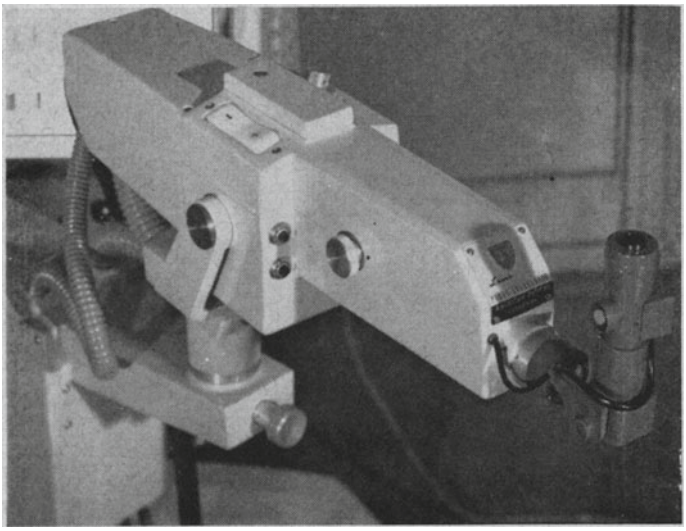


Fig. 2.17 Ruby laser photocoagulator. *Source* Campbell CJ, Koester CJ, Curtice V, Noyori KS, Rittler MC. Clincal studies in laser photocoagulation. Arch Ophthalmol. 1965 Jul;74:57–65

500 human subjects with different disorders were treated by him using argon laser photocoagulation. This has opened a new dimension in photocoagulation therapy. The argon laser permitted precise focusing and the placement of photocoagulation spots as small as 30 to 50 micra in diameter, thus was well suited to the treatment of macular disorders. The continuous gas phase allowed relatively slow release of energy avoiding the "explosive effect" that occurred with the ruby laser. The experimental and human studies by L'Esperance [77, 78], Patz, Little, Zwang, Peabody [79–85] and Behrendt [86] led to the introduction of a commercially available unit in 1971. Patz et al. presented 100 consecutive cases of macular diseases treated with the argon laser photocoagulator. They pointed advantages of this therapy due to the precise focusing qualities of the argon laser beam and the ability to place spots of coagulation as small as 30 to 50 micra [82]. Meanwhile, krypton and YAG laser were used in clinical trials (Fig. 2.19).

In 1990 Pankratov invented a novel laser modality, in which the laser energy was delivered in short pulses or "micro pulses" instead of continuous wave [87]. Micropulsing allowed selective treatment of the retinal pigment epithelium (RPE) and sparing of the neurosensory retina [88, 89]. Micropulsed lasers due to use of high treatment powers and / or micropulse duty cycles reduced the thermal retinal damage. However, the belief that achieving a therapeutic effect is directly related to laser-induced thermal retinal injury was very strong. Further developments in producing shorter microsecond continuous-wave laser pulses, including Birngruber and colleagues in 1992, helped sparing the photoreceptors and other intraretinal cells and selectively target the retinal pigment epithelium (RPE) leading to coin the term "Selective Retina Therapy" [90, 91]. In the beginning of 1990s Journee-de Korver

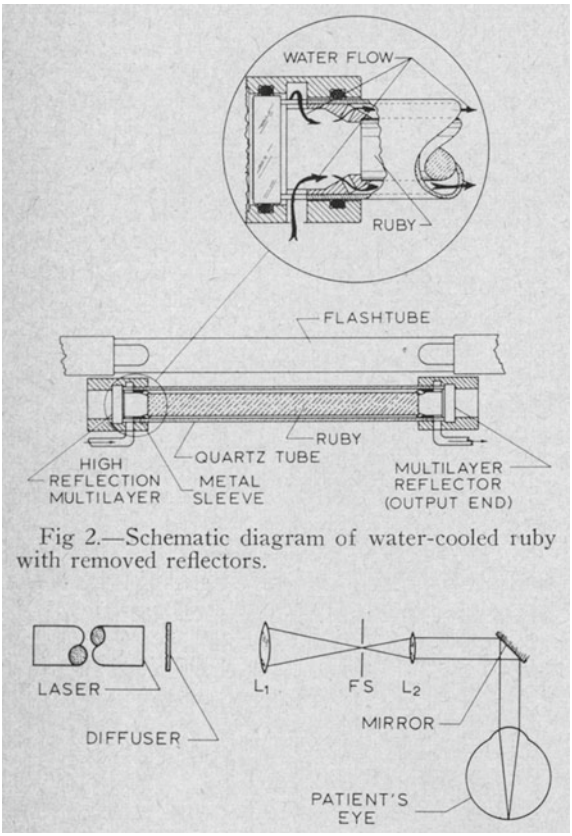


Fig. 2.18 Schematic diagram of a portion of the optical system. *Source* Campbell CJ, Koester CJ, Curtice V, Noyori KS, Rittler MC. Clincal studies in laser photocoagulation. Arch Ophthalmol. 1965 Jul;74:57–65

et al. studied the destructive effect of hyperthermia at sub-photocoagulation level of 45–60 °C on melanomas. They performed transpupillary thermotherapy (TTT) with a diode laser at 810 nm in patients with choroidal melanomas prior to enucleation and showed the possible advantages of this approach [92]. Later, the concept that micropulsed laser parameters (high-density/low-intensity "true" Subthreshold Diode Micropulse laser, or "SDM") without any laser-induced retina injury can be clinically effective was confirmed [93].

Conclusions

Light is the source of life on earth for both plants and animals. Since ancient times it has been understood that light can be the source of life and death. The awareness that light is a source of great energy that can be dangerous to health, including vision existed already in antiquity. From antiquity, this knowledge could also be used for military purposes, as evidenced by the history of Archimedes. In the middle of the

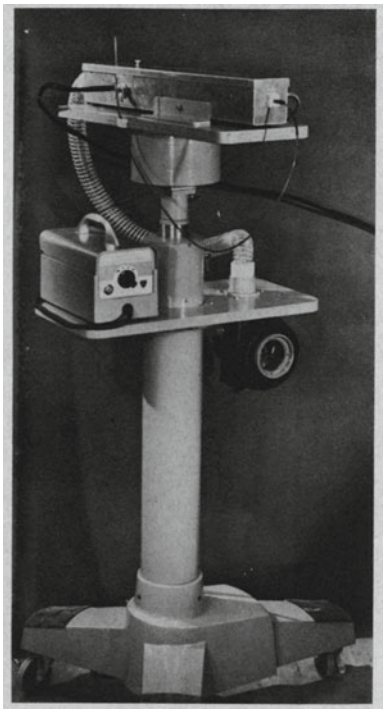


Fig. 2.19 Neodymium fiber laser, fiber optics iluminator, and curved tip for scleral surgery. *Source* Campbell CJ, Noyori KS, Rittler MC, Innis RE, Koester CJ. The application of fiber laser techniques to retinal surgery. Arch Ophthalmol. 1964 Dec;72:850–7

twentieth century, after earlier unsuccessful attempts, Meyer-Schwickerath was able to show that light can be used treat some retinal disorders. This, later supported by lasers led to the introduction of standard laser treatment in ophthalmology. The main weakness of this approach, however, was its disruptive nature, which for years was assumed to be essential and inextricably linked to the potential benefits of treatment.

This, however, has changed in recent years. The concept of subthreashold laser therapy radically changes our current thinking about this form of treatment. According to this concept, it is possible to achieve therapeutic effects in various diseases of the retina without simultaneously destroying the relevant areas of the retina. Although, presently we cannot evaluate all pathophysiology pathways behind this approach in very complicated cellular and molecular environment of the retina, however, the accumulating data shows that this the future of laser therapy. The future experimental studies should help us to better adjust the laser beam characteristics (wavelength, power, size, duration, etc.) to expected outcomes, what should make this approach even more effective than it is nowadays. It might also help to enter new fields for lasers, including early treatment, that was not possible with destructive character of traditional laser therapy. Moreover, new disorders might be treated with a therapy that is safe, and non-destructive. Although we still did not enter the field of known knowns in subthreshold laser therapy, but in recent decades we certainly moved from unknown unknowns to known unknowns.

References

1. Sherwood AN, Nikolic M, Humphrey JW, Oleson JP. Greek and roman technology: a sourcebook of translated greek and roman texts, p 25. Routledge; 2019
2. Plantzos D. Crystals and lenses in the graeco-roman world. Am J Archaeol. 1997;101(3):451–64.
3. Stavroudis ON. Comments on: on archimedes' burning glass. Appl Opt. 1973;12(10):A16.
4. Claus AC. On archimedes' burning glass. Appl Opt. 1973;12(10):A14.
5. Rashed R. A pioneer in anaclastics: Ibn Sahl on burning mirrors and lenses. Isis. 1990;81(3):464–91.
6. Lynall G. 'Bundling up the sun-beams': burning mirrors in eighteenth-century knowledge and culture. J Eighteenth-Century Stud. 2013;36(4):477–90.
7. Plato. Phaedo: The last hours of Socrates (Jowett B, Trans). Createspace Independent Pub; 2013.
8. Galen. On the usefulness of the parts of the body translated from the Greek with an introduction and commentary by Margaret Tallmadge May. Ithaca, N.Y. : Cornell University Press, 1968; vol. 2; the 10th book [II, 68], p: 474.
9. Birch-Hirschfeld, Die Wirkung der strahlenden Energie auf das Auge, Allgem. Path, des Auges, Lubarsch-Ostertag; 1910.
10. Bonetus T. Sepulchretum sive anatomia practica: Cramer & Pérachon; 1700.
11. Coccius EA. Ueber Die Anwendung Des Augen-Spiegels Nebst Angabe Eines Neuen Instrumentes. 1853.
12. Charcot, Erytheme de la face et ophtalmie produits par l'action de la lumiere electrique, Comptes rendus des seances et memoires de la Soc. de Biologie 1858:63–65.
13. Birch-Hirschfeld, Stimmel Beitrag zur Schädigung des Auges durch Blendung. Graefe's Arhiv für Ophthalmologie. 1915;90:138–154
14. Blessig: Über Schädigung der Augen durch Beobachtung der Sonnenfinsternis Petersb. med. Z. 1912;37:365
15. Czerny W. Über die Blendung der Netzhaut durch Sonnenlicht. Sitzungsberichte d. mathem-naturwiss Klasse der Kaiserl Akad d Wiss, Wien, 56 II Abtl. 1867 409–428.
16. Deutschmann R. Über die Blendung durch direktes Sonnenlicht. Graefe's Arch f Ophthalm. 1882; XXVIII (3):241–244.
17. Herzog H. Diskussion zum Vortrag Birch-Hirschfeld, Bericht d. ophth. Ges, p. 164. Heidelberg; 1903.
18. Widmark J. Uber Blendung der Netzhaut. Skandinavisches Archiv Für Physiologie. 1893; 4:281–295.
19. Verhoeff FH, Bell L, Walker CB. The pathological effects of radiant energy on the eye: an experimental investigation, with a systematic review of the literature. Proc Am Acad Arts Sci. 1916; 51(13):627, 629–818.
20. Maggiore L. Contributo sperimentale alle alterazioni retiniche negli occhicemani esposti a luce intense. Rome: Atti Congr Soc Ital Oftal; 1927. p. 42.
21. Cordes FC. A type of foveo-macular retinitis observed in the U S. Navy. Am J Ophthalmol. 1944;27(8):803–16.
22. Meyer-Schwickerath GR. The history of photocoagulation. Aust N Z J Ophthalmol. 1989;17(4):427–34.
23. Meyer-Schwickerath G. History and development of photocoagulation. Am J Ophthalmol. 1967;63(6):1812–4.
24. Kirchhof B, Joussen A, Bornfeld N, Wessing A. Prof. Dr. med. Dr. h.c. mult. Gerd Meyer-Schwickerath inventor of light coagulation on his 100th birthday; 2020.
25. Hamm H. Zentralskotom nach Sonnenblendung. [dissertation]. University of Hamburg, Hamburg, Germany; 1947.
26. Meyer-Schwickerath G. Koagulation der Netzhaut mit Sonnenlicht. Ber Dtsch Ophthalmol Ges. 1949;55:256–9.

27. Meyer-Schwickerath G. Lichtkoagulation; eine Methode zur Behandlung und Verhütung der Netzhautablösung [Light coagulation; a method for treatment and prevention of the retinal detachment]. Albrecht Von Graefes Arch Ophthalmol. 1954;156(1):2–34.
28. Meyer-Schwickerath G. Prophylactic treatment of retinal detachment by light-coagulation. Trans Ophthalmol Soc U K. 1956;76:739–50.
29. Meyer-Schwickerath G. Further progress in the field of light coagulation. Trans Ophthalmol Soc U K. 1957;77:421–37; discussion 437–40.
30. Meyer-Schwickerath G. Lichtkoagulation, p. 2. Stuttgart; 1959.
31. Meyer-Schwickerath RE, Schott K. Diabetic retinopathy and photocoagulation. Am J Ophthalmol. 1968;66(4):597–603.
32. Schott K. Weitere Erfahrungen mit der Lichtcoagulation bei Retinopathia diabetica [Further experiences in the use of light coagulation in the treatment of diabetic retinopathy]. Ber Zusammenkunft Dtsch Ophthalmol Ges. 1965;66:349–55.
33. Ascaso FJ, Grzybowski A. José Morón was the first to introduce the retinal light photocoagulation. Acta Ophthalmol. 2022;100(2):234–6.
34. Grzybowski A, Ascaso FJ. The evolution of laser therapy in ophthalmology: a perspective on the interactions between photons, patients, physicians, and physicists: the LXX Edward Jackson Memorial Lecture. Am J Ophthalmol. 2015;159:206.
35. Morón J. Sobre etiología y patogenia de los fototraumatismos retinianos. Doctoral dissertation. Madrid, November 22 (Complutense University Library, Madrid, Spain). 1946.
36. Morón J. Obliteración de los desgarros retinianos por quemadura con luz. Arch Soc Oftalmol Hisp Am. 1950;10:566–78.
37. Guerry D 3rd, HAM WT Jr, WIESINGER H. Photocoagulation of the retina: report of a successfully treated case of angiomatosis retinae. Am J Ophthalmol. 1958;46(4):463–6.
38. Shaffer MC. Experimental production of flash burns in the rabbit retina. Trans Am Ophthalmol Soc. 1956;54:259–71; discussion, 271–3.
39. Guerry D 3rd, Ham WT Jr, Ruffin RS, Schmidt FH, Tiller CO, Wiesinger H, Williams RC. The transmission of light; through the ocular media of the rabbit eye. Am J Ophthalmol. 1956;42(6):907–10.
40. Ham WT Jr, Wiesinger H, Guerry D 3rd, Schmidt FH, Williams RC, Ruffin RS, Shaffer MC. Experimental production of flash burns in the rabbit retina. Am J Ophthalmol. 1957;43(5):711–8.
41. Guerry D 3rd, Wiesinger H. Light coagulation. Am J Ophthalmol. 1960;49:87–96.
42. Geeraets WJ, Williams RC, Chan G, Ham WT Jr, Guerry D 3rd, Schmidt FH. The loss of light energy in retina and choroid. Arch Ophthalmol. 1960;64:606–15.
43. Guerry D 3rd, Ham WT Jr, Wiesinger H, Schmidt FH, Williams RC, Ruffin RS, Wiesinger H, Guerry D 3rd, Geeraets WJ. Recent experiences with light coagulation. Arch Ophthalmol. 1960;64:254–9.
44. Guinan PM. Where light-coagulation stands today: a visit to Dr. Meyer-Schwickerath at Bonn. Trans Ophthalmol Soc U K. 1958;78:681–91.
45. Doesschate TEN. Light-coagulation of fundus lesions: demonstration of an apparatus and a report on the first clinical results. Ophthalmologica. 1958;135(4):317–24.
46. Heinzen H, Ricci A, Dubler H, Dufour R. Premiers résultats obtenus en Suisse avec le photocautère de Meyer-Schwickerath [First results obtained with photocautery of Meyer-Schwickerath in Switzerland]. Ophthalmologica. 1959;137(3):194–203.
47. Brockhurst RJ, Wolf E, Schepens CL. Light coagulation with indirect ophthalmoscopy. AMA Arch Ophthalmol. 1959;61(4):528–32.
48. Linnen HJ. Symposium on light coagulation. Lausanne, September; 1959.
49. Boeke W. On the combination of scleral buckling with light coagulation in the therapy of retinal detachment. Klin Monbl Augenheilkd Augenarztl Fortbild. 1960;136:355–62.
50. Girard LJ. Full thickness scleral buckling using silicon rubber rodding and the light coagulator. Highlights Ophthal. 4:42:1960–1961.
51. Havener WH. Clinical experiences with the photocoagulator. Am J Ophthalmol. 1960;49:1212–8.

52. Murrahwf Jr. Surgery and light coagulation in the treatment of retinal detachment. J Tn State Med Assoc. 1960; 53:305.
53. Pischel DK. The present status of retinal detachment operations. Trans Ophthalmol Soc N Z. 1960;12:50–67.
54. Pischel DK, Colyear BH Jr. Clinical results of light coagulation therapy. Am J Ophthalmol. 1960;50:590–5.
55. Colyear BH Jr, Pischel DK. Preventive treatment of retinal detachment by means of light coagulation. Trans Pac Coast Otoophthalmol Soc Annu Meet. 1960;41:193–217.
56. Nowell JF, Haik GM. Light coagulation in retinal detachment surgery. J La State Med Soc. 1960;112:354–9.
57. Nowell JF, Ellis GS. Light coagulation in the treatment of retinal disease. South Med J. 1961;54:395–402.
58. Cibis PA. Limits and hazards of photocoagulation. Trans Am Acad Ophthalmol Otolaryngol. 1962;66:71–87.
59. Heinzen H. Die **prophylaktische** Behandlung der Netzhautablösung. Stuttgart: Enke; 1960.
60. https://digitalassets.lib.berkeley.edu/rohoia/ucb/text/richopthalmologist00guerrich.pdf.
61. https://ia800501.us.archive.org/13/items/americanlinks00piscrich/americanlinks00piscrich.pdf.
62. Torsiglieri AJ, Baker WO. The origins of the laser. Science. 1978;199(4333):1022–6.
63. Myers RA, Dixon RW. Who invented the laser: an analysis of the early patents. Hist Stud Phys Biol Sci. 2003;34:115–149.
64. Hertzberg R. A short history of ophthalmic laser. Aust N Z J Ophthalmol. 1986;14(4):387–8.
65. Schawlow AL, Townes CH. Infrared and optical masers. Phys Rev. 1958; 112(6–15):1940–1949.
66. Maiman T. Stimulated optical radiation in ruby. Nature. 1960;187:493–4.
67. Sixty years of lasers. Nat Rev Phys. 2020;2:221. https://doi.org/10.1038/s42254-020-0181-9.
68. Taylor N. Laser: the inventor, the nobel laureate, and the thirty-year patent war. New York: Simon & Schuster; 2000.
69. Campbell CJ, Rittler MC, Koester CJ. The optical maser as a retinal coagulator: an evaluation. Trans Am Acad Ophthalmol Otolaryngol. 1963;67:58–67.
70. Campbell CJ, Noyori KS, Rittler MC, Innis RE, Koester CJ. The application of fiber laser techniques to retinal surgery. Arch Ophthalmol. 1964;72:850–7.
71. Campbell CJ, Koester CJ, Curtice V, Noyori KS, Rittler MC. Clinical studies in laser photocoagulation. Arch Ophthalmol. 1965;74:57–65.
72. Campbell CJ, Rittler MC, Koester CJ. Laser photocoagulation of the retina. Trans Am Acad Ophthalmol Otolaryngol. 1966;70(6):939–43.
73. Flocks M, Zweng HC. laser coagulation of ocular tissues. Arch Ophthalmol. 1964;72:604–11.
74. Kapany NS, Peppers NA, Zweng HC, Flocks M. Retinal photocoagulation by lasers. Nature. 1963;13(199):146–9.
75. Noyori KS, Campbell CJ, Rittler MC, Koester C. Ocular thermal effects produced by photocoagulation. Arch Ophthalmol. 1963;70:817–22.
76. Ham WT Jr, Williams RC, Geeraets WJ, Ruffin RS, Mueller HA. Optical masers (Lasers). Acta Ophthalmol. 1963; (76):60–78.
77. Javan A, Bennett WR Jr, Herriott DR. Population inversion and continuous optical maser oscillation in a gas discharge containing a He-Ne mixture. Phys Rev Lett. 1961;6:106.
78. Lèsperance FA Jr. An opthalmic argon laser photocoagulation system: design, construction, and laboratory investigations. Trans Am Ophthalmol Soc. 1968;66:827–904.
79. Lèsperance FA Jr. The treatment of ophthalmic vascular disease by argon laser photocoagulation. Trans Am Acad Ophthalmol Otolaryngol. 1969 Nov-Dec;73(6):1077–96.
80. Zweng HC, Flocks M, Kapany NS, Silbertrust N, Peppers NA. Experimental laser photocoagulation. Am J Ophthalmol. 1964;58:353–62.
81. Zweng HC. Retinal laser photocoagulation. Trans Pac Coast Otoophthalmol Soc Annu Meet. 1964;45:423–39.

82. Zweng HC, Little HL, Peabody RR. Laser photocoagulation and retinal angiography. St. Louis, C. V. Mosby Co.; 1969.
83. Patz A, Maumenee AE, Ryan SJ. Argon laser photocoagulation in macular diseases. Trans Am Ophthalmol Soc. 1971;69:71–83.
84. Little HL, Zweng HC, Peabody RR. Argon laser slit-lamp retinal photocoagulation. Trans Am Acad Ophthalmol Otolaryngol. 1970;74(1):85–97.
85. Peabody RR, Zweng HC, Little HL. Treatment of retinal vascular disease with argon laser slit lamp photocoagulation. Trans Pac Coast Otoophthalmol Soc Annu Meet. 1970;51:307–26.
86. Behrendt T. Multiline argon laser. Arch Ophthalmol. 1971;85(3):355–8.
87. Pankratov MM. Pulsed delivery of laser energy in experimental thermal retinal photocoagulation. Proc SPIE. 1990;1202:205–13.
88. Roider J, Hillenkamp F, Flotte TJ, Birngruber R. Microphotocoagulation: selective effects of repetitive short laser pulses. Proc Natl Acad Sci USA. 1993;90(11):2037–8.
89. Pankratov MM. Pulsed delivery of laser energy in experimental thermal retinal photocoagulation. Proc Soc Photo Opt Instrum Eng. 1990;1202:205–213.
90. Roider J, Brinkmann R, Wirbelauer C, Laqua H, Birngruber R. Subthreshold (retinal pigment epithelium) photocoagulation in macular diseases: a pilot study. Br J Ophthalmol. 2000;84(1):40–7.
91. Brinkmann R, Roider J, Birngruber R. Selective retina therapy (SRT): a review on methods, techniques, preclinical and first clinical results. Bull Soc Belge Ophthalmol. 2006;302:51–69.
92. Journee-de Korver JG, Oosterhius JA, Kakebeeke-Kemme HM, de Wolff-Rouendaal D. Transpupillary thermotherapy (TTT) by infrared irradiation of choroidal melanoma. Doc Ophthalmol. 1992;82(3):185–91
93. Kozak I, Luttrull JK. Modern retinal laser therapy. Saudi J Ophthalmol. 2015;29(2):137–46.

Chapter 3
Basics of Laser Use in Ophthalmology

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Most recently, the laser (acronym for Light Amplification by Stimulated Emission of Radiation) celebrated its 60th anniversary. Although this original meaning denotes a principle of operation (stimulated emission from excited atoms or ions), the term is now mostly used for devices generating light based on the laser principle. More specifically, it is usually laser oscillators, but sometimes also includes devices with laser amplifiers. A laser oscillator usually comprises an optical resonator (laser resonator, laser cavity) in which light can circulate (e.g. between two mirrors), and within this resonator a gain medium (e.g. a laser crystal), which serves to amplify the light (Fig. 3.1). Without the gain medium, the circulating light would become weaker and weaker in each resonator round trip, because it experiences some losses, e.g. upon reflection at mirrors. However, the gain medium can amplify the circulating light, thus compensating the losses if the gain is high enough. The gain medium requires some external supply of energy—it needs to be "pumped", e.g. by injecting light (optical pumping) or an electric current (electrical pumping → semiconductor lasers) (Fig. 3.1) [1].

As mentioned above, the principle of laser amplification is stimulated emission. "Stimulated emission" is the process by which photon emission is stimulated by interaction of an atom in excited state with a passing photon. The photon emitted by the atom in this process will have the same phase, direction of propagation and wavelength as the stimulating photon. The stimulating photon does not lose energy during this interaction. For stimulated emission to occur more frequently than absorption—and consequently result in light amplification—the optical material should have more atoms in an excited state than in a lower state. This "inversion of population" can

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_3

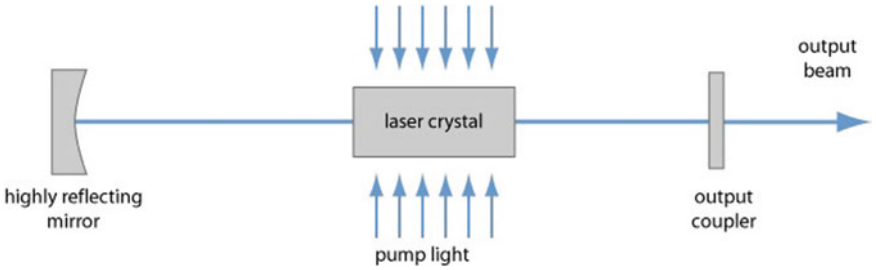

Fig. 3.1 Setup of a simple optically pumped solid-state laser. The laser resonator is made of a highly reflecting curved mirror and a partially transmissive flat mirror, the output coupler, which extracts some of the circulating laser light as the useful output. The gain medium is a laser crystal or rod, which is side-pumped. (*Source* Dr. R. Paschotta: RP Photonics Encyclopedia, https://www.rp-photonics.com/lasers.html)

be accomplished in certain materials through the utilisation of an excitation source. Population inversions can be produced in a gas, liquid, or solid, and these can be pumped by continuous discharge lamps, pulsed by flash lamps, by electric discharges in the laser medium, by chemical reactions, by an electron beam, by direct conversion of electric current into photons in semiconductors, or by light from other lasers [2].

An additional critical element of the laser is an optical cavity which circulates the emitted light between the two mirrors, one at either end. This results in the circulation of photons through the lasing material multiple times to efficiently stimulate emission of radiation from excited atoms. Pulsing methods used to achieve different ranges of pulse durations comprise of electronic shutters (down to 1 ms), pulsed flash lamps (a few μs), Q-switching (a few ns), or mode locking (a few fs). The light entrapped inside the cavity stimulates emission of new photons from the excited laser material with the same wavelength, direction and phase, thereby forming a coherent, precisely directed laser beam. Lasers are thus ideal for focusing light in space, time, or particular wavelengths. Monochromaticity of the light beam helps prevent chromatic aberration in the optical system, and permits precise targeting of the tissue absorption spectrum [2, 3].

Lasers are especially well suited for ophthalmic therapy as the eye is optimally designed for the transmission of light rays. The interactions of light rays with biological tissues depends on both the spectral absorption properties characteristics of the interacting tissue (scattering, conductivity), and certain radiation parameters—wavelength, delivered spot size, pulse energy, pulse intensity and pulse duration [4]. Adequately high photon energy can induce photochemical reactions. At even higher laser powers, absorption of light energy by the tissue can result in thermal effects that result in thermal denaturation and tissue coagulation. This occurs at approximately 60 °C. At approximately 300 °C, tissue vaporization occurs. This occurs more frequently with shorter pulse duration, and can lead to the mechanical disruption of tissue structures. With very short pulses of high peak irradiance in the nano, pico, or femtosecond range, atoms in focus are ionized producing micro-plasma

that can expand extremely fast and create an acoustic shock wave which enables high-precision ablation [4–10].

Interactions of light with biological tissues depend predominantly on laser wavelength, pulse duration, and irradiance. The following three categories of laser interactions with biological tissues are applicable to ophthalmic lasers and serve as basis of ocular laser therapies [10–12].

1. Photochemical
2. Photothermal
3. Photomechanical/Ionizing.

Photochemical Interactions

This is light-induced damage that occurs at energy levels below those that cause thermal damage and occur when single photons have enough quantum energy to convert molecules into one or more free radial particles that have the potential of being toxic to living cells. Free radicals are short-lived molecular fragments that have unpaired electrons in their outer orbit which makes them highly unstable and therefore, highly reactive. The photochemical damage described depends on the differing absorption properties of different molecules and hence such damage tends to be highly wavelength specific.

Photochemical interactions underlie retinal photodynamic therapy (PDT) with verteporfin and corneal collagen cross-linking with riboflavin. To avert possible photothermal damage subsequent to an increase in temperature, these therapies are generally performed at minimal irradiances with prolonged exposure times [13, 14]. The idea of PDT is grounded in two important mechanisms: firstly, the accumulation of a light-activated chromophore in the pathologic tissue and secondly, the induction of a chemical reaction through the absorption of laser-delivered light energy.

In corneal collagen cross linking (CXL), for the treatment of progressive keratoconus or secondary corneal ectasia, riboflavin is the photosensitizer. Its absorption peak of 370 nm makes UV-A light ideal for CXL, whilst ensuring other ocular structures are well protected. UV-A light exposure results in the generation of reactive oxygen species by riboflavin and this stimulates the photopolymerization process by stimulating the formation of intrafibrillar and interfibrillar carbonyl-based collagen covalent bonds. This photochemical reaction causes an increase in the rigidity of the anterior corneal stromal, an increase of collagen fiber thickness and a consequent resistance to enzymatic degradation—mediated by pepsin, trypsin and collagenase with lengthening of the turnover time of the collagen [15].

Excimer lasers in ophthalmology also exploit the effect of a photochemical interaction. The change they affect in tissues occurs through a process called photoablation as photochemical reactions at the target tissues not only decompose, but additionally volatilise, molecules. When pulsed ultraviolet light is used in the nanosecond range it causes fractures in the intermolecular bonds of the polymer chains of corneal collagens, disintegrating the target tissue and providing precise corneal incisions,

with submicron accuracy, to predetermined depths. Photoablation does not cause much collateral damage as the vast majority of the laser energy is absorbed by the target tissue without a resultant increase in tissue temperature. This is because the diffusion time for heat conduction into the surrounding milieu is greater than the millisecond range pulse duration. Laser vision correction procedures constitute the bulk of excimer laser procedures in the field of ophthalmology however, this technology is also used in phototherapeutic keratectomy to treat corneal dystrophies, in particular pathologies involving the epithelial basement membrane such as recurrent epithelial erosions [16–18].

Photothermal Interactions

Thermal energy is related to the kinetic energy of individual molecules. Molecules absorbing laser energy, experience an increase in their vibration and an increase in their thermal agitation. The most important signature of the photothermal reaction is the change in tissue temperature which causes the breakage of the weak van der Waals forces that help to stabilize molecular structures. Depending on the magnitude of temperature increase and the duration of exposure, different tissue effects may ensue. These include denaturation of proteins, necrosis, or cell vaporization depending on the amount and duration of laser energy. The main chromophores of ocular tissues are water, proteins, melanin, haem, and macular pigments, and their absorption coefficients are dependent on the wavelength of laser. Denaturation of cellular proteins varies as an exponential function of temperature and demonstrates a linear relationship with laser pulse duration. These parameters can therefore be utilised to deliver the desire effect at the tissue level [3, 19, 20].

Photothermal effects involve *photocoagulation* and *photovaporization.* Retinal *photocoagulation* involves application of pulses with durations ranging from 10 to 200 ms, and transient hyperthermia by only tens of degrees Celsius above body temperature. History has demonstrated the use of a multitude of lasers for retinal photocoagulation including ruby (694 nm), argon (488, 514 nm), and krypton (647 nm) lasers. At present, green frequency-doubled neodymium–yttrium–aluminum-garnet (Nd:YAG) (532 nm) and yellow semiconductor lasers (577 nm) are used for this purpose [21, 22]. The laser energy is absorbed primarily by melanin in the retinal pigment epithelium (RPE) and choroid, and by haemoglobin. Blood vessel thrombosis is caused by light absorption resulting in structural changes in the haemoglobin molecule and shrinkage of the collagen structures that form the walls of blood vessels and its surrounding connective tissues. Coagulation of blood vessels involves higher energy than other tissue due to cooling by the blood flow. Heat generated by the absorption of the laser light in the RPE and choroid diffuses into the retina and causes coagulation of the photoreceptors and, at times, of the inner retinal structures. Inner retinal damage can be mitigated by restricting the energy to the RPE and outer retina through the use of shorter pulse durations and smaller spot sizes [3, 5, 23].

The photocoagulation effect of retinal laser as described above leads to tissue coagulation and photoreceptor destruction leading to damage of what we actually want to save—the vision. For that reason photocoagulation techniques have been developed to treat selectively the RPE sparing of the photoreceptors [24]. Producing a train of millisecond laser pulses separated by variable quiet intervals, micropulsing allowed selective treatment of the retinal pigment epithelium (RPE) and sparing of the neurosensory retina. The low energy levels of the pulses are purported to stimulate renewal of RPE as oppose to causing any tissue destruction. In subthreshold micropulse laser, diffusion of heat to surrounding tissues is minimized and thereby scarring is prevented [25]. It has been utilized in the treatment of numerous retinovascular diseases. Treatment titration is challenging in using this technology. As the laser surgeon does not see an effect of the treatment, there is a high risk of undertreatment and treatment failure. However, treatment guidelines have been elaborated to assist physicians [26–29].

Photovaporization occurs when even higher energy laser light is absorbed by the target tissue, resulting in vaporization of both intracellular and extracellular water. The advantage of this type of tissue response is that adjacent blood vessels are also treated, resulting in a bloodless surgical field. The carbon dioxide laser, with its wavelength in the far infrared, uses this method of action and is indicated in the treatment of numerous vascular pathologies [30, 31].

Photomechanical/Ionising Interactions

Photodisruption is the process by which short pulse Nd: YAG lasers disrupt transparent tissues by delivering near infrared (1064 nm) irradiances of a large magnitude to tissue targets. These excessively high irradiances ionize material in a small volume of space at the target of the laser beam, decaying it into an assortment of ions and electrons given the name ‘plasma’. With the formation of plasma, subsequent radiation is absorbed or scattered radiation arriving later in the pulse, thereby effectively protecting the underlying tissues. The plasma then rapidly expands producing shock and acoustic waves that mechanically disrupt tissues. The advantage of this ionisation process is that it is not a prerequisite for target tissues to be pigmented. The operator needs to just focus on the area of desired disintegration. YAG lasers are used to remove posterior capsular opacification, disrupt vitreous membranes and in the creation of peripheral irodotomies which alleviate the effects of an occludable or closed angle [32, 33].

References

1. Paschotta R. Field guide to lasers. Bellingham, WA: SPIE Press; 2007.
2. Koechner WK. Solid state laser engineering. London: Spriger-Verlag; 2006.
3. Palanker D, Blumenkranz MS. Retinal laser therapy: biophysical basis and applications. In: Ryan SJ, Schachat A, Wilkinson CP, Hinton DR, Sadda SR, Wiedemann P, editors. Retina, vol. 3, 5th edition. St Louis, MO: Mosby Inc; 2012.
4. Palanker DV, Blumenkranz MS, Marmor MF. Fifty years of ophthalmic laser therapy. Arch Ophthalmol. 2011;129(12):1613–9.
5. Luttrull JK, Sramek C, Palanker D, Spink CJ, Musch DC. Long-term safety, high-resolution imaging, and tissue temperature modeling of subvisible diode micropulse photocoagulation for retinovascular macular edema. Retina. 2012;32:375–86.
6. Brinkmann R, Koinzer S, Schlott K, et al. Real-time temperature determination during retinal photocoagulation on patients. J Biomed Opt. 2012;17(6): 061219.
7. Lubatschowski H. Ultrafast lasers in ophthalmology. Phys Procedia. 2010;5(2):637–40.
8. Trokel SL, Srinivasan R, Braren B. Excimer laser surgery of the cornea. Am J Ophthalmol. 1983;96(6):710–5.
9. Nagy Z, Takacs A, Filkorn T, Sarayba M. Initial clinical evaluation of an intraocular femtosecond laser in cataract surgery. J Refract Surg. 2009;25(12):1053–60.
10. Blumenkranz MS. The evolution of laser therapy in ophthalmology: a perspective on the interactions between photons, patients, physicians, and physicists: the LXX Edward Jackson Memorial Lecture. Am J Ophthalmol. 2014;158(1):12-25.e1.
11. Mainster MA. Wavelength selection in macular photocoagulation tissue optics, thermal effects, and laser systems. Ophthalmology. 1986;93(7):952–8.
12. Thomsen S. Pathologic analysis of photothermal and photomechanical effects of laser-tissue interactions. Photochem Photobiol. 1991;53(6):825–35.
13. Woodburn K, Engelman C, Blumenkranz MS. Photodynamic therapy for choroidal neovascularization a review. Retina. 2002;22(4):391–405.
14. Krueger RR, Kanellopoulos AJ. Stability of simultaneous topography-guided photorefractive keratectomy and riboflavin UVA cross-linking for progressive keratoconus: case reports. J Refract Surg. 2010;26(10):827–32.
15. Spoerl E, Mrochen M, Sliney D, Trokel S, Seiler T. Safety of UVA-riboflavin cross-linking of the cornea. Cornea. 2007;26(4):385–9.
16. Seiler T, McDonnell PJ. Excimer laser photorefractive keratectomy. Surv Ophthalmol. 1995 Sep-Oct;40(2):89–118.
17. Flowers CW Jr, McDonnell PJ, McLeod SD. Excimer laser photorefractive keratectomy. Ophthalmol Clin North Am. 2001;14(2):275–83.
18. Netto MV, Wilson SE. Indications for excimer laser surface ablation. J Refract Surg. 2005;21(6):734–41.
19. Knappe V, Frank F, Rohde E. Principles of lasers and biophotonic effects. Photomed Laser Surg. 2004;22(5):411–7.
20. Denton ML, Foltz MS, Estlack LE, Stolarski DJ, Noojin GD, Thomas RJ, Eikum D, Rockwell BA. Damage thresholds for exposure to NIR and blue lasers in an in vitro RPE cell system. Invest Ophthalmol Vis Sci. 2006;47(7):3065–73.
21. Ham WT Jr, Ruffolo JJ Jr, Mueller HA, Guerry III D. The nature of retinal radiation damage: dependence on wavelength, power level and exposure time. Vision Res. 1980;20:1105–1111.
22. Berger JW, D'Amico DJ. Modeling of erbium: YAG laser-mediated explosive photovaporization: implications for vitreoretinal surgery. Ophthalmic Surg Lasers. 1997;28(2):133–9.
23. Sramek C, Leung LS, Leng T, Brown J, Paulus YM, Schuele G, Palanker D. Improving the therapeutic window of retinal photocoagulation by spatial and temporal modulation of the laser beam. J Biomed Opt. 2011;16(2): 028004.
24. Schuele G, Rumohr M, Huettmann G, Brinkmann R. RPE damage thresholds and mechanisms for laser exposure in the microsecond-to-millisecond time regimen. Invest Ophthalmol Vis Sci. 2005;46(2):714–9.

25. Roider J, Hillenkamp F, Flotte T, et al. Microphotocoagulation: selective effects in biological tissue using repetitive short laser pulses. Proc Natl Acad Sci USA. 1993;90:8643–7.
26. Luttrull JK, Musch DC, Mainster MA. Subthreshold diode micropulse photocoagulation for the treatment of clinically significant diabetic macular oedema. Br J Ophthalmol. 2005;89(1):74–80.
27. Považay B, Brinkmann R, Stoller M, Kessler R. Selective retina therapy. In: High resolution imaging in microscopy and ophthalmology: new frontiers in biomedical optics [Internet]. Cham (CH): Springer; 2019. Chapter 11. 2019 Aug 14.
28. Keunen JEE, Battaglia-Parodi M, Vujosevic S, Luttrull JK. International retinal laser society guidelines for subthreshold laser treatment. Transl Vis Sci Technol. 2020;9(9):15.
29. Moore SM, Chao DL. Application of subthreshold laser therapy in retinal diseases: a review. Expert Rev Ophthalmol. 2018;13(6):311–20.
30. Gailitis RP, Patterson SW, Samuels MA, Hagen K, Ren Q, Waring GO 3rd. Comparison of laser phacovaporization using the Er-YAG and the Er-YSGG laser. Arch Ophthalmol. 1993;111(5):697–700.
31. Holschbach A, Wirbelauer C, Krämer T, Wollensak J. Photovaporization rate and profile of an erbium-chromium:YAG laser in the fundamental mode. J Cataract Refract Surg. 1997;23(5):726–30.
32. Capon MR, Docchio F, Mellerio J. Nd:YAG laser photodisruption: an experimental investigation on shielding and multiple plasma formation. Graefes Arch Clin Exp Ophthalmol. 1988;226(4):362–6.
33. Vogel A, Busch S, Jungnickel K, Birngruber R. Mechanisms of intraocular photodisruption with picosecond and nanosecond laser pulses. Lasers Surg Med. 1994;15(1):32–43.

Chapter 4
Retinal Laser Treatment for Age-Related Macular Degeneration (AMD)

Jeffrey K. Luttrull

Introduction

How we understand a problem informs the solutions we propose. The answers we get are only as good as the questions we ask. Ignorance, where all investigations begin, allows false premises to be adopted that then lead to false conclusions, or none at all. As information and understanding are gained, the questions, and thus answers, improve. Eventually, useful understanding is achieved and generalizable principles are developed that foster effective action and move us forward to the next unknown. The history of retinal laser treatment for AMD follows these common trajectories.

Fundamental to the nature of ophthalmology is that it is a field of medicine blessed by the ability to directly visualize the eye and its parts. Thus, anatomy, structure, and imaging of the anatomic features of the eye have always been at the core of our conceptualization of retinal disease, informing the questions asked and answers that followed. Thus, manipulating retinal anatomy appeared to be a sensible approach to the problems posed by AMD.

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_4

Conventional Suprathreshold Macular Photocoagulation (MPC)

Overview

Continuous-wave macular photocoagulation (MPC) presented itself as well-suited to address the problems of AMD due to its ability to alter anatomy by applying precise photothermal cautery to the retina.

The literature concerning MPC for AMD is massive, consisting of many hundreds of studies and thousands of reports covering nearly 6 decades of work by tens of thousands of investigators. Only a high-level summary of general conclusions and impressions leading to current treatment approaches can even be attempted here. Apologies are in order to the vast majority of authors worse work cannot be even touched on in these few pages.

In the early days of retinal laser use as MPC for AMD, intense "suprathreshold" treatment characterized by full-thickness thermal retinal photocoagulation, evident by a white retinal laser spot produced in the retina at the time of treatment, was favored. A time of exploration and experimentation, MPC was employed in various ways in hopes of reducing visual loss and limiting scotoma size from the common complications of AMD, particularly choroidal neovascularization (CNV) and pigment epithelial detachment (PED). MPC was used to attempt "wall-off" often large extrafoveal CNV by creating a barrier of chorioretinal scarring, hoping to prevent subfoveal extension; and both grid and ablative application of MPC was tried for CNV and age-related PEDs [1–7].

Prophylactic MPC, or "Laser for Drusen"

Early in the experience with MPC it was noted that MPC often resulted in resolution of nearby drusen not directly exposed to the laser [8–10]. Thus, photocoagulation to reduce drusen, the *sine qua non* of AMD and suspected proximate cause of CNV and geographic atrophy (GA), became of interest. This included both direct focal and indirect (nearby grid) photocoagulation of the drusen themselves [10–13] (Fig. 4.1). While MPC was effective at causing drusen to resolve, the effectiveness of drusen reduction paralleled treatment intensity, which, in turn, paralleled an increased incidence of subsequent CNV, increasing the risk of visual loss despite drusen reduction [11–13]. A metanalysis of laser for drusen studies suggested that photocoagulation for drusen also promoted and accelerated age-related geographic atrophy (GA) [13]. The lack of treatment benefits from low-intensity MPC for drusen, and adverse effects of higher intensity treatment, led to eventual abandonment of "laser for drusen" effort [9–18].

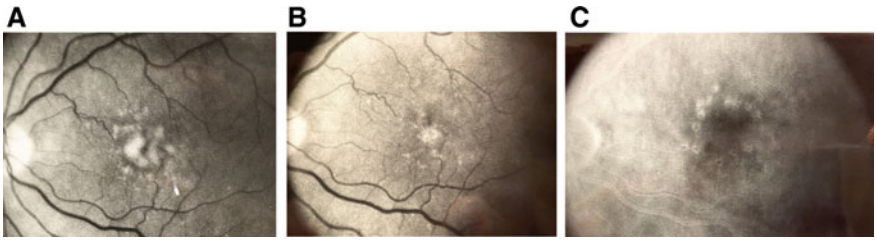

Fig. 4.1 **A** Red-free fundus photograph of eye with intermediate AMD. **B** Red free fundus photograph of same eye 3 months following krypton laser grid laser. Note resolution of drusen. **C** Intravenous fundus fluorescein angiogram (FFA) of same eye 3 months following laser treatment showing drusen resolution and ring of laser burns around the macula

MPC for Neovascular AMD

Extrafoveal CNV

PC ablation of CNV did offer benefits, however, but only in a minority of highly select eyes and usually only for a time. Few, only about 5%, eyes with CNV were eligible for treatment of extrafoveal CNV in the MPSG, as most eyes NAMD presented with subfoveal CNV [1]. Further, in the small number of eyes with extrafoveal NAMD presenting as candidates for MPC, most (54% at 5 years) developed subfoveal recurrence and further visual loss [1–6]. Thus, for MPC of even extrafoveal CNV, VA was measured in lines lost, rather than vision gained. Overall, at 5 years post MPC, eyes treated for extrafoveal neovascular AMD (NAMD) in the Macular Photocoagulation Study Group (MPSG) lost an average of 5.2 lines of VA, compared to 7.1 lines for untreated eyes [1–6]. Patients with systemic hypertension did not benefit from MPC, due to the high rate of subfoveal recurrence [2]. Despite such limitations, PC ablation of age-related CNV may still be a reasonable treatment option in select eyes with relatively small and well-defined CNV distant from the fovea, especially if unresponsive to other therapy.

Subfoveal CNV

Thus, subfoveal CNV remained the most important cause of vision loss in AMD. Absent other treatments, this led to investigation of transfoveal MPC for subfoveal CNV [5]. In such eyes, it was hypothesized that immediate visual loss due to PC ablation might be less adverse, in the long-term, than subsequent visual loss due to continued growth and exudation from the subfoveal CNV. This was subsequently confirmed in a randomized clinical trial (RCT) [4, 5]. In this study, no significant differences were found between the outcomes of suprathreshold argon and diode (810 nm CW) laser [1, 2, 4, 5]. The benefits of transfoveal MPC were, as one would

expect, dictated by the size of the lesion, degree of subfoveal involvement, and presenting visual acuity. The larger the lesion, more centered on the fovea, and better the initial visual acuity, the less benefit from foveal PC and the greater the likelihood of immediate treatment associated visual loss [4, 5]. At 4 years follow up following transfoveal MPC for subfoveal CNV, 47% of untreated and 22% of treated eyes suffered profound visual loss of 6 or more lines of VA [5]. Despite these statistical benefits, the immediate treatment-associated visual loss caused by foveal PC in most eyes made treatment unpopular with doctors and patients alike.

The limitations of MPC for AMD were largely due to three main factors. First, the difficulty of fully defining, based on the only available diagnostic technologies available at the time—clinical examination and intravenous fundus fluorescein angiography (FFA)—the presence, exact location, and full extent thus the boundaries of the CNV. This frequently led to incomplete treatment. Incomplete treatment did not stop, but tended to accelerate growth and progression of the CNV, due to treatment associated inflammation and tissue damage [1–5]. Second, even in the absence of direct fovea injury or membrane recurrence, was the tendency to develop pigmentary atrophy and visual loss following PC-induced resolution of large or confluent SD and/or PEDs, or MPC lesions near the fovea. Once developed, such post-PC pigment atrophy tended to become geographic and progress, causing further visual loss [6, 13, 14, 15]. Third, was the facility of PC (often used to create experimental models of neovascular AMD), to incite development of new CNV by destroying the retinal pigment epithelium (RPE) and damaging Bruch's membrane, and thus compromising the blood retinal barrier and other native inhibitions to macular neovascularization [16, 17]. Inflammation from photocoagulative necrosis of the overlying neurosensory retina in suprathreshold PC added neoangiogenic stimuli. As noted above, incomplete treatment of CNV tended to accelerate growth of residual membranes, and subthreshold treatment of the macula in eyes with PED (often harboring occult CNV) or SD, already compromised by AMD, often lead to development of de-novo CNV, and further visual loss [2–6, 13–18]. The advent of improved macular imaging, such as optical coherence tomography (OCT), indocyanine green angiography (ICG), and OCT angiography (OCTA), have improved our ability to identify and better define the full extent of macular neovascularization [19–21]. While better identification of the entire area of CNV raised the possibility of improved outcomes of ablative PC in NAMD by increasing the likelihood of complete treatment of the CNV, the adverse effects of ablative MPC and the tendency for CNV recurrence continued to limit the usefulness of PC, led to the general abandonment of ablative MPC for macular neovascularization in favor of retina-sparing treatment with anti-vascular endothelial growth factors (VEGF) [22].

Our definition of "safe and effective" and "success vs. failure" when it comes to treatments is ever evolving. Early in the application of most new treatments there is a generally high tolerance for risk and adverse treatment effects due to the absence of other treatments and the consequences of disease progression absent intervention. Thus, it is important to remember that, in the absence of alternatives at the time, the results of MPC could only be compared with no treatment at all. Thus, the bar for success was low, and tolerance for the inherent risks and adverse effects was high.

Prior to the advent of drug therapy for NAMD, the limited benefits of MPC in NAMD, and failure of laser for drusen to prevent NAMD, led to investigation of alternative approaches to macular laser treatment, hoping to improve safety, efficacy, and utility, by reducing treatment associated macular damage. These were transpupillary thermotherapy (TTT), photodynamic therapy (PDT) and feeder vessel treatment (FVT).

Transpupillary Thermotherapy (TTT)

Rather than short-duration high-intensity full-thickness suprathreshold retinal photocoagulation, TTT employed an 810 nm continuous wave (CW) diode laser single large spot covering the macula, up to 3 mm in diameter, applied slowly, using a long treatment exposure of 60 s. The goal of TTT was to achieve heating of the CNV by approximately 10 °C, sufficient to induce involution and reduce exudation, while avoiding photocoagulation of the RPE and neurosensory retina. Initial reports of TTT for subfoveal NAMD were encouraging, and the technique was, in the absence of other effective therapies, rapidly adopted [23–26]. Improvements and vision retention benefits following TTT were generally modest if present, comparable in some studies to photodynamic therapy (PDT) but TTT was simpler and less invasive [24, 25]. According to the American National Standards Institute (ANSI), the 50/50 retinal burn risk from CW laser arrives at 10 × the Maximum Permissible Exposure (MPE) (defined as just below the threshold for any biologic effect) [27]. TTT operated as 9X the MPE [23, 24, 27]. Thus, TTT resulted in frequent and unexpected, but sometimes catastrophic macular burns, leading to significant visual loss in many treated patients [28, 29]. This was because the narrow therapeutic range of CW TTT (the interval between the MPE to a 50/50 risk of retinal damage) precluded predictable safety, close to the burn threshold with variable uptake influenced by factors such as media opacity, fundus pigmentation, and retinal thickness that exceed the limits of the therapeutic range. At the same time, the large spot size made visual loss from inadvertent macular burns often severe. Thus, TTT for NAMD fell out of favor relative to PDT, which, while also modestly effective, was safer and more predictable [26].

Photodynamic Therapy (PDT)

In PDT, long application of CW laser in a large spot is also employed. In PDT, however, the therapeutic effect is not achieved by any direct thermal effect of the very low power (and thus otherwise ineffective) laser, but indirectly through a wavelength dependent activation of a photosensitive drug (thus “photodynamic therapy”) circulating through the macula following brachial intravenous infusion. Various sensitizing drugs were examined, with verteporfin eventually being favored in large part

due to faster systemic clearing, reducing the time patients needed to avoid direct sun exposure to the skin to prevent injury from skin photosensitization [30, 31].

The result of PDT is marked angiographic hypofluorescence of the area exposed to the activating laser, blocking visualization of the choroidal circulation on FFA, but without evidence of significant inflammation or retinal or choroidal damage. The reason(s) for this characteristic angiographic appearance remain unclear, as actual non-perfusion of the macula would almost certainly be associated with visual loss [31–34]. Despite the dramatic appearance of the PDT treated macula, acute treatment associated visual loss was infrequent, occurring in about 4% of treated eyes. Prolongation of the effect could be achieved with concomitant intravitreal steroid administration, which may reduce the need for retreatments [33]. With repeated treatment over a prolonged period, some eyes developed macular atrophy and further visual loss [32–34].

Most of what is known about verteporfin PDT comes from 2 randomized clinical trials (RCTs) funded by the drug maker (the Treatment of Age-related Macular Degeneration with Photodynamic Therapy/TAP trial; and the Verteporfin in Photodynamic Therapy / VIP trial) [34, 35]. In these trials, PDT was found to help stabilize visual acuity by reducing or eliminating exudation from subfoveal NAMD, reducing visual loss compared to untreated controls (relative risk 0.62). Visual improvements were rare. Usually, this suppression of exudation was temporary, requiring retreatment on average 5 times in the first two years [31, 34]. Treatment benefits were mainly seen in eyes with well-defined CNV, and generally absent in eyes with predominantly ill-defined or "occult" CNV. This may reflect the increased density of the photosensitizing dye in the better perfused well-defined membranes [31, 34]. The invasive nature of treatment, requiring a 10-min intravenous infusion of verteporfin, the drug expense, modest visual results, the need to avoid sunlight after treatment due to dermal photosensitization, and small but not inconsequential risk of acute visual loss, have limited use of PDT since the introduction of anti-VEGF drugs. However, PDT may still be of value in eyes with NAMD unresponsive to anti-VEGF therapy, and eyes with posterior polypoidal choroidal vasculopathy, especially in combination with anti-VEGF therapy [35–37]

Feeder Vessel Treatment

Histopathology of age-related CNV revealed that many had a tree-like structure, with multiple branches arising and spreading out from a single trunk arising in the choroid, a choroidal "feeder vessel" [38–41]. Occasionally, such structures can be seen clinically by biomicroscopy, and by FFA. Because the shorter excitation wavelength of FFA maximizes absorption and thus imaging of the neurosensory retina, and leakage of fluorescein dye in the choroid tends to obscure individual, especially smaller, choroidal vessels, indocyanine green angiography (ICGA), imaged

by infrared illumination that penetrates more deeply to the level of the choroid, can improve visualization of the choroid and thus feeder vessels by remaining intravascular. Video ICGA can further enhance identification of feeder vessels by capturing the dynamic nature of blood flow, demonstrating filling of a CNV from a main choroidal feeder vessel trunk—and occasionally, more than one [39–41].

The idea of trying to eliminate a CNV by closing the feeder vessel and cutting off its circulation was thus appealing. Attempts in this regard based on clinical examination and FFA were challenging, in part due to the difficultly of identifying and defining the feeder. In early studies, however, 68% of eyes treated by focal PC of the suspected feeder vessel were stable or improved in short-term follow up [38]. However, even suprathreshold PC was frequently ineffective in closing the feeder, which often remained patent or re-perfused shortly after treatment. A relatively high rate of blood flow through such vessels may act as heat sink by caring heat away from the laser application site, reducing heat accumulation enough to prevent photocoagulative vessel closure [38–41]. This required use of more intense suprathreshold PC and/or repeated treatments to try to achieve final feeder vessel closure. Such intense PC lesions near the fovea are undesirable due to the induced scotomata, the risk of rupture of Bruch's membrane, and the laser burn serving as a nidus for new choroidal neovascularization.

Because the green color of ICG absorbs laser wavelengths in the red and near infrared spectrum, which are also less damaging to the neurosensory retina, the feeder vessel treatment strategy shifted to use of an 810 nm CW laser. Videographic monitoring of choroidal vessel filling during infusion of ICG was used to better visualize and more accurately target the feeder vessel, while the same ICG increased intravascular absorption of the diode laser to improve the prospects for feeder vessel closure while also reducing damage to the neurosensory retina [39–41]. Despite such technical improvements, there was little improvement in the long-term results of treatment.

The limited benefits from MPC, TTT, PDT and feeder vessel treatment for treatment of both dry and wet AMD, the advent of effective drug therapy for NAMD in the form of VEGF inhibitors, and the treatment limitations imposed by laser-induced retinal damage (LIRD) from conventional CW PC, led to general abandonment of PC for use in AMD. However, significant needs remain. Foremost among them is the need for a treatment for dry AMD to more effectively prevent neovascular conversion, the main cause of irreversible visual loss worldwide [42]. To date, other than modestly effective antioxidant vitamins, there is no drug therapy that has been shown to be effective in this regard [43]. This has led to exploration of new laser approaches for AMD focused on treatment of dry AMD to reduce drusen, improve visual acuity, slow progression of geographic atrophy, and prevent neovascular conversion.

As the most important cause of visual loss from AMD, prevention of neovascular conversion is thus the highest priority in the clinical management of AMD. The number, size and density of macular drusen, focal subretinal deposits of oxidative waste material, are strongly associated with the presence and severity of AMD, and likelihood of visual loss [1–6, 44]. Thus, getting rid of drusen has been an area of intense interest, particularly because macular laser treatment is effective in this

regard [8–15]. It must be remembered, however, that drusen are a manifestation of the underlying age-related disease process and are not the disease process itself [43, 44]. While the presence of drusen clearly indicates increased risks of vision loss from neovascular conversion and/or geographic atrophy, drusen also reflect the eye's attempt to compensate for worsening macular function. While drusen are a sign of this dysfunction, it is unclear whether drusen contribute to the risks of vision loss independent from the generalized age-related macular dysfunction that leads to drusen formation [45]. While drusen reduction was appealing, drusen reduction by MPC was unhelpful due to the increased risk of CNV. Beyond this, it had not established that drusen reduction alone, even uncomplicated, could materially alter the course of age-related macular disease. Thus new retinal laser approaches were developed and investigated in an attempt to separate drusen reduction from causation of CNV.

A Newer Approach to Drusen Reduction: Short-Pulse Lasers

Conventional PC employs a high-powered, generally visible wavelength CW laser at exposure durations of a relatively long duration, on the order of 50–500 ms. Laser wavelengths in the visible range and longer are primarily absorbed by melanin in the RPE and choroid. In general, the shorter the wavelength, the greater the absorption by melanin. However, wavelengths shorter than 550um have neurosensory retinal absorption that can range from ionizing and phototoxic to photocoagulative, with sufficient power and duration of the laser exposure [46, 47]. When there is sufficient heat spread from the RPE and choroid, coagulation of the overlying neurosensory retina occurs, causing light scattering and opacity of the otherwise optically clear tissue. Photocoagulated tissue is killed, retinal architecture destroyed, and function lost. If only the outer retina is affected, opacification of neurosensory retina may be difficult to see on biomicroscopy, particularly at the time of treatment or shortly thereafter. However, FFA will show breakdown of the blood retinal barrier with leakage at the laser spots. Post PC retinal opacification tends to become more apparent hours and days after treatment, during which time abnormalities of fundus autofluorescence appear due to damage to the RPE. Weeks later, frank pigment clumping and chorioretinal atrophy develop at the site of the PC. Such were the events associated with classic "subthreshold" PC [47]. The more intense the PC, the more obvious and immediately apparent these effects, and the greater the extend of the retinal opacification and photocoagulation above the RPE at the laser spot, until, with traditional suprathreshold PC, full thickness photocoagulation occurs leading to white blanching of the treated retina. After even subthreshold PC, focal chorioretinal atrophy at the site of the laser spots develops and, like GA, tends to progress and expand, enlarging over time. If close to the fovea, this progressive expansion of atrophy from prior laser spots can lead to late vision loss from foveal atrophy, or the development of choroidal neovascularization [14, 48].

The TR of CW PC is narrow, about 10X MPE [27]. Suprathreshold MPC, generally done at 70-100X MPE, reliably produces full-thickness retinal photocoagulation in virtually all eyes, as it far exceeds the retinal damage threshold. As higher intensity MPC in eyes with drusen was associated with an increased the risk of CNV and visual loss, performing effective treatment while avoiding excessive laser damage appeared desirable [13]. However, as noted above, the narrow TR makes the response to CW MPC highly variable as it can be easily influenced by many patient-specific factors such as fundus pigmentation, retinal thickness, and media opacity [47]. If one hoped to limit the damage caused by MPC, titration of the laser exposure in the treated eye to adjust the treatment intensity to the desired level for treatment would be necessary, both to avoid ineffectual treatment below the TR; and to avoid excessive retinal damage and treatment complications above the TR. However, the narrowness of the MPC TR renders titration an unreliable guide [47, 49, 50]. These characteristics of MPC precluded the ability to achieve both predictably safe and effective treatment for drusen, assuming that drusen reduction would indeed pay dividends. A new approach was needed. Thus, in the 1980s work began on new laser modalities designed to better confine retinal laser damage hoping to preserve the drusen-reducing effects of MPC while increasing treatment safety.

Pattern Scanning Laser (PASCAL)

The concept behind the PASCAL was that photoreceptor metabolic demand was the major driver of diabetic retinopathy development and progression. (Daniel Palanker, PhD, personal communication, 2004) To address this hypothesis, a short-pulsed (~20 μs) 532 CW laser was chosen to selectively destroy the photoreceptors in the outer retina, while attempting to reduce damage to the adjacent RPE and balance of the neurosensory retina [51]. One human pathologic study confirmed PASCAL destruction of the outer retina and photoreceptors, but also the RPE, leading to formation of hyperplastic chorioretinal scars at the treatment sites [52]. Little has yet been reported regarding PASCAL treatment of AMD. In one study, PASCAL was used to treat the margins of areas of drusenoid PEDs. To prevent CNV, all PASCAL treated eyes in this study received regular anti-VEGF injections as well. At the end of 12 months, lasered eyes show a reduction in drusen area and PED height, with an average of 4.6 letters of VA improvement, compared to 1.1 letter for untreated controls. One PASCAL treated eye developed an RPE rip and CNV [53]. In another study, the PASCAL was used to treat reticular pseudo drusen (RPD) in eyes with dry AMD. At 3 months, the proportion of early type 1 increased following treatment, with a decrease in the proportion of more advanced type 3 RPD. Outer nuclear layer thickness was improved, and visual acuity and microperimetry unchanged [53].

Selective Retinal Laser Therapy (SRT)

Selective retinal (laser) therapy, or SRT, shortens the pulse duration further in an attempt to further restrict LIRD to the RPE. Using Q-switched Nd:YLF, wavelength 527 nm, and pulse duration 1.7 μs, the short exposure precludes significant heat dissipation from the absorbing RPE melanosomes. With sufficient energy, this causes precipitous gas bubble formation at the melanosome, resulting in intracellular cavitation and cell death, with potential preservation of the cell wall with limitation of transmural extension of the laser damage beyond the RPE. SRT is thus photodisruptive to the RPE [54]. Formation and rupture of these intracellular gas bubbles can be "heard" by real-time optoacoustic monitoring via a corneal contact lens. By using a pulse-energy "ramping" algorithm and optoacoustic monitoring, treatment can be titrated to maximize RPE destruction while minimizing damage to adjacent structures, by listening for bubble formation threshold within the RPE [55].

Application of SRT to AMD is thus far limited. SRT remains focused on altering macular morphology in AMD by causing sufficient retinal damage to incite an inflammatory response from selective destruction of the RPE sufficient to eliminate drusen, but sparing Bruch's membrane and the outer neurosensory retinal in hopes of minimizing secondary CNV. There are three studies of note. In a murine model of AMD, SRT was able to limit damage to the RPE and reduce drusen-like lesions without notable collateral damage [56]. In a 12-month study of patients with intermediate AMD, SRT appeared to slow the increase in drusen volume. Visual acuity was unchanged, but mean retinal sensitivity in treated eyes was improved compared to fellow eye controls. No adverse treatment effects were reported [57]. In another study, 6 eyes of 6 patients were treated with SRT to the margins of areas of GA, with the fellow eyes serving as controls. In this study, SRT caused significant acceleration of GA progression compared to untreated controls, causing the study to be stopped prior to planned completion [58].

Nanosecond Laser ("2RT")

In nanosecond laser ("2RT") laser pulse durations were shortened even further with the continuing goal of destroying the RPE while even more effectively avoiding damage to collateral structures. In 2RT spots are applied around the macula with energies titrated to 0.15–0.45 mJ. using 400 μm diameter spot, 3 ns pulse duration, 532 nm wavelength using a frequency-doubled YAG laser [59]. The ultrashort exposure of 2RT results in explosion/vaporization of the RPE so quickly that the controlled gas bubble formation and intracellular cavitation produced by SRT do not have time to develop. Thus, the thermal effects of 2RT are insignificant as the RPE is vaporized before heat accumulation and spread can occur. One may think of 2RT as a "cookie cutter", removing the RPE at the point of exposure by photodisruption

[47]. Despite the intent and effect of 2RT is RPE destruction, treatment is described by the investigators as "non-damaging" and "rejuventating" [45, 48, 49].

2RT was initially explored clinically for treatment of diabetic macular edema. In a 2013 report, although retinal damage was noted in 2/17 eyes, the authors reported that this damage resolved completely with observation. The authors claimed the first retina-sparing laser treatment for diabetic retinopathy, despite the fact that numerous studies of MPL sublethal the RPE had by this time been published as early as 2005 using micropulsed lasers [60–65].

The primary source of information regarding application of 2RT to AMD is found in the "Laser Intervention in Early Stages of Age-Related Macular Degeneration" or "LEAD" trial reports [66]. The LEAD trial represents a re-visitation of the "laser for drusen" project, hoping to improve results through sufficient, but reduced and more predictable LIRD. In a prior exploratory study of 50 patients and mice, 2RT was noted to reduce drusen "without damage to retinal structure", despite focal ablations of the RPE and treatment-associated inflammatory response [67].

At 36 months, the LEAD trial found no benefit from 2RT in the 292 treated eyes, compared to sham treated controls. However, eyes with more advanced and high-risk dry AMD, particularly those with RPD, suffered from treatment with higher rates of new GA, acceleration of existing GA progression, and a higher rate of visual loss compared to untreated controls [68]. In a two-year extension of the trial (60 months post initial 2RT treatment), there continued to be no overall benefit of 2RT in intermediate AMD, other than significant worsening of treated eyes with RPD [69]. In eyes without RPD, drusen progression was slowed without incident CNV, and on this basis further study of 2RT was recommended as a promising preventive treatment for dry AMD. The results of the LEAD trial prompted an editorial in a major ophthalmic journal recommending against subthreshold laser treatment for dry AMD, suggesting all types of subthreshold laser treatment, and therefore the expected results, were the same [70].

No clinical fundus photographs or other images of treated LEAD trial patients have been provided in the LEAD trial publications. This is a perplexing omission from a study with morphologic endpoints, and the claim of non-damaging treatment. Despite the report of no retina damage, some treated eyes were reported to develop "retinal" hemorrhages at treatment, suggesting possible choroidal rupture [69]. It is notable that most images of treated study eyes shown at conferences reporting the LEAD trial results did exhibit focal laser scars. The study investigators indicated that such lesions were the norm in the study. These 2RT laser lesions did not appear substantially different from photocoagulation lesions. (LEAD study panel presentation, Guymer R, Marshall J, et al., Euretina, Barcelona 2017).

Acceleration of GA and worsening of more advanced forms of dry AMD in the LEAD trial is consistent with the prior MPC "laser for drusen" studies, and SRT for GA. It has been suggested that such eyes, particularly those with GA and/or RPD, are already in a tenuous state, severely taxed by the effort to maintain structure and function against progressive age-related macular dysfunction, and that the added trauma and inflammation from LIRD may cause these eyes to decompensate and progress more rapidly [44]. It is noteworthy that highly selective ablation of the RPE

by SRT and 2RT with substantial preservation of the integrity of Bruch's membrane does appear to reduce the risk of new CNV compared to MPC [11, 58, 67, 69].

Micropulse Laser (MPL)

The micropulse laser (MPL) was developed in 1990 by Pankratov and first reported for use in the retina by Friberg and Venkatesh in 1995 [71, 72]. MPL may employ various wavelengths from 532 to 810 nm applied at pulse frequencies, or "duty cycles", from 1 to 100%. Within the train of MPL laser pulses, the pulse length of each laser burst in MPL is 40–100us duration each. At this pulse duration, the individual pulses in a MPL pulse train are of sufficiently short to preferentially heat the RPE compared to the choroid, altering the distribution of the heating of the RPE/choroid from 20/80% in CW, to 80/20% for MPL. However, MPL pulse durations are long enough to allow intracellular heating of the RPE cavitation or photodisruption, but still short enough to prevent significant extracellular transmural heat spread. Like 2RT and SRT, MPL is preferentially selective for the RPE [45]. Unlike SRT and 2RT, MPL can be applied in such a way as to cause therapeutic sublethal thermal photostimulation of the RPE, persevering and improving retinal function where it is applied, while avoiding LIRD and thus adverse treatment effects [46–49, 73]. Successful avoidance of RPE damage allows for repeated treatment *ad lib*, and has permitted new applications prohibited to destructive CPC, SRT and 2RT laser modalities [48–50]. For 810 nm, studies have shown that at DCs $\geq$10%, MPL behaves clinically like CW, due to rapid narrowing of the inter-pulse cooling interval leading to rapid intracellular heat accumulation between laser pulses. This effect is exponentially increased with higher DCs, and shorter, higher energy wavelengths [65, 73]. Thus, akin to CPC but unlike 2RT and SRT, MPL can produce, and has been used clinically for, a wide spectrum of retinal laser effects from sublethal photostimulation of the RPE, to full-thickness suprathreshold photocoagulation [46–49, 62–66] Thus, MPL is a technical description of the laser functionality and not a particular type or approach to treatment; MPL is a laser mode. Like a scalpel, MPL is a tool, not a procedure. Failure to appreciate this distinction is a common source of misunderstanding [69]. For this reason, to say one performed "MPL" is, in fact, to say nothing.

The first MPL units employed the near-infrared 810 nm wavelength. As LIRD was considered necessary for a therapeutic effect, DCs of 15% or more were employed to promote visible "subthreshold" retinal burns, as producing retinal burns with 810 nm MPL below a 15% DC is difficult [46–49, 64].

The first report of MPL for AMD is a case report from 2009 from Battaglia-Parodi and associates of a 60 year old woman with an age-related serous PED, which resolved following MPL [74].

In 2015, use of SDM in eyes tolerant and unresponsive to all available anti-VEGF medications was reported [74]. This application was prompted by a new theory of retinal laser action as triggering a retinal physiologic "reset" phenomenon. Based

on the "reset" theory, panmacular SDM in eyes tolerant to anti-VEGF drugs should "reset" them to the state prior to the development of tolerance, restoring responsiveness to anti-VEGF medication. This application of reset theory was particularly novel in that reversal of drug tolerance had never previously been observed in medicine [74]. Rechallenged with the last-failed anti-VEGF drug, aflibercept, one month after SDM treatment, 12/13 eyes demonstrated reversal of drug tolerance with resolution of subretinal fluid.

In 2016, 158 eyes of 108 consecutive patients with dry AMD were reported, tested by various methods after panmacular subthreshold diode micropulse (SDM) treatment [75]. SDM is a specific application of MPL that uses a uniform treatment approach in all eyes, consisting of identical laser parameters, treatment area (panmacular), and number of laser spot applications in every eye. Laser parameters employed preclude the possibility of LIRD without the need for individual patient adjustment. Thus, there are no reports of adverse treatment effects or LIRD by any means of detection following SDM in any application [45–49]. There was no notable effect of treatment on macular morphology or drusen in any study eye. Following SDM MPL, retinal function measured by pattern electroretinography (PERG) was significantly improved ($p = 0.0001$); and visual function was improved by microperimetry ($P = 0.0439$) and contrast acuity ($p = 0.006$). These findings of retinal and visual functional improvements in AMD and IRDs following SDM MPL, sublethal to the retina, suggested such testing results might serve as useful surrogate indicators of long-term slowing disease progression and reduced risks of vision loss.

In 2018, the effect of SDM MPL on the incidence of neovascular conversion in eyes with dry AMD was reported [76]. This retrospective study included all eyes with dry AMD in a vitreoretinal practice in which regular periodic panmacular SDM was offered, in addition to conventional care, in hopes of slowing disease progression and reduce vision loss through improving retinal function [75]. This study included 547 eyes of 363 patients treated between 2008 and 2017. Risk factors in this patient cohort were especially high, with an average age of 84 years, RPD in 39% of eyes, fellow eye CNV in 23%, and AREDS category 3 and 4 AMD in 78%. Despite these high risks, with follow up ranging from 6–108 months (avg. 22) new CNV developed in 9/547 eyes (1.6%, annualized rate 0.87%), with an age-adjusted reduction in the expected annual incidence of new CNV of 95–98%, compared to 4% for standard care alone. Patients suffering neovascular conversion averaged 82 years, with an average AREDS category in the treated eye of 3.2 and fellow eye of 3.7. 5/9 converting eyes had NAMD in the fellow eye. 8/9 converting eyes had RPD in both eyes. Neither smoking nor systemic hypertension were risk factors for conversion, likely due to the small number of conversions observed. Over the study period there was no notable effect of treatment on macular drusen [76].

The effect of SDM on progression of GA was then studied, examining only the eyes with GA in this same cohort of eyes with AMD treated by regular periodic SDM [77]. 67 eyes of 49 patients with GA were identified for study, documented an average 2.5 years prior to beginning SDM treatment, and an average 2.2 years after beginning SDM, performed on average every 3–4 months over that period of time. The average age of this group was 86 years old. 78% of eyes had coincident RPD. Thus, these

were particularly high-risk eyes, the same type that worsened following SRT and 2RT nanosecond laser treatment [58, 68, 69]. Reported in 2020, the rate of radial linear GA progression after regular periodic panmacular SDM MPL slowed from an average annual rate of 137 to 73 um per year, a 47% per year decline. There was no LIRD or adverse treatment effects. GA lesions with a diameter of <1000 um at the time of first treatment slowed nearly twice the average rate, although this difference was not statistically significant due to the small number of eyes. However, this observation suggests that, as one might expect, with GA like most other things, less advanced disease may respond better to treatment than more advanced disease [77].

Retrospective studies of the results of a novel procedure in a single practice, especially one that reports remarkable results, should be taken with caution [76, 77]. The potential for various biases is high. Mitigating factors were the all-comers nature of the study cohort, excellent long-term follow up, uniform nature of the treatment, and robust results. To challenge the results of the first study showing an age-adjusted reduction in the expected incidence of new CNV in AMD by 95–98% per year in a very high-risk population, two additional studies were performed.

In the first, the effect of regular periodic panmacular SDM (now termed "vision protection therapy", or VPT) on neovascular conversion in dry AMD was examined using real world data (RWD) [78]. Vestrum Health, Inc (Naperville, Ill, USA) (VH) aggregates patient unidentified data from over 300 retina practices in the United States. Member practices are provided monthly benchmarking reports and given access to the database for analyses. All eyes in the VH database with ICD 9 and 10 codes for dry AMD between January 2016 and September 2021 were examined. Inclusions included, in addition to dry AMD, age of 50 years or more. The comparator was whether they were treated with standard care alone (SCA) (AREDS vitamins, hypertension control, smoking cessation and healthy lifestyle and nutritional advice) vs the addition of VPT to standard care. Exclusions were various diagnoses that may require intravitreal injection such as diabetes mellitus and retinal vascular occlusion, and diagnoses that predispose to CNV, such as prior macular photocoagulation, high or degenerative myopia and ocular histoplasmosis. Because data included ICD 9 coding which did not stratify AMD beyond wet or dry, dry AMD subtyping could not be performed. Patients were then matched by propensity scoring for identifiable risk factors, including age, sex, systemic hypertension, smoking and use of AREDS vitamins. Patients were also matched for number of clinical encounters, as a clinical encounter was required for diagnosis and recognition of conversion, and thus represented an independent risk factor. Confirmation of neovascular conversion required both a new ICD 9 or 10 diagnosis of neovascular AMD and initiation of anti-VEGF therapy. Using the Match-it program, the study groups were matched in a 1/10 ratio for statistical analysis with 830 eyes in the VPT group, and 8,300 in the SCA group for a total study group of 9,130 eyes [78].

Over the 4.75 year study window, eyes receiving VPT in addition to standard care were significantly less likely to suffer neovascular conversion than eyes managed by SCA (Hazard ratio 13.04). The advantage of VPT over standard care maintain for every propensity score risk stratum quintile, with the advantage of VPT over standard

care greatest in the highest risk quintile. Over the same period, the average VA of VPT eyes improved, while the VA of SCA eyes progressively worsened.

The effect of VPT on management of eyes already being treated with anti-VEGF injections for neovascular AMD was also examined. Compared to eyes managed with injections alone, eyes that received VPT in addition to anti-VEGF injections required 69% fewer injections to achieve the same visual results.

Because this first RWD study included ICD9 data that precluded matching for dry AMD severity subtypes, a second RWD study was performed using VH data to include only eyes with ICD 10 dry AMD coding. This study did not include early, low-risk AMD eyes, but only intermediate to advanced dry AMD subtypes at high risk for neovascular conversion. Currently in manuscript, this study, otherwise employing the same inclusions and exclusion of the first RWD study, found, once again, that VPT markedly reduced the risk of neovascular conversion compared to standard care alone (JKL, unpublished data, May 2022).

An additional interesting observation that has not yet been studied, is the frequent observation of nerve fiber layer thickening, and retinal thinning, by OCT during the course of VPT. This retinal thinning is not due to thinning of the neurosensory retina. Instead, it is due to gradual debris removal and thinning of the Bruch's membrane/RPE complex toward a more normal, healthy appearing anatomy. The reason for NFL thickening is unclear, but may reflect the neuroprotective effects of SDM MPL (Fig. 4.2).

Synthesis

Conventional suprathreshold retinal photocoagulation for AMD rose in a time absent any other treatment options. Because the natural history of AMD, and particularly those eyes with advanced complications of AMD such as CNV, PED, and geographic atrophy, is one of fairly rapid progression and profound visual loss, any treatment offering any possible benefit to even a small proportion of affected eyes was important and valuable, even if the overall impact of such treatment on the general AMD population was minimal. The literature on MPC for AMD is vast, including many large RCTs and population-based natural history studies. This reflects a natural advantage of older well-established treatments over newer, even far superior treatments. The weight of evidence, at least in the beginning, always favors the status quo. This is certainly the case if one restricts one's interest to macular laser treatment for AMD, as the studies of the newer approaches to laser treatment of AMD are few, small, and largely retrospective. This is not true when the weight of MPC literature in AMD is considered in comparison to anti-VEGF drug therapy for neovascular AMD. The only application of MPC in AMD that yielded significant benefit was ablative treatment for extrafoveal CNV. However, the very few patients who enjoyed any lasting benefit from this treatment caused MPC to be largely abandoned promptly in favor of drug therapy. Such a sea-change in medicine is uncommon, as progress is typically incremental. The move away from MPC for AMD was due not just due to the

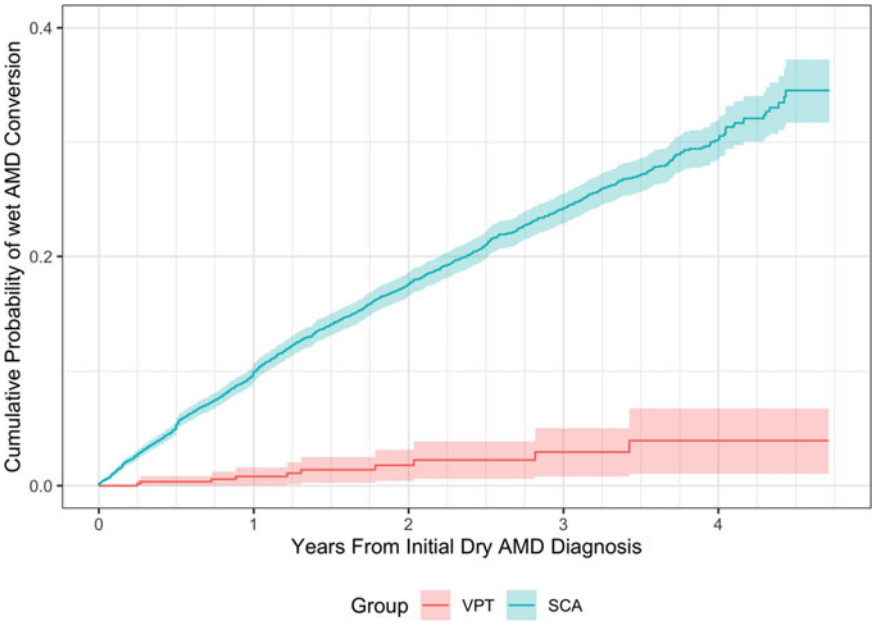

Fig. 4.2 Overall Kaplan-Meier cumulative wet AMD conversion probability by group. Shaded areas indicate 95% confidence intervals. Note the that VPT reduced the risk of neovascular conversion over standard care by a hazard ratio of 13.04. VPT = Vision Protection TherapyTM. SCA = standard care alone. AMD = age-related macular degeneration. Cum = cummulative [78]

excellent results from drug therapy, but also due to the very poor results associated with MPC. The limitations of MPC were principally due to the destructive nature of suprathreshold photocoagulation. This markedly restricted the location and area of macula that could be safely treated, and ability to retreat without treatment-associated visual loss. Inherent with MPC was loss of visual function in the areas of the macula treated, and aggravation of the disease process due to treatment-associated inflammation which at least temporarily pro-angiogenic, and compromises the key physical barrier to subretinal neovascularization, the Bruch's membrane/RPE complex. Only the physically destructive attributes of MPC as cautery were applied to the treatment of AMD. Thus, inherent adverse effects of PC—all the result of LIRD—featured prominently. During the years of MPC for AMD, the therapeutic mechanism of action of retinal laser treatment, apart from cautery, was unknown [1–16, 45, 46, 48].

The short-pulse laser strategies were developed toward the latter part of the MPC era, prior to the advent of anti-VEGF drugs, but by the time that the limitations of conventional MPC had become very apparent. The idea that LIRD was both a necessary and sufficient cause of all therapeutic laser effects was still universal, and thus LIRD remained a prerequisite of treatment. However, by more selectively destroying the RPE and minimizing damage to Bruch's membrane and the neurosensory retina it was hoped that the benefits of MPC—drusen reduction—could be maintained while

reducing adverse effects, particularly incitement of CNV. Because elimination of drusen was proportional to treatment intensity, the degree of tissue destruction and inflammation caused by treatment, the short-pulse strategies were somewhat less effective at drusen reduction than MPC. However, it does appear that reducing inflammation and damage to Bruch's membrane and the choriocapillaris did indeed reduce the risk of treatment associated new CNV, as this has not been a significant finding in the few short-pulse laser for drusen studies done thus far [11, 57, 58, 67, 68].

The propensity of short-pulse laser treatments, both SRT and 2RT, to worsen eyes with more advanced dry AMD, specifically those with GA and /or RPD, is particularly interesting. Why might this be?

Because short-pulse laser obliterates the RPE with minimal lateral or basal/apical heat spread, tissue damage and inflammation are reduced compared to MPC. As we will discuss in the section of the mechanism of retinal laser, the critical initiating trigger of therapeutic laser effects (for other than cautery) is thermal but sublethal activation of RPE heat shock proteins (HSPs) and associated enhancement of HSP protein repair kinetics [64, 72]. Because short-pulse lasers vaporize the RPE before RPE HSPs can be activated, the therapeutic effects of short-pulse lasers are indirect, rather than direct [48]. For short-pulse lasers, the spots denuded of RPE heal by sliding of adjacent RPE and outer retinal cells in to fill the gap and restore the blood retinal barrier [48, 51, 52]. This has a number of implications. First, the tissue healing response is a stress that always involves if not depends on HSP activation and the cascades of subsequent reactions it recruits [45]. Thus, HSP activation is a feature of both sublethal and photodisruptive/photoablative treatments [48]. The salvific (existential, as opposed to surveillance homeostatic) response of HSPs is a stress response to a threat to the cell. It is thus reparative and restorative. In eyes treated by short-pulse lasers, the cells that are threatened and stressed are those at the immediate margins of the denuded laser spot, tasked with the job of repairing the RPE defect. Because this margin is thin, the degree of therapeutic HSP activation is relatively limited [47]. Secondly, eyes with advanced dry AMD with GA and RPD are in a tenuous state, likely maximizing their already highly compromised ability to maintain function and compensate for the advance age-related dysfunction they manifest [44, 45]. Selective destruction of the RPE in such eyes may simply push them over edge to decompensation, further compromising their already marginal function leading to even more rapid deterioration, as seen with both SRT and 2RT lasers (information regarding the PASCAL is insufficient in this regard) [57, 58, 67, 68]. Third, while replication and replacement of injured RPE has been noted in animals, it has not been in humans [60]. Thus, the sliding and expansion of surviving RPE cells, rather than regeneration, fills the laser-created gaps reduces macular RPE density. What impact this may have is unclear, but it would be neutral at best if limited in area, and most likely detrimental to function, especially if wider areas are subjected to treatment, and even more so if repetitive. As there is no evidence of RPE replication in humans, the RPE may be analogous to the corneal endothelium—a critical finite resource [48]. If so, this recommends against deliberate RPE destruction. Fourth, and finally, the RPE has tensile properties. This is seen clinically in cases of RPE rips. When the RPE tears, it generally contracts, and often scrolls as if under tension.

In this respect, it may be thought of as a drumhead. Drumheads vibrate when struck. Photodisruption, such as use of the YAG laser for posterior capsulotomy, causes shock waves due to cavitation. The same that occurs in short-pulse laser photodisruption of the RPE. Analysis of the physics of this effect on the retina using the laser parameters employed in the LEAD trial show that each nanosecond laser spot causes a shock wave in the plane of the RPE extending more than 1 mm from the center of each laser spot. In the LEAD trial, this means that if each eye was treated with 7–10 laser spots just inside the major vascular arcades, 7–10 shock waves would have traversed the macula at each treatment session. (DB Chang, PhD, unpublished data, 2020) The effect of such multiple shock waves sent through the macula is unknown, but would unlikely be good, or neutral. Further, they may explain the ability of short-pulse lasers to reduce drusen at some distance to the laser spot, despite the limited laser-induced retinal damage and inflammation. It is not hard to imagine that the added trauma of shock waves across the macula might also further compromise already marginally functional eyes, such as those with GA and RPD that are worsened by short pulse laser treatment [23, 27, 48, 57, 58, 67, 68].

As noted above, MPL has a wide range of possible effects, from suprathreshold PC to thermal photostimulation sublethal to the RPE. Except for a single case report by Parodi, all studies of MPL for AMD thus far report use of the SDM (low-intensity/high-density subthreshold microsecond pulse laser) use of MPL [73]. As the extended name implies, SDM denotes a specific use of MPL that is reliably sublethal to the RPE yet effective. SDM is applied in contiguous spots across the entire macular area (including the fovea) to maximize the clinical effects ("panmacular" treatment). The studies of SDM MPL for AMD are generally large and varied but few in number compared to CPC, reporting treatment to reverse tolerance to anti-VEGF drugs in wet AMD, to improve visual and retinal function in dry AMD, to slow progression of GA in dry AMD, to reduce visual loss in AMD by preventing neovascular conversion, and to reduce the need for anti-VEGF injections for eyes with wet AMD [73–79]. None of these studies are RCTs, as is the LEAD trial of nanosecond laser. All are various forms of retrospective studies. However, in each case the results of SDM MPL for AMD show robustly positive effects without any adverse effects. This is consistent with the literature of SDM and MPL for all indications. In contrast to MPC, SDM MPL does not reduce drusen in the short term, and reduces rather than increases the risk of CNV. Rather than worsening high-risk eyes with RPD and GA like 2RT and SRT, SDM MPL improves these eyes by improving retinal and visual function and significantly slowing, rather than accelerating, disease progression [73–79]. This fundamental difference in the effects of SDM MPL and MPC, SRT and 2RT for AMD is attributable to the fact that SDM MPL preserves and normalizes retinal and RPE function, while the others destroy the RPE and worsen retinal function and, to varying degrees, compromise retinal structural integrity as well. Seen in that context, the results of each mode of retinal laser treatment are quite predictable as reflecting the direct effect of treatment on the treated retina [45, 48].

AMD is the most common cause of irreversible visual loss worldwide, and by far the most important cause in persons over 60 years of age. Although the incidence of AMD is declining, likely a reflection of improvements in general health and nutrition

with time, the prevalence of AMD is rapidly increasing as the global population ages and longevity increases [42]. The main cause of visual loss in AMD is the development of neovascular AMD. Therefore, despite the great benefits of anti-VEGF drugs for treating wet AMD, preventing neovascular conversion in wet AMD is the most important way to prevent age-related visual loss [42, 43, 80, 81]. Currently, retinal laser treatment appears to offer the best prospects for achieving this goal safely and effectively. Studies have shown no significant difference between the results of RCTs and large RWD studies with robust results, such as those looking at VPT to prevent wet AMD [82]. However, prospective studies are needed to confirm these results and encourage adoption. These are expensive. Industry, primarily the pharmaceutical industry, currently sponsors over 95% of all RCTs in ophthalmology. In the absence of governmental interest, the sources of funding for the RCTs needed to confirm the benefits of laser for AMD are not immediately apparent.

References

1. Macular Photocoagulation Study Group. Argon laser photocoagulation for neovascular maculopathy: five-year results from randomized clinical trials. Arch Ophthalmol. 1991;109(8):1109–14. Erratum in: Arch Ophthalmol 1992 Jun;110(6):761. PMID: 1714270.
2. Macular Photocoagulation Study Group. Laser photocoagulation for juxtafoveal choroidal neovascularization: five-year results from randomized clinical trials. Arch Ophthalmol. 1994;112(4):500–9. PMID: 7512336.
3. Bressler NM, Maguire MG, Murphy PL, Alexander J, Margherio R, Schachat AP, Fine SL, Stevens TS, Bressler SB. Macular scatter ('grid') laser treatment of poorly demarcated subfoveal choroidal neovascularization in age-related macular degeneration: results of a randomized pilot trial. Arch Ophthalmol. 1996;114(12):1456–64. https://doi.org/10.1001/archopht.1996.01100140654002. PMID: 8953976.
4. Macular Photocoagulation Study Group. Laser photocoagulation of subfoveal neovascular lesions of age-related macular degeneration: updated findings from two clinical trials. Arch Ophthalmol. 1993;111(9):1200–9. https://doi.org/10.1001/archopht.1993.01090090052019. PMID: 7689827.
5. Macular Photocoagulation Study Group. Visual outcome after laser photocoagulation for subfoveal choroidal neovascularization secondary to age-related macular degeneration: the influence of initial lesion size and initial visual acuity. Arch Ophthalmol. 1994;112(4):480–8. https://doi.org/10.1001/archopht.1994.01090160056023. PMID: 7512334.
6. Barondes MJ, Pagliarini S, Chisholm IH, Hamilton AM, Bird AC. Controlled trial of laser photocoagulation of pigment epithelial detachments in the elderly: 4 year review. Br J Ophthalmol. 1992;76(1):5–7. https://doi.org/10.1136/bjo.76.1.5. PMID: 1371225; PMCID: PMC504139.
7. Schatz H. Laser photocoagulation of retinal disease. San Francisco: Pacific Medical Press; 1988. p. 281. ISBN 10 0960810242 ISBN 13 9780960810246.
8. Bressler SB, Maguire MG, Bressler NM, Fine SL, The Macular Photocoagulation Study Group. Relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular macular degeneration. Arch Ophthalmol. 1990;108(10):1442–7. https://doi.org/10.1001/archopht.1990.01070120090035. PMID: 1699513.
9. Gass JD. Drusen and disciform macular detachment and degeneration. Arch Ophthalmol. 1973;90:206–17.
10. Gass JD. Photocoagulation of macular lesions. Trans Am Acad Ophthalmol Otolaryngol. 1971;75:580–608.

11. Complications of Age-Related Macular Degeneration Prevention Trial Study Group. The Complications of Age-Related Macular Degeneration Prevention Trial (CAPT): rationale, design and methodology. Clin Trials. 2004;1(1):91–107. https://doi.org/10.1191/1740774504cn007xx. PMID: 16281465.
12. Frennesson CI, Bek T, Jaakkola A, Nilsson SE, Prophylactic Laser Treatment Study Group. Prophylactic laser treatment of soft drusen maculopathy: a prospective, randomized Nordic study. Acta Ophthalmol. 2009;87(7):720–4. https://doi.org/10.1111/j.1755-3768.2008.01396.x. Epub 2008 Oct 3. PMID: 18937820.
13. Virgili G, Michelessi M, Parodi MB, Bacherini D, Evans JR. Laser treatment of drusen to prevent progression to advanced age-related macular degeneration. Cochrane Database Syst Rev. 2015;10(10):CD006537. https://doi.org/10.1002/14651858.CD006537.pub3. PMID: 26493180; PMCID: PMC4733883.
14. Morgan CM, Schatz H. Atrophic creep of the retinal pigment epithelium after focal macular photocoagulation. Ophthalmology. 1989;96(1):96–103. https://doi.org/10.1016/s0161-6420(89)32924-1. PMID: 2919053.
15. Ruiz-Moreno J, De la Vega C, Zarbin MA. Macular atrophy after photocoagulation of soft drusen. Retina. 2003;23(3):315–21. https://doi.org/10.1097/00006982-200306000-00005. PMID: 12824830.
16. Sacconi R, Bandello F, Querques G. Foveal chorioretinal anastomosis secondary to macular focal photocoagulation in diabetic retinopathy. Ophthalmol Retina. 2018;2(2):127. https://doi.org/10.1016/j.oret.2017.10.004. Epub 2018 Feb 2. PMID: 31047338.
17. Sreekumar PG, Zhou J, Sohn J, Spee C, Ryan SJ, Maurer BJ, Kannan R, Hinton DR. N-(4-hydroxyphenyl) retinamide augments laser-induced choroidal neovascularization in mice. Invest Ophthalmol Vis Sci. 2008;49(3):1210–20. https://doi.org/10.1167/iovs.07-0667. PMID: 18326751.
18. Lim JI. Hastening choroidal neovascularization: the irony of prophylactic laser in unilateral eyes with high-risk drusen. Am J Ophthalmol. 2006;141(2):354–5. https://doi.org/10.1016/j.ajo.2005.09.027. PMID: 16458694.
19. Gabriele ML, Wollstein G, Ishikawa H, Kagemann L, Xu J, Folio LS, Schuman JS. Optical coherence tomography: history, current status, and laboratory work. Invest Ophthalmol Vis Sci. 2011;52(5):2425–36. https://doi.org/10.1167/iovs.10-6312. PMID: 21493951; PMCID: PMC3088542.
20. Slakter JS, Yannuzzi LA, Guyer DR, Sorenson JA, Orlock DA. Indocyanine-green angiography. Curr Opin Ophthalmol. 1995;6(3):25–32. https://doi.org/10.1097/00055735-199506000-00005. PMID: 10151085.
21. Querques G, Corvi F, Querques L, Souied EH, Bandello F. Optical coherence tomography angiography of choroidal neovascularization secondary to pathologic myopia. Dev Ophthalmol. 2016;56:101–6. https://doi.org/10.1159/000442800. Epub 2016 Mar 15. PMID: 27023343.
22. Ciulla TA, Rosenfeld PJ. Anti-vascular endothelial growth factor therapy for neovascular ocular diseases other than age-related macular degeneration. Curr Opin Ophthalmol. 2009;20(3):166–74. https://doi.org/10.1097/ICU.0b013e328329d173. PMID: 19381089.
23. Mainster MA, Reichel E. Transpupillary thermotherapy for age-related macular degeneration: long-pulse photocoagulation, apoptosis, and heat shock proteins. Ophthalmic Surg Lasers. 2000;31(5):359–73. PMID: 11011704.
24. Reichel E, Berrocal AM, Ip M, Kroll AJ, Desai V, Duker JS, Puliafito CA. Transpupillary thermotherapy of occult subfoveal choroidal neovascularization in patients with age-related macular degeneration. Ophthalmology. 1999;106(10):1908–14. https://doi.org/10.1016/S0161-6420(99)90400-1. PMID: 10519584.
25. Myint K, Armbrecht AM, Mon S, Dhillon B. Transpupillary thermotherapy for the treatment of occult CNV in age-related macular degeneration: a prospective randomized controlled pilot study. Acta Ophthalmol Scand. 2006;84(3):328–32. https://doi.org/10.1111/j.1600-0420.2005.00623.x. PMID: 16704693.
26. Odergren A, Algvere PV, Seregard S, Kvanta A. A prospective randomised study on low-dose transpupillary thermotherapy versus photodynamic therapy for neovascular age-related

macular degeneration. Br J Ophthalmol. 2008;92(6):757–61. https://doi.org/10.1136/bjo.2007.133561. Epub 2008 Mar 20 PMID: 18356266.
27. American National Standards Institute. American national standard for the safe use of lasers, ANSI Z136.1–2000. Washington, DC: American National Standards Institute; 2000.
28. Tsai TH, Yang CM, Yang CH, Ho TC, Huang JS, Chen MS. Transpupillary thermotherapy for the treatment of choroidal neovascularization in age-related macular degeneration in Taiwan. Eye (Lond). 2007;21(6):721–6. https://doi.org/10.1038/sj.eye.6702312. Epub 2006 Mar 17 PMID: 16543926.
29. Squirrell DM, Stewart AW, Joondeph BC, Danesh-Meyer HV, McGhee CN, Donaldson ML. Large-spot subthreshold infrared laser to treat diabetic macular edema. Retina. 2008;28(4):615–21. https://doi.org/10.1097/IAE.0b013e31815ee567. PMID: 18398365.
30. Wu L, Murphy RP. Photodynamic therapy: a new approach to the treatment of choroidal neovascularization secondary to age-related macular degeneration. Curr Opin Ophthalmol. 1999;10(3):217–20. https://doi.org/10.1097/00055735-199906000-00011. PMID: 10537782.
31. Wormald R, Evans J, Smeeth L, Henshaw K. Photodynamic therapy for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD002030. https://doi.org/10.1002/14651858.CD002030.pub3. PMID: 17636693.
32. Schmidt-Erfurth U, Kiss C, Sacu S. The role of choroidal hypoperfusion associated with photodynamic therapy in neovascular age-related macular degeneration and the consequences for combination strategies. Prog Retin Eye Res. 2009;28(2):145–54. https://doi.org/10.1016/j.preteyeres.2009.01.001. PMID: 19272333.
33. Luttrull JK, Spink CJ. Prolongation of choroidal hypofluorescence following combined verteporfin photodynamic therapy and intravitreal triamcinolone acetonide injection. Retina. 2007;27(6):688–92. https://doi.org/10.1097/IAE.0b013e318030e999. PMID: 17621176.
34. Barbazetto I, Burdan A, Bressler NM, Bressler SB, Haynes L, Kapetanios AD, Lukas J, Olsen K, Potter M, Reaves A, Rosenfeld P, Schachat AP, Strong HA, Wenkstern A; Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study Group; Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization with verteporfin: fluorescein angiographic guidelines for evaluation and treatment--TAP and VIP report No. 2. Arch Ophthalmol. 2003;121(9):1253–68. doi: https://doi.org/10.1001/archopht.121.9.1253. PMID: 12963608.
35. Azab M, Benchaboune M, Blinder KJ, Bressler NM, Bressler SB, Gragoudas ES, Fish GE, Hao Y, Haynes L, Lim JI, Menchini U, Miller JW, Mones J, Potter MJ, Reaves A, Rosenfeld PJ, Strong A, Su XY, Slakter JS, Schmidt-Erfurth U, Sorenson JA; Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group; Verteporfin in Photodynamic Therapy (VIP) Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: meta-analysis of 2-year safety results in three randomized clinical trials: treatment of age-related macular degeneration with photodynamic therapy and verteporfin in photodynamic therapy study report no. 4. Retina. 2004;24(1):1–12. https://doi.org/10.1097/00006982-200402000-00001. PMID: 15076937.
36. Cruess AF, Zlateva G, Pleil AM, Wirostko B. Photodynamic therapy with verteporfin in age-related macular degeneration: a systematic review of efficacy, safety, treatment modifications and pharmacoeconomic properties. Acta Ophthalmol. 2009;87(2):118–32. https://doi.org/10.1111/j.1755-3768.2008.01218.x. Epub 2008 Jun 13. PMID: 18577193.
37. Lim TH, Lai TYY, Takahashi K, Wong TY, Chen LJ, Ruamviboonsuk P, Tan CS, Lee WK, Cheung CMG, Ngah NF, Patalauskaite R, Margaron P, Koh A; Everest II Study Group. Comparison of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: the everest II randomized clinical trial. JAMA Ophthalmol. 2020;138(9):935–942. https://doi.org/10.1001/jamaophthalmol.2020.2443. PMID: 32672800; PMCID: PMC7366282.
38. Shiraga F, Ojima Y, Matsuo T, Takasu I, Matsuo N. Feeder vessel photocoagulation of subfoveal choroidal neovascularization secondary to age-related macular degeneration. Ophthalmology. 1998;105(4):662–9. https://doi.org/10.1016/S0161-6420(98)94021-0. PMID: 9544641.

39. York J, Glaser B, Murphy R. High-speed ICG. Used for pinpoint laser treatment of feeder vessels in wet AMD. J Ophthalmic Nurs Technol. 2000;19(2):66–7. PMID: 11075075.
40. Desatnik H, Treister G, Alhalel A, Krupsky S, Moisseiev J. ICGA-guided laser photocoagulation of feeder vessels of choroidal neovascular membranes in age-related macular degeneration indocyanine green angiography. Retina. 2000;20(2):143–50. PMID: 10783946.
41. Brancato R, Introini U, Bolognesi G, Pacelli G, Trabucchi G, Pece A. ICGA-guided laser photocoagulation of occult choroidal neovascularization in age-related macular degeneration indocyanine green angiography. Retina. 2000;20(2):134–42. PMID: 10783945.
42. Wong WL, Su X, Cheung CMG, Klein R, Cheng C, Wong TY. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systemic review and meta-analysis. Lancet Glob Health. 2014;2(2). https://doi.org/10.1016/S2214-109X(13)70145-1.
43. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report number 8. Arch Ophthalmol 2001;119:1417–36. PMID: 11594942.
44. Sarks SH. Ageing and degeneration in the macular region: a clinico-pathological study. Br J Ophthalmol. 1976;60(5):324–41. https://doi.org/10.1136/bjo.60.5.324. PMID: 952802; PMCID: PMC1042725
45. Luttrull JK, Kent D. Laser therapy to prevent choroidal neovascularization. In: Chhablanni J, editors. Choroidal neovascularization. Springer Verlag; 2020. https://doi.org/10.1007/978-981-15-2213-0_30.
46. Dorin G. Subthreshold and micropulse diode laser photocoagulation. Semin Ophthalmol. 2003;18:147–53.
47. Luttrull JK, Dorin G. Subthreshold diode micropulse photocoagulation as invisible retinal phototherapy for diabetic macular edema a review. Current Diabetes Rev. 2012;8:274–84.
48. Chhablani J, Roh YJ, Jobling AI, Fletcher EL, Lek JJ, Bansal P, Guymer R, Luttrull JK. Restorative retinal laser therapy: present state and future directions. Surv Ophthalmol. 2018;63(3):307–328.
49. Luttrull JK, Sinclair SD. Safety of transfoveal subthreshold diode micropulse laser for intrafoveal diabetic macular edema in eyes with good visual acuity. Retina. 2014;34(10):2010–20.
50. Hamada M, Ohkoshi K, Inagaki K, Ebihara N, Murakami A. Subthreshold photocoagulation using endpoint management in the PASCAL® system for diffuse diabetic macular edema. J Ophthalmol. 2018;31(2018):7465794. https://doi.org/10.1155/2018/7465794. PMID: 29651345; PMCID: PMC5831979
51. Kriechbaum K, Bolz M, Deak GG, Prager S, Scholda C, Schmidt-Erfurth U. High-resolution imaging of the human retina in vivo after scatter photocoagulation treatment using a semiautomated laser system. Ophthalmology. 2010;117(3):545–51. https://doi.org/10.1016/j.ophtha.2009.07.031. Epub 2010 Jan 19. PMID: 20031226.
52. Kim MS, Ryoo NK, Park KH. Laser and anti-vascular endothelial growth factor treatment for drusenoid pigment epithelial detachment in age-related macular degeneration. Sci Rep. 2020;10(1):14370. https://doi.org/10.1038/s41598-020-71401-3. PMID: 32873842; PMCID: PMC7462975.
53. Querques G, Sacconi R, Gelormini F, Borrelli E, Prascina F, Zucchiatti I, Querques L, Bandello F. Subthreshold laser treatment for reticular pseudodrusen secondary to age-related macular degeneration. Sci Rep. 2021;11(1):2193. https://doi.org/10.1038/s41598-021-81810-7. PMID: 33500505; PMCID: PMC7838261.
54. Minhee K, Park YG, Kang S, Roh YJ. Comparison of the tissue response of selective retina therapy with or without real-time feedback-controlled dosimetry. Graefes Arch Clin Exp Ophthalmol. 2018;256(9):1639–51. https://doi.org/10.1007/s00417-018-4067-9. Epub 2018 Jul 28 PMID: 30056549.
55. Seifert E, Tode J, Pielen A, Theisen-Kunde D, Framme C, Roider J, Miura Y, Birngruber R, Brinkmann R. Algorithms for optoacoustically controlled selective retina therapy (SRT). Photoacoustics. 2021;10(25): 100316. https://doi.org/10.1016/j.pacs.2021.100316. PMID: 34926158; PMCID: PMC8649889

56. Tode J, Richert E, Koinzer S, Klettner A, von der Burchard C, Brinkmann R, Lucius R, Roider J. Selective retina therapy reduces bruch's membrane thickness and retinal pigment epithelium pathology in age-related macular degeneration mouse models. Transl Vis Sci Technol. 2019;8(6):11. https://doi.org/10.1167/tvst.8.6.11. PMID: 31737435; PMCID: PMC6855371.
57. Kim M, Park YG, Roh YJ. One-year functional and anatomical outcomes after selective retina therapy with real-time feedback-controlled dosimetry in patients with intermediate age-related macular degeneration: a pilot study. Lasers Surg Med. 2021;53(4):499–513. https://doi.org/10.1002/lsm.23305. Epub 2020 Aug 5 PMID: 32757324.
58. Prahs P, Walter A, Regler R, Theisen-Kunde D, Birngruber R, Brinkmann R, Framme C. Selective retina therapy (SRT) in patients with geographic atrophy due to age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2010;248(5):651–8. https://doi.org/10.1007/s00417-009-1208-1. Epub 2009 Dec 22. PMID: 20024687.
59. Guymer RH, Brassington KH, Dimitrov P, Makeyeva G, Plunkett M, Xia W, Chauhan D, Vingrys A, Luu CD. Nanosecond-laser application in intermediate AMD: 12-month results of fundus appearance and macular function. Clin Exp Ophthalmol. 2014;42(5):466–79. https://doi.org/10.1111/ceo.12247. Epub 2013 Nov 11 PMID: 24118741.
60. Pelosini L, Hamilton R, Mohamed M, Hamilton AM, Marshall J. Retina rejuvenation therapy for diabetic macular edema: a pilot study. Retina. 2013;33(3):548–58. https://doi.org/10.1097/IAE.0b013e3182670fea. PMID: 23023529.
61. Luttrull JK, Musch MC, Mainster MA. Subthreshold diode micropulse photocoagulation for the treatment of clinically significant diabetic macular edema. Br J Ophthalmol. 2005;89(1):74–80.
62. Luttrull JK, Spink CJ. Serial optical coherence tomography of subthreshold diode laser micropulse photocoagulation for diabetic macular edema. Ophthalmic Surg Lasers Imaging. 2006;37:370–7.
63. Luttrull JK, Spink CJ, Musch DA. Subthreshold diode micropulse panretinal photocoagulation for proliferative diabetic retinopathy. Eye. 2008;22(5):607–12.
64. Luttrull JK, Sramek C, Palanker D, Spink CJ, Musch DC. Long-term safety, high-resolution imaging, and tissue temperature modeling of subvisible diode micropulse photocoagulation for retinovascular macular edema. Retina. 2012;32(2):375–86.
65. Cohn AC, Runciman J, Hodgson LAB, Caruso E, Arnold JJ, Chen FK, Chakravarthy U, Heriot WJ, Guymer RH, Wu Z; LEAD Study Group. Dose response in the subthreshold nanosecond laser trial in early stages of AMD: a lead study report. Ophthalmic Surg Lasers Imaging Retina. 2021;52(7):380–386. https://doi.org/10.3928/23258160-20210628-04. Epub 2021 Jul 1. PMID: 34309427.
66. Jobling AI, Guymer RH, Vessey KA, Greferath U, Mills SA, Brassington KH, Luu CD, Aung KZ, Trogrlic L, Plunkett M, Fletcher EL. Nanosecond laser therapy reverses pathologic and molecular changes in age-related macular degeneration without retinal damage. FASEB J. 2015;29(2):696–710. https://doi.org/10.1096/fj.14-262444. Epub 2014 Nov 12. PMID: 25392267.
67. Guymer RH, Wu Z, Hodgson LAB, Caruso E, Brassington KH, Tindill N, Aung KZ, McGuinness MB, Fletcher EL, Chen FK, Chakravarthy U, Arnold JJ, Heriot WJ, Durkin SR, Lek JJ, Harper CA, Wickremasinghe SS, Sandhu SS, Baglin EK, Sharangan P, Braat S, Luu CD; Laser Intervention in Early Stages of Age-Related Macular Degeneration Study Group. Subthreshold nanosecond laser intervention in age-related macular degeneration: The LEAD randomized controlled clinical trial. Ophthalmology. 2019;126(6):829–838. https://doi.org/10.1016/j.ophtha.2018.09.015. Epub 2018 Sep 20. PMID: 30244144.
68. Guymer RH, Chen FK, Hodgson LAB, Caruso E, Harper CA, Wickremashinghe SS, Cohn AC, Sivarajah P, Tindill N, Luu CD, Wu Z; LEAD Study Group. Subthreshold nanosecond laser in age-related macular degeneration: observational extension study of the LEAD clinical trial. Ophthalmol Retina. 2021;5(12):1196–1203. https://doi.org/10.1016/j.oret.2021.02.015. Epub 2021 Mar 1. PMID: 33662615.
69. Rosenfeld PJ, Feuer WJ. Warning: do not treat intermediate AMD with laser therapy. Ophthalmology. 2019;126(6):839–40. https://doi.org/10.1016/j.ophtha.2018.12.016. PMID: 31122360.

70. Pankratov MM. Pulse delivery of laser energy in experimental thermal retinal photocoagulation. Proc Soc Photo Opt Instrum Eng. 1990;1202:205e13
71. Friberg TR, Venkatesh S. Alteration of pulse configuration affects the pain response during diode laser photocoagulation. Lasers Surg Med. 1995;16(4):380–3. https://doi.org/10.1002/lsm.1900160409. PMID: 7651059.
72. Chang DB, Luttrull JK. Comparison of subthreshold 577 nm and 810 nm micropulse laser effects on heat-shock protein activation kinetics: Implications for treatment efficacy and safety. Transl Vis Sci Tecnol. 2020;9(5):23. https://doi.org/10.1167/tvst.9.5.23.eCollection.
73. Battaglia-Parodi M, Sheth S, Papayannis A, Bandello F. Treatment of serous pigment epithelium detachment with subthreshold micropulse diode laser photocoagulation: a case report. Eur J Ophthalmol. 2009;19(5):887–9. https://doi.org/10.1177/112067210901900501. PMID: 19787617.
74. Luttrull JK, Margolis BW. Functionally guided retinal protective therapy for dry age-related macular and inherited retinal degenerations: a pilot study. Invest Ophthalmol Vis Sci. 2016;57(1):265–75. https://doi.org/10.1167/iovs.15-18163. PMID: 26818793.
75. Keunen JEE, Battaglia-Parodi M, Vujosevic S, Luttrull JK. International retinal laser society guidelines for subthreshold laser treatment. Transl Vis Sci Technol. 2020;9(9):15. https://doi.org/10.1167/tvst.9.9.15. eCollection 2020 Aug. PMID: 32879771
76. Luttrull JK, Sinclair SH, Elmann S, Glaser BM. Low incidence of choroidal neovascularization following subthreshold diode micropulse laser (SDM) in high-risk AMD. PLoS ONE. 2018;13(8): e0202097. https://doi.org/10.1371/journal.pone.0202097. PMID: 30138455; PMCID: PMC6107149.
77. Luttrull JK, Sinclair SH, Elmann S, Chang DB, Kent D. Slowed progression of age-related geographic atrophy following subthreshold laser. Clin Ophthalmol. 2020;1(14):2983–93. https://doi.org/10.2147/OPTH.S268322. PMID: 33061284;PMCID: PMC7534850.
78. Luttrull JK, Gray G. Real world data comparison of standard care vs SDM laser vision protection therapy for prevention of neovascular AMD. Clin Ophthalmol. 2022;16:1555–68.
79. Luttrull JK, Chang DB, Margolis BW, Dorin G, Luttrull DK. Laser resensitization of medically unresponsive neovascular age-related macular degeneration: efficacy and implications. Retina. 2015;35(6):1184–94. https://doi.org/10.1097/IAE.0000000000000458. PMID: 25650711.
80. Wong WL, Su X, Cheung CMG, Klein R, Cheng C, Wong TY. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systemic review and meta-analysis. Lancet Glob Health. 2(2) https://doi.org/10.1016/S2214-109X(13)70145-1.
81. The Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol. 2004;122(4): 564–572. https://doi.org/10.1001/archopht.122.4.564. PMID: 15078675.
82. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. Cochrane Database Syst Rev. 2014, Issue 4. Art. No.: MR000034. https://doi.org/10.1002/14651858.MR000034.pub2.

Chapter 5
Lasers in Diabetic Retinopathy

Maciej Gawęcki, Jeffrey K. Luttrull, and Andrzej Grzybowski

Abstract Diabetic retinopathy (DR) is one of the most prevalent ophthalmic complications in patients with diabetes and one of the leading causes of blindness in developed countries. Treatment of DR includes different strategies, starting from systemic therapies, lifestyle issues, as well as local treatments, among them different forms of laser photocoagulation. Management of DR has faced a significant change since introduction of intravitreal drugs such as steroids and anti-VEGF agents and that fact influenced the strategies of laser application in that disorder. A significant shift is observed towards the non-damaging to retina forms of laser application, especially subthreshold micropulse or selective retinal therapy. These issues are thoroughly discussed in that chapter together with the outline of practical protocols for different lasers used in DR. Historical milestone diabetic retinopathy studies on retinal photocoagulation are placed in the modern perspective and availability of new technologies.

Introduction

Diabetic retinopathy (DR) is one of the most prevalent ophthalmic complications in patients with diabetes mellitus (DM). Nevertheless, data on incidence of retinopathy in diabetic patients vary significantly among different populations. Large metanalysis of data from 35 studies found the overall prevalence of any stage of retinopathy (DR) in the diabetic population at 35.4% with the most advanced form of DR, proliferative DR (PDR) in 7.5% [1]. Most of the studies report higher prevalence of DR in

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_5

patients with type 1 of diabetes mellitus (DM1). This rule applies also to proliferative retinopathy [2, 3].

Pathomechanism of Diabetic Retinopathy in the Context of Laser—Tissue Interaction

High blood glucose levels trigger or interfere with various metabolic paths that effects in damage to retinal vessel walls Fig. 5.1. The most important processes involved in the development of diabetic retinopathy include initiating of the polyol path (accumulation of sorbitol in the cells), protein kinase C activation, accumulation of advanced glycation end products (AGE), oxidative stress and subclinical inflammatory processes and alterations in the balance of enzymatic renin–angiotensin–aldosterone complex, which maintains normal hemodynamics of the body [4].

Damage to vessel endothelium that occurs in DR has three major consequences. Firstly, it causes weakening of the vessel wall, with loss of pericytes and development of microaneurysms, followed by increased permeability of the capillaries [5]. This results in retinal edema, including diabetic macular edema (DME) [6]. Secondly, the sites of damaged endothelium are the locations of increased aggregation of blood morphotic elements and development of clots in retinal vessels. This process is aggravated by anomalous erythrocytes that occur in DM, which are less pliable, promoting small vessels closure. At the same time, DM increases the number of leucocytes, as a result of local inflammation, which is an important accompanying process in DR, lead to leukostasis [7]. This further increases blood viscosity and micro-thrombotic complications. The third important consequence of impaired microcirculation is retinal hypoxia and subsequent up-regulation of vasoproliferative factors, such as vascular endothelial growth factor (VEGF) from the retina and down-regulation of opposing cytokines such as pigment epithelial-derived factor (PEDF) resulting in increased vessel hyperpermeability and retinal neovascularization. These processes

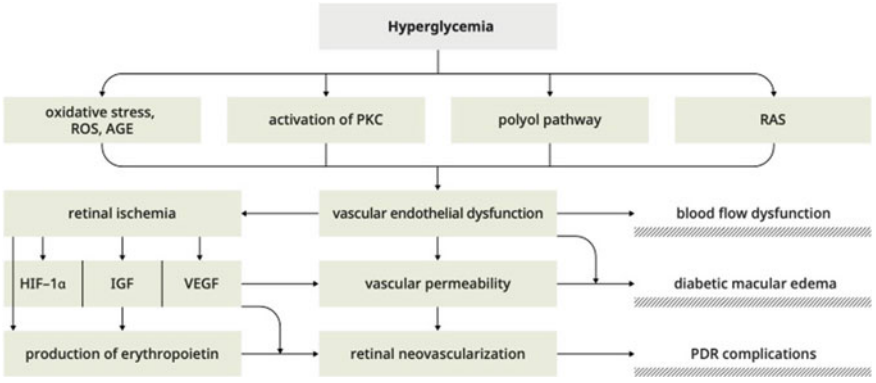

Fig. 5.1 Summary of metabolic paths elicited in diabetic retinopathy. PKC—protein kinase C, RAS–renin-angiotensin system, ROS–reactive oxygen species, AGE—advanced glycation end products, HIF—hypoxia inducible factor, IGF—insulin-like growth factor

lead to the characteristic lesions of DR we observe in advanced diabetic retinopathy, such as hemorrhages, retinal edema, hard and soft exudates, venous anomalies and abnormal retinal vessels.

DR is a neurodegenerative processes, which results in nerve cell apoptosis, increased reactivity of glial cells, microglia activation and disturbances in glutamic acid metabolism [8–10]. Activation of microglial cells stimulates subclinical inflammatory processes that are the hallmark of diabetic retinopathy. 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. Some studies show the progressive atrophy of retinal neurons in diabetic patients, even in the absence of retinopathy, reflecting early subclinical neurovascular inflammation prior to the development of clinical DR in patients with DM [11–13].

The pathomechanism of diabetic retinopathy can be analyzed in the context of therapeutic mode of action of different forms of retinal laser treatment. In an attempt to explain the therapeutic mechanism of laser-induced retinal damage (LIRD), which was the presumed prerequisite for effective retinal laser photocoagulation (LPC), several hypotheses were proposed. The most popular one was referred to as vascular theory and included simple reduction of pathologic retina by laser ablation; increased oxygen diffusion to the inner retina and vitreous from the choroid through the thinned chorioretinal laser scars; and reduction in metabolic demand by laser destruction of retinal photoreceptors. In consequence, downregulation of vasoproliferative factors was to be observed, followed by regression of neovascularization and retinal edema [14].

The effectiveness of subthreshold laser modes, such as low-intensity/high-density subthreshold micropulse laser (SML) showed that LIRD was unnecessary for therapeutic effectiveness in many retinal disorders. Retinal laser treatment was found to trigger a biologic “reset” initiated by activation of retinal pigment epithelial (RPE) heat shock proteins (HSP). The reset effect of retinal laser, absent tissue destruction, is functionally normalizing, anti-inflammatory, and apoptotic in vitro, in vivo, and in human studies [15–18]. Thus, absent LIRD retinal laser is fundamentally neuroprotective—critically important because DR is a neurodegenerative disorder [19, 20].

Clinical Picture and Classifications of Diabetic Retinopathy

Diabetic retinopathy presents in two main forms: non-proliferative (NPDR—non-proliferative diabetic retinopathy) and proliferative (PDR—proliferative diabetic retinopathy), when retinal neovascularization develops. Depending on the stage, various intensity of vascular lesions is observed at the fundus. In cases of mild NPDR these are usually microaneurysms, retinal hemorrhages and soft and hard exudates. Progression of retinopathy along with increased retinal ischemia results in onset of such changes as venous abnormalities (constriction, beading, loops), intraretinal

Table 5.1 Simplified classification of diabetic retinopathy, according to Wilkinson

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—non-proliferative diabetic retinopathy, PDR—proliferative diabetic retinopathy, IRMA—intraretinal microvascular abnormalities

microvascular abnormalities (IRMA) and increased number of deep retinal hemorrhages, which is typical for severe NPDR. Defining of severe NPDR sometimes named a "threshold disease" enabled to put in order recommendations for the LPC in DR. Panretinal photocoagulation (PRP) can be considered in cases of severe NPDR accompanied by additional risk factors, such as poor glycemia control, type 2 of diabetes, loss of vision due to DR in other eye or planned cataract surgery.

Simplified classification of DR is presented in Table 5.1 [21].

On the other hand, defining the high-risk PDR enabled to indicate patients, in whom PRP is strongly recommended without any delay. Cases with initial PDR with just minor neovascularization can be closely observed or treated with anti-VEGF intravitreal injections with possible deferral of PRP.

Definition of high-risk proliferative diabetic retinopathy (HR PDR) [22]:

1.	NVD with a surface area of 1/4 to 1/3 DA on or within one disc diameter of the optic disc
2.	NVD with pre-retinal or vitreous hemorrhage
3.	NVE with > 1/2 DA and with pre-retinal or vitreous hemorrhage

DA—area of the optic nerve disc, NVD—neovascularization on the optic disc, NVE—neovascularization elsewhere

Progression of PDR leads to proliferation of fibrovascular tissue, that may lead to development of retinal traction and subsequent vitreous hemorrhage and/or traction retinal detachment. In such cases treatment of choice is pars plana vitrectomy (PPV). Occurrence of vitreous or subhyaloidal hemorrhages is not rare in PDR. If non-resorbing, the hemorrhage is usually qualified for surgical treatment. Indications,

Table 5.2 Classification of diabetic macular edema (DME) according to Wilkinson [26]

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

when surgical approach is preferred over laser treatment will be provided later in that chapter.

Every stage of DR can be accompanied by diabetic macular edema (DME). Back in the 1980s, when LPC was a main form of treatment of DME, definition of clinically significant macular edema (CSME) was introduced. According to Early Treatment Diabetic Retinopathy Study Group (ETDRS) CSME was defined as at least one of the following [23]:

a. 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.

Focal or GRID laser treatment was recommended by ETDRS for such cases. It is important to keep in mind that the threshold for LPC was strongly influenced by the risks and adverse effects of RPC. Thus, LPC was recommended late, when visually compromising or threatening complications of DR had already developed (CSME). Contemporary guidelines in ophthalmology still recommend classic LPC only in selected types of DME, with intravitreal therapies applied in most cases with foveal involvement. This is despite the increasing evidence that retina-sparing non-inflammatory retina laser compares favorably to LPC, with superior visual results [17, 24, 25]. Hence, nowadays, simple definition of DME intensity is used more often, as it responds better to modern treatment guidelines—Table 5.2.

Diagnostics

Performing precise LPC in DR required conducting proper diagnostic tests prior to laser. Diagnostics, similarly as treatment, is conducted in two areas: central part of the retina (macula) and peripheral retina. Central retinal area is evaluated

according to the presence and severity of the edema and the presence of ischemia (ischemic maculopathy). Assessment of peripheral retina concerns the range of areas of hypoperfusion and the presence of retinal neovascularization.

Diagnostic Tests for Macular Area

Historically, the substantial diagnostic test for assessment of macular area was fluorescein angiography (FA). It was always performed before planned laser photocoagulation in the macular area. FA still remains the most reliable tool for detection of microaneurysms and macular ischemia. Nowadays, when LPC is rarely performed in the macular area, FA is not used that often, especially when non-invasive imaging with spectral domain optical coherence angiography (SD-OCT) and OCT angiography (OCTA) are available. European Retinal Society EURETINA recommends to perform FA at the beginning of the diagnostic and therapeutic process in diabetic macular edema [27]. Nevertheless, in cases eligible for subthreshold laser treatment such as SML, which does not target focal or local leaks, FA is generally unnecessary [28].

Figures 5.2, 5.3 and 5.4—Figs. 5.2 and 5.3 present focal and diffuse macular edema in DME. Figure 5.4 shows area of capillary non-perfusion in the course of ischemic maculopathy.

Monitoring of efficacy of treatment of DME does not require repeatedly performed fluorescein angiographies. In the course of monitoring of DME, fluorescein is usually repeated in cases with diagnostic dilemmas, cases non-responsive to treatment or in cases suspicious of macular ischemia. It has to be emphasized, that often FA can be substituted with OCTA. OCT angiography can precisely visualize enlargement of foveal avascular zone (FAZ), deficiencies of capillary network in the macular area (so called "capillary drop-out") and alterations in the density of capillary network throughout the treatment period [29, 30] (Fig. 5.5). Considering technological advancements of OCTA and improvement of the quality of the imaging, it can be expected that this test will soon become the most important tool for evaluation of capillary vessels in DME.

Optical coherence tomography, at present typically used in spectral domain mode, is the diagnostic tool employed most often for the evaluation of DME. This non-invasive imaging provides cross-section of the retina and allows for morphological assessment of macular edema. Four most important features of the macular edema are classified as follows [31]:

- General thickening of the retina, sometimes described as retinal sponginess
- Cystoid edema (cystoid macular edema—CME)
- Subretinal fluid (SRF)
- Vitreoretinal traction (VRT).

Additionally, SD-OCT provides the possibility to measure total retinal thickness and its layers, what has practical implications for monitoring of effects of treatment,

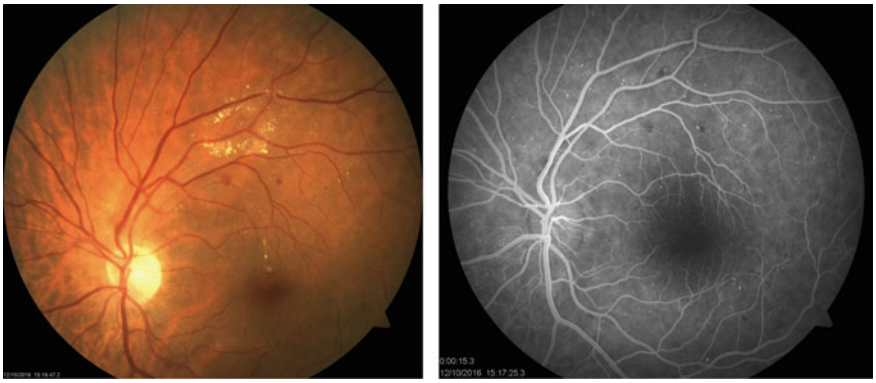

Fig. 5.2 Focal macular edema on color fundus photography and fluorescein angiography. A cluster of microaneurysms is visible inside the arch of hard exudates outside foveal region. The source of leakage is detected at FA images

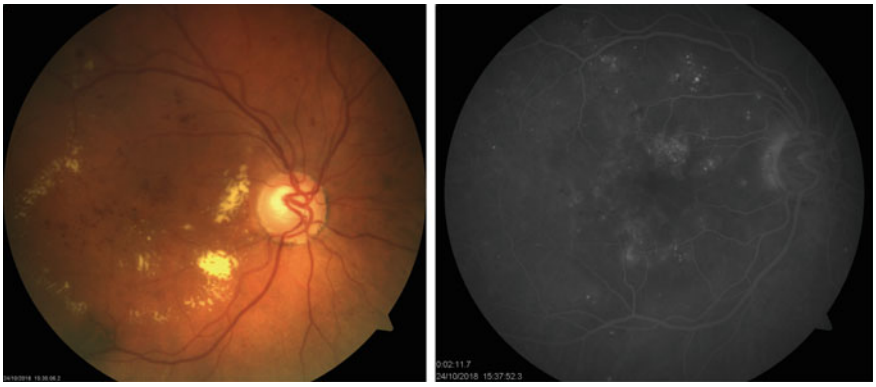

Fig. 5.3 Diffuse macular edema on color fundus photograph and fluorescein angiography. Diffuse retinal staining is visible at FA images

including laser therapy. Assessment of retinal architecture and thickness simplifies the decision making about the planned treatment. Severe macular edema, with central subfoveal thickness (CST) of 400 μm and more, rarely responds well to laser photocoagulation, likely reflecting the limitation of LPC placement and density in the macula, and treatment-induced inflammation resulting from tissue destruction. Retina sparing treatments, including drugs and subthreshold laser, do not have such limitations or drawback. Drugs will work more quickly in such eyes, but combined treatment with laser might be more effective for long-term control [32]. In such cases, one may begin with anti-VEGF intravitreal injections to obtain rapid improvement if necessary, and then switch to subthreshold laser to achieve long-term elimination of the DME while minimizing the number of injections required. Eyes with central SRF respond poorly to LPC due to significant inflammation which is worsened by

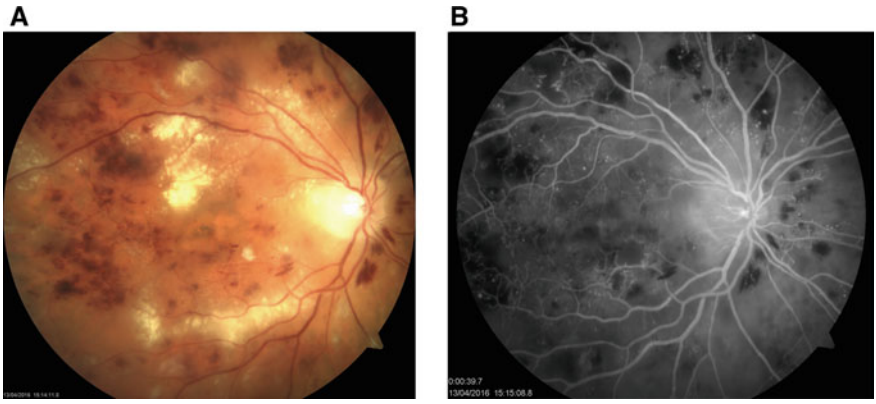

Fig. 5.4 Ischemic maculopathy on color fundus photographs and fluorescein angiography. FA reveals large areas devoid of capillary perfusion in the macular center and at the periphery

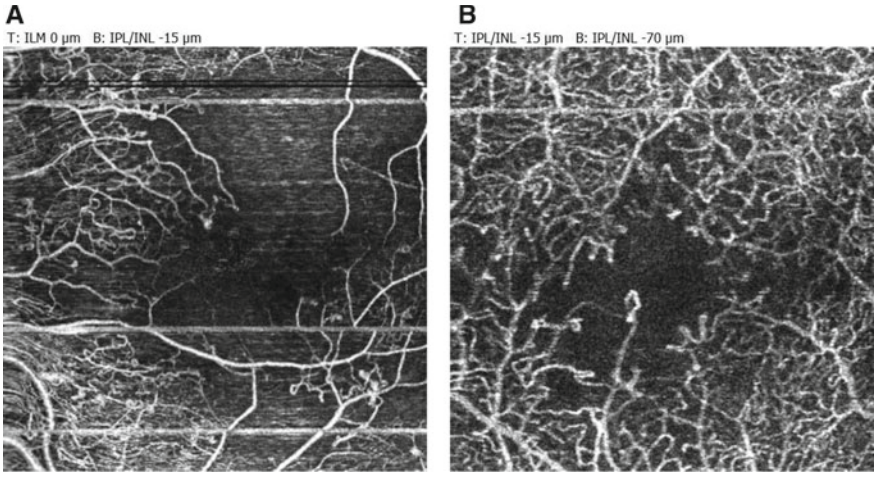

Fig. 5.5 **A** and **B** Capillary drop-out in the course of DME observed on OCT-angiography. Scan a shows loss of capillaries at the level of superficial capillary plexus and scan b at the level of deep capillary plexus

LPC. Thus, diffuse DME with central CME should not be treated with LPC, but can be addressed effectively by either drugs or SML laser which can both safely treat the fovea [33, 34]. Finally, detection of vitreomacular traction allows to qualify patient for pars plana vitrectomy (Fig. 5.6).

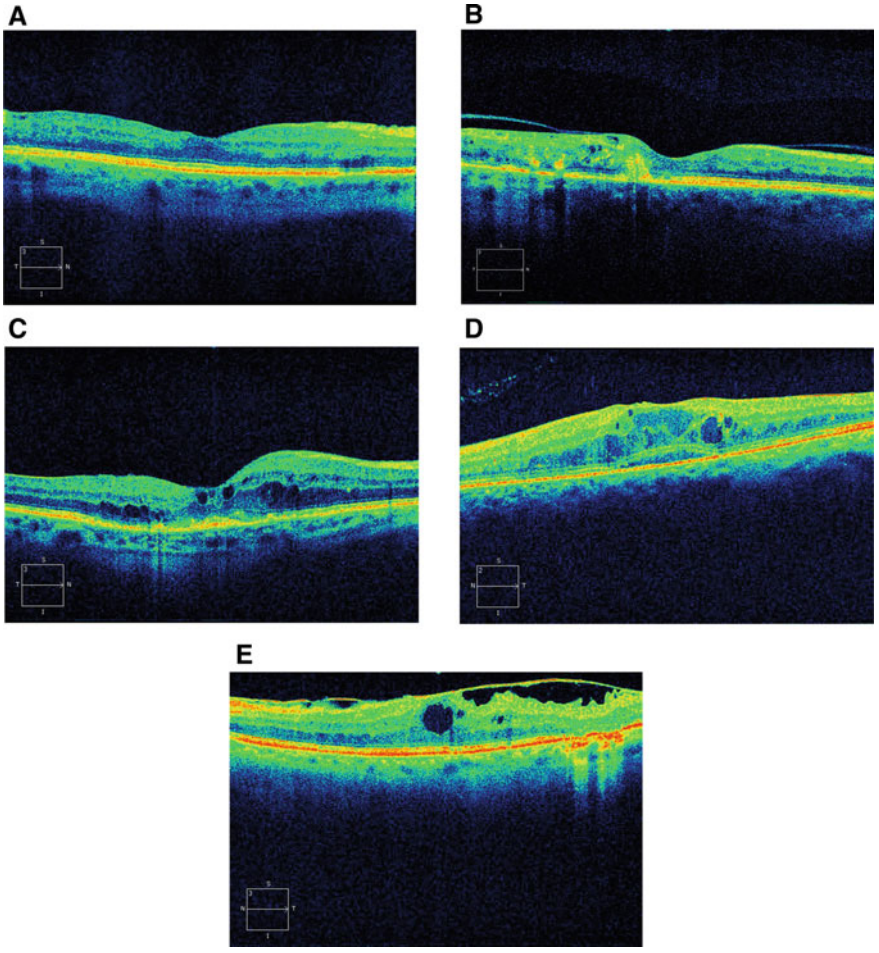

Fig. 5.6 **A**, **B**, **C**, **D**, **E** Different types of diabetic macular edema in SD-OCT, A—diffuse retinal sponginess without large cysts in sensory retina, B—retinal sponginess with hard exudates visible as hyperreflective foci, C—cystoid macular edema, D—cystoid macular edema with subretinal fluid, E—macular edema with traction and epiretinal membrane

Diagnostics of the Retinal Periphery

Analysis of the lesions at the retinal periphery allows for classification of the retinopathy. The most reliable tool to assess the peripheral retinal changes and peripheral vascular perfusion currently is fluorescein angiography (FFA). Basing on FFA, it is possible to classify retinopathy as proliferative or non-proliferative and define its severity within these categories. The standard for such evaluation for a few decades was performing of FA in seven standard retinal fields according to ETDRS

protocols. In recent years, ophthalmological diagnostics faced the advent of ultra-wide field (UWF) imaging of the fundus. The advantage of these devices over the classic fundus-cameras is simplicity, allowing capture on a single photograph rather than via a montage of multiple photos (the angle of 200° vs. 30–45° with classic fundus-cameras) (Fig. 5.7).

Diagnostics of DR with employment of UWF-FA allowed for more precise determining of DR stage, usually revealing lesions indicating its greater severity than appreciated by standard ETDRS composites (ex. foci of NVE localized at the far periphery) [35–37]. Research on UWF-FA have indicated that the presence of peripheral lesions, especially vascular abnormalities and areas of hypoperfusion, increases the risk of diabetic retinopathy progression [38]. Moreover, Wessel et al. confirmed a correlation between the extensiveness of the peripheral areas of hypoperfusion diagnosed with UWF-FA and the prevalence of DME [39].

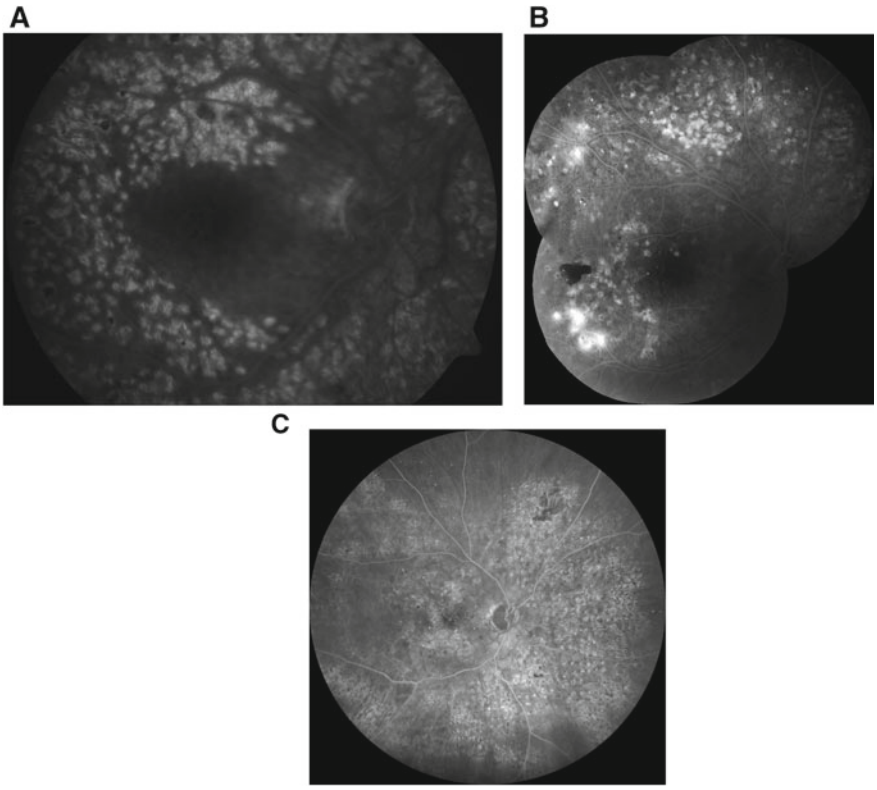

Fig. 5.7 **A**, **B**, **C**—Fluorescein angiography images of patients after panretinal photocoagulation the from the standard fundus camera (**A** and **B**) versus wide field device (**C**). Images on the b photograph are a mosaic of three visual fields

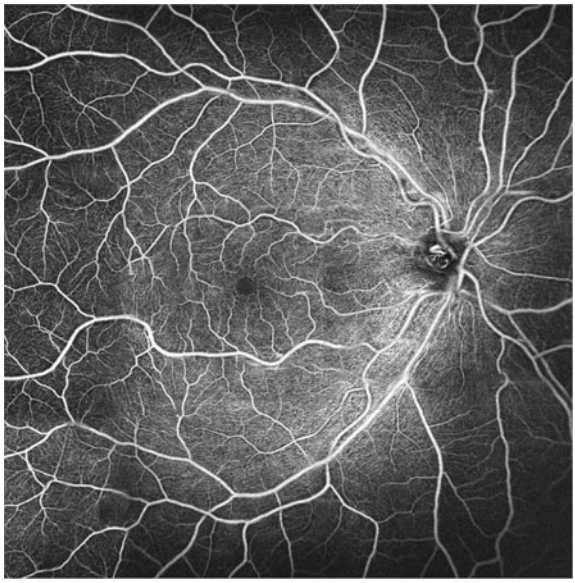

Fig. 5.8 Example of wide field OCTA exam in DR (Optopol REVO device 2022)

Wide-field fundus camera can also be utilized in screening programs for DR detection and severity assessment, facilitating relatively fast and reliable diagnosis [40, 41]. Despite many advantages, UWF systems of imaging are at present very costly and thus not standard in ophthalmological outpatient clinics.

Wide field systems of OCTA imaging are at present being introduced to modern ophthalmic diagnostics. Images obtained from such devices present not only the central part of the retina but also the periphery. Research on validation and reliability of such UWF devices are ongoing [42, 43]. Hopefully, in the future non-invasive angio-OCT exams will replace classic angiography, which requires injection of dye with the risk of allergic reactions (Fig. 5.8).

Principles of Management of DR

Management of diabetic retinopathy should always be simultaneously conducted in two scopes: treatment of DME and treatment of the retinopathy itself, including the retinal periphery. Among different therapeutic modalities important position take various forms of laser treatment, depicted further in this chapter. At this point most important treatment algorithms for DR are presented.

Treatment of Diabetic Retinopathy Itself

Table 5.3 comprises the compendium of the recommendations of treatment of diabetic retinopathy based on recommendations of American Academy of Ophthalmology (Preferred Practice Pattern) and Royal College of Ophthalmology [44, 45]. The rules presented in this short manual situates the panretinal laser photocoagulation (PRP) among other treatment options available for different stages of retinopathy. Details concerning PRP technique are provided further in that chapter. At this point it needs to be emphasized, that the key to successful local treatment of the patient with DR is the strict control of systemic factors influencing the development or progression of diabetic retinopathy. These include of control of glycemia, blood pressure, plasma lipids, body-mass index and stress. Correlation between good control of systemic indexes and diminishing the risk of development of ocular complications has been shown in large clinical studies conducted with diabetic patients. 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). In particular, the DCCT study showed that in DM1 intensive glycemic control was the most important preventive 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 [46, 47]. UKPDS study provided evidence, that adequate blood pressure control is 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% [48, 49]. In the Steno-2 study, a multifactorial intervention for glycemia, hypertension, dyslipidemia and micro-albuminuria—using hypoglycemic drugs, converting enzyme inhibitors, and statins—reduced the risk of microvascular and macrovascular complications (including DR) by 50% [50]. This study demonstrated the effectiveness of a proactive, multifactorial approach to risk factors in patients with DM2.

Table 5.3 Management of diabetic retinopathy (based on AAO recommendations, including and RCO recommendations) [34, 35]

Severity of the retinopathy	DME present	Frequency of monitoring	PRP	Focal/GRID laser treatment	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 or when intravitreal injections are not available	Usually with CI DME, sometimes with NCI 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	Sometimes: with NCI DME or when intravitreal injections are not available	Usually with CI DME, sometimes with NCI DME
Severe	No	Every 3–4 months	Sometimes with coexisting risk factors	No	Sometimes to reduce retinopathy severity (off-label)
	Yes	– For CI DME: every month at the beginning of the intravitreal therapy – For NCI DME: 3 months after laser treatment or every 2–4 months at follow-up only	Sometimes with coexisting risk factors	Sometimes: with NCI DME or when intravitreal injections are not available	Usually with CI DME, sometimes with NCI DME

(continued)

Table 5.3 (continued)

Severity of the retinopathy	DME present	Frequency of monitoring	PRP	Focal/GRID laser treatment	Intravitreal anti-VEGF therapy
Non-HR PDR	No	Every 2–4 months	Usually yes	No	Sometimes in combination therapy with PRP, or in monotherapy instead of PRP
	Yes	– For CI DME: every month at the beginning of the intravitreal therapy – For NCI DME: 3 months after laser treatment or every 2–4 months at follow-up only	Usually yes	Sometimes: with NCI DME or when intravitreal injections are not available	Usually with CI DME, sometimes with NCI DME
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: 3 months after laser treatment or every 2–4 months at follow-up alone	Yes	Sometimes: with NCI DME or when injections are not available	Usually with CI DME, sometimes in NCI DME

AAO—American Academy of Ophthalmology, (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

Comments

In the case of CI DME and BCVA $\geq$ 20/25, treatment should be postponed until the decline in BCVA if only LPC or anti-VEGF injection is considered. In the case of NCI DME with BCVA > 20/32 and close monitoring, observation and delay of treatment may be considered. This does not apply to LPE-sparing lasers such as SML as there are no adverse treatment effects and thus no reason to delay treatment. Delay in treatment is detrimental, as worsening of DME is the rule, and once VA is decreased, many eyes do not recover 20/20 VA even following elimination of DME [34]. For severe NPDR without DME, the efficacy of anti-VEGF (regression of retinopathy) therapy is under investigation.

Treatment Algorithms for DME

General Remarks

Contemporary guidelines place intravitreal injections of anti-VEGF agents in the first line of treatment of central involved DME. In large part, this reflects the adverse treatment effects of RPC, to which drugs have been compared in all large randomized clinical trials (RCTs) for DME. The following medications from that group are in use at the moment: ranibizumab (Lucentis), aflibercept (Eylea), brolucizumab (Beovue), and bevacizumab (Avastin) used off label. The other medications are awaiting registration with the faricimab being the first in line at the moment of publishing of that book. Second line therapy for central involved DME are intravitreal injections with corticosteroids, among which dexamethasone (Ozurdex) is the first choice. Other drugs from that group are the triamcinolone acetonide (Kenalog, Vitreal S), used off-label, and fluocinolne (Iluvien) applied in refractory cases of central DME of long duration. Intravitreal corticoids may be used as the first choice of treatment in patients burdened with systemic vascular comorbidities. The use of intravitreal corticosteroids is associated with potential side effects, such as increase in intraocular pressure and cataract formation, which will develop in majority of patients. In general, psudophakic patients are preferred for that form of treatment.

In this day, classic LPC is not recommended in cases with central involved DME. Nevertheless, it is accepted in extrafoveal and vasogenic form of DME, in which microaneurysms responsible for the leakage and subsequent edema can be visualized with FA. Subthreshold and non-damaging to the retina modes of laser treatment, which are non-targeted, absent adverse treatment effects and able to treat through the fovea like drugs, are not limited by these considerations.

Surgical treatment in DME (usually PPV) is recommended in cases with accompanying anomalies of vitreoretinal interface, such as epiretinal membranes (ERM), vitreomacular traction (VMT) or vitreomacular adhesion (VMA). The question of

Fig. 5.9 Proposed treatment algorithm for DME based on recommendations of different ophthalmic societies around the world

performing PPV for DME resistant to other treatments without vitreoretinal alterations remains the question of debate. Nevertheless, this mode of treatment is used in refractory cases of DME by experienced vitreoretinal surgeons (Fig. 5.9).

Laser Treatment of Diabetic Retinopathy and Diabetic Macular Edema

Historical Milestone Studies on Laser Treatment of DR and DME

Laser treatment had been used in clinics to treat diabetic retinopathy for decades before precise recommendations were formulated based on the results of randomized clinical trials.

First prospective randomized studies on the efficacy of PRP in preventing severe visual loss in DR, defined as decrease of BCVA below the level of 5/200, was conducted by the Diabetic Research Study Group (DRS). For the purpose of the study, definition of HR-PDR was conceptualized, indicating the group of eyes that would benefit the most from the prompt PRP. The study proved that immediate PRP in HR-PDR reduces the risk of SVL by almost half at 4 years of the follow-up (Table 5.4). Definition of HR-PDR has been used ever since in clinical practice.

Table 5.4 Results of diabetic retinopathy study 1972–1979 [51]

Type of retinopathy	Follow up (years)	Eyes with SVL in control group (%)	Eyes with SVL in PRP group (%)
Severe NPDR	2	3	3
	4	13	4
Mild PDR	2	7	3
	4	21	7
HR-PDR	2	26	11
	4	44	20

SVL—severe visual loss defined as BCVA < 5/200 at two subsequent follow up visits, PRP—panretinal photocoagulation, NPDR—non-proliferative diabetic retinopathy, PDR–proliferative diabetic retinopathy, HR-PDR—high risk proliferative diabetic retinopathy

The DRS and later also Early Treatment Diabetic Retinopathy Study (ETDRS) Group continued clinical research, this time including in the analysis also efficacy of focal and GRID laser photocoagulation in preventing of the visual loss in DME. Results of the ETDRS group showed that early LPC in DME can significantly reduce the risk of moderate visual loss, defined as at least doubling of visual angle [19, 52]. Results of that studies are presented in Table 5.5.

Results of the milestone studies can serve as a reference, nevertheless it has to be remembered, that they were published decades ago. Since then, ophthalmology has benefited by the advent of intravitreal therapies inhibiting the progression of neovascularization and reducing the macular edema without damaging the retina. Similarly, safe and non-damaging subthreshold laser photocoagulation in the pulsed mode was developed and proved effective in the treatment of macular edema. Thus, the use of classic laser photocoagulation, that causes retinal scarring, has to be nowadays considered in the context of available other treatments that do not damage the retina. Because of the inherent adverse effects and poor visual results of LPC, LPC should

Table 5.5 Results of the efficacy study of laser photocoagulation for DME treatment (ETDRS) [19]

Extent of DME	Follow-up time (years)	Eyes with SVL in control group (%)	Eyes with SVL in RPC group (%)
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

MVL—moderate visual loss defined as at least doubling of visual angle, CSME—clinically significant macular edema, LPC—laser photocoagulation

no longer be considered a first-line treatment due to the availability of effective retina sparing alternatives.

Contemporary Application of Laser Photocoagulation in the Treatment of DR

Classic LPC is still considered an effective and reliable method of treatment of proliferative diabetic retinopathy. This fact has been reflected in the guidelines published by different ophthalmic societies around the world. PRP is strongly recommended in HR PDR and in the case of neovascularization of the iris or presence of neovascular glaucoma.

ETDRS does not recommend PRP in eyes with mild or moderate retinopathy. In cases of severe NPDR, ETDRS advised to defer laser treatment until development of HR PDR stage [53].

Remember that these recommendations reflect the risks and adverse effects of LPC that necessitate waiting for more severe disease to develop before intervention is justified, and does not reflect the availability of retina-sparing treatments. Nevertheless, PRP should also be considered in selected cases of mild PDR and severe NPDR in the presence of additional risk factors.

According to RCO, PRP in non HR-PDR is allowed in the following situations [43]:

a. Older patients with DM2
b. In cases with poor visibility of the fundus
c. Before planned cataract surgery
d. In a better eye, in case of visual loss in the other eye due to PDR
e. In cases with poor compliance.

Traditionally, 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 experience of pain. In such a situation, multispot laser therapy is very useful, because 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 with a diameter of 500 μm. As a standard, the exposure time was set at 0.1 s, and the laser power was adjusted to obtain a visible full-thickness retinal burn. The distance between the spots should be 0.5–1 of the diameter of the impact made. 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 s and often smaller spots, for example with a diameter of 300–400 μm. In such a situation, it is sometimes necessary to perform more burns, but the procedure can actually be performed in a single session.

Principles of ETDRS PRP Protocol

- Setting the focal diameter to 500 μm and the time to 0.1 s in the case of classic photocoagulation.
- Setting the laser power (titration) to obtain a slight fading full-thickness retinal burn of the retina in the 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 nerve disc.
- Performing PRP peripherally from the designated boundaries.
- Reduction of the laser power when conducting PRP on the periphery.
- Avoiding direct photocoagulation of vessels, including NVD; it is permissible to treat flat areas of NVE with scatter or confluent laser spots.

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.
- Higher intensity treatment increases adverse effects and complications of treatment.

In technical terms, complete panretinal photocoagulation can be planned in two ways. In the first case, after marking the boundaries of the laser therapy by means of individual rows of photocoagulation spots, we divide the procedure into individual quadrants of the retina and perform it successively in each quadrant. In the second form of PRP, used by more experienced clinicians, we perform scatter laser therapy at once in all quadrants, successively condensing the spacing of spots and moving the procedure peripherally during subsequent sessions.

PRP with Multispot Laser

Conventional LPC PRP can be made more comfortable with the use of multispot lasers, which have been introduced to the market about 20 years ago and now are used commonly to treat retinal diseases. The improved comfort of treatment is owing to much shorter spot durations, minimizing heat spread from the spot of LPC. 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. The time of a single exposure is usually from 0.01 to 0.02 s (compared to the standard time in classic photocoagulation: 0.1 to 0.2 s).

Performing a photocoagulation spot with the multispot laser results in delivering less energy to the tissue than in the case of a classic photocoagulator. Admittedly, performing a spot with such a short exposure time 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 adjacent retina, and consequently smaller defects in the field of vision [54, 55]. 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 [56]. Research shows that performing full PRP with a multispot laser in one session can achieve the same results as conventional PRP spread over several sessions [57–60]. As a consequence, performing full PRP (1500 spots) in one session is possible, safe and effective. 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 [61]. Moreover, completion of PRP in a single session resulted in better regression of neovascularization compared with a procedure spread over several sessions. Nevertheless, it has to be noted, that some studies of short-pulse multisport lasers show that, compared to conventional PRP, short-pulse laser is less effect and this effectiveness is not improved by increasing treatment density [33].

Strategies for PRP Treatment

The RCO, based on the recommendations of ETDRS (1985), recommends the following strategies for performing primary PRP [43]:

1. early PDR (early neovascularization (NV): neovascularization elsewhere (NVE) and on the disc (NVD) when NV is flat and less than 1/2 DD): 1,200–1,800 spots over two weeks; follow up after four months (unless the patient is pregnant);
2. moderate PDR (NVD > 1/2 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): 3000 exposures over 3–4 weeks; for vitreous hemorrhage, photocoagulation of the areas of the retina that are visible then remaining as blood is absorbed; additional anti-VEGF intravitreal therapy is possible.

Remark in the box

In the case of severe PDR with hemorrhages and traction, immediate surgical treatment—posterior vitrectomy—is usually recommended. The ETDRS recommendations date back to the years when the technique of vitrectomy was not as developed as it is today.

PRP should be continued or condensed in the following situations (combined therapy with anti-VEGF intravitreal injections or PPV can also be considered).

- Insufficient regression of neovascularization
- Progression of retinal neovascularization or neovascularization of the iris
- New intravitreal hemorrhage
- New areas of neovascularization.

The Number of Spots in Panretinal Photocoagulation

The most common mistake made by ophthalmologists in heavy DR laser therapy with PRP is making too few burns. For example, in the United 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 [62]. 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. Due to the frequent use of multispot lasers for PRP, it is worth considering the number of spots required for this photocoagulation technique. The RCO suggests that this number should be greater than for classic PRP. The Manchester Pascal Study (MAPASS study) determined the mean cumulative number of multispot laser burns required to achieve PDR regression in patients treated within the 18 months period of the follow up: 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) [63]. (Data for Pascal laser from Topcon Medical Laser System) (Fig. 5.10).

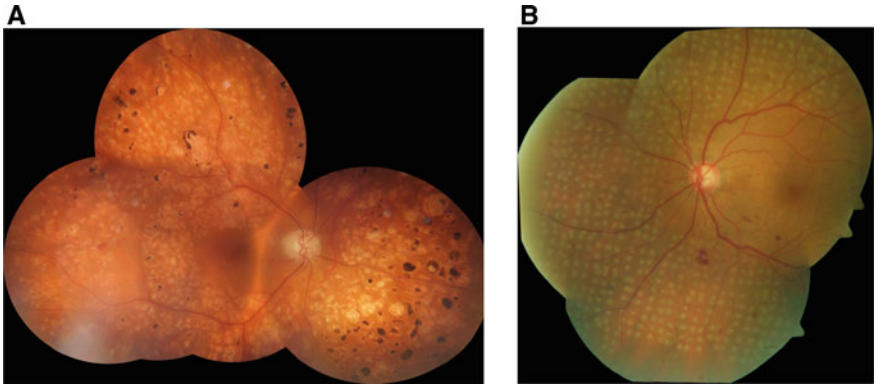

Fig. 5.10 **A**, **B** Panretinal photocoagulation performed with classic laser (**A**) and multispot laser (**B**). Images are the mosaic of the photographs from the standard fundus camera

Lenses for Scatter Laser Therapy

Panfundoscopes are used to perform panretinal photocoagulation, i.e. wide-angle imaging lenses, for example Super Quad or Equator Plus (Volk) or NMR Mainster PRP 165 (Ocular). Using a Goldmann three mirror lens to perform PRP is not recommended. It is important to remember that the photocoagulation burn that is created on the retina with the panfundoscope is twice as large as the laser setting, i.e. with a choice of 200 μm we actually obtain a 400 μm diameter burn.

Most panretinal laser photocoagulation procedures are performed under topical anesthesia—tetracaine or proparacaine drops. In some situations, when we want to quickly perform panretinal photocoagulation, and the patient is unable to withstand a longer session (e.g. due to perception 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.

Functionally restorative and retinal sparing lasers such as SML is generally painless and thus both panmacular and peripheral retinal treatment can be performed with the use of non-contact 90D lens, precluding the need for topical anesthetic drops. Nevertheless laser treatment with non-contact lens always requires more skills and practice.

Panretinal Photocoagulation Intensity

The standard of using full-thickness photocoagulation burns for treatment of diabetic retinopathy was based on the presumption, that LIRD was necessary for a therapeutic effect. This was then codified by the ETDRS [23]. Not surprisingly, progress has been made in the past 40 decades and it is not clear now that full-thickness retinal burns and RPC are necessary and bring optimal treatment outcomes. Reducing LPC treatment intensity can improve outcomes and diminish the complications, as per the ETDRS finding of the adverse effects of increased intensity, and improved outcomes associated with increased treatment density. Bandello et al. compared the effectiveness of mild PRP with classic PRP in HR PDR [64]. Mild PRP relied on the use of low argon laser powers: only barely visible retinal fading was targeted during laser therapy. That strategy corresponded to median laser power of 235 mW versus 420 mW used for classic PRP. The results of the study showed that mild PRP had comparable efficacy to classical PRP, with fewer complications.

PRP in Subthreshold Mode

Subthreshold micropulse laser treatment is not a standard form of managing the PDR, but studies showing its effectiveness in treating this disease should be mentioned (Table 5.6). Luttrull et al. emphasize the lack of fibrovascular tissue shrinkage

Table 5.6 Studies demonstrating the effectiveness of subthreshold micropulse laser therapy in the treatment of proliferative diabetic retinopathy

Study	No. of eyes	Study design	Results
Luttrull et al. [65]	99 with severe NPDR or PDR	– Retrospective study – The following parameters were assessed: BCVA, occurrence of VH, the need for PPV after 12 months	– No change in BCVA but increased eyes with VA > 20/40 – Estimated probability of VH = 12.5% and of PPV = 14.6% (most for ERM not DR) – No cases of post treatment TRD or neovascular glaucoma – DR progression in 4/99 (4%) eyes at 12 months post SML
Jhingan et al. [66]	20–10 patients with symmetric severe NPDR or low-risk PDR	– Prospective, randomized study–each eye randomized to classic PRP or SML – Assessed parameters: BCVA, contrast sensitivity, visual field and ERG in both groups at 9 months	– One eye of the SML group developed VH and required classic PRP – The classic PRP group had worse retinal sensitivity compared to the SML 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, SML–subthreshold micropulse laser, VH–vitreous hemorrhage TRD—tractional retinal detachment ERM—epiretinal membrane

after PRP performed with laser micropulses [65]. This quiet postoperative course was attributed to the absence of treatment associated inflammation. Only 4/99 eyes (4%) progressed following peripheral retinal SML, and no eye developed new DME following treatment. 35 eyes entered the study with severe NPDR. At 12 months follow up, only 3 had progressed to PDR (8%). This is substantially lower than the expected 50% rate of progression ($p < 0.001$). Of note, subthreshold treatment, because there are no adverse effects or treatment pain, can be completed in a single session. Nevertheless, due to the small number of clinical trials on PRP performed in PDR in the SML mode, this form of laser treatment should be classed as promising option, however further research is needed to confirm its efficacy.

PPV Versus PRP for PDR

Contemporary advancements in surgical ophthalmic techniques have changed therapeutic decision making in cases of advanced and aggressive forms of proliferative retinopathies. More often surgical treatment (PPV) is recommended instead of LPC. In large part, this is because conventional PRP aggravates preretinal fibrosis and contraction of proliferative membranes due to inflammation arising from tissue destruction. Anti-VEGF injections can also predispose to tractional retinal detachment and vitreous hemorrhage in eyes with advanced PDR by causing precipitous contraction of the fibrovascular membranes [67].

PPV should be considered in the treatment of PDR are the following [42, 68].

- Non-resorbing vitreous or subyaloidal hemorrhage
- Non-resorbing vitreous hemorrhage after PPV
- Tractional, rhegmatogenous or mixed retinal detachment
- Advanced fibrovascular proliferations threatening macula if the potential for improvement is present
- Epiretinal membrane in the macular area, traction in the macular area
- DME unresponsive to other therapies.

Combined Therapies: Laser Plus Anti-VEGF

Combined therapies of anti-VEGF plus PRP have been used in practice to treat PDR for more than a decade, nevertheless there are just a few randomized studies that would confirm efficacy of such therapy. So far, clear recommendations for such treatment have not been outlined, so considerations have to base on available clinical reports. Main goals of combined treatment in PDR can be described as follows:

- Faster and more effective regression of neovascularization compared to monotherapy
- Effective treatment of accompanying DME
- Prevention of macular edema occurring post intensive PRP.

Studies analyzing incidence of macular edema after panretinal photocoagulation prove the advantages of combined therapy (intravitreal anti-VEGF or corticosteroids plus PRP) compared to PRP alone [69, 70].

Regression of retinal neovascularization after combined treatment (PRP plus anti-VEGF) in DR was analyzed in a large randomized trial: PROTEUS study [71]. Participants of the study were divided into two groups depending on the received treatment: PRP alone and combined (PRP plus 3 monthly doses of intravitreal ranibizumab 0.5 mg). At 12 months, significantly better regression of NV was noted in the combination treatment group. Similar results were reported also in IBeHi study [72]. Anti-VEGF injections proved effective also in the treatment of PDR refractory to treatment with LPC, despite repeated treatments [73].

The question to be solved remains the arrangement of the algorithm, according to which combined therapy should be conducted. Mechanism of action and information provided in the Summary of Product Characteristics of anti-VEGF medications a loading dose at the beginning of treatment with PRP performed after or parallel to loading dose. This recommendation reflects the design of the clinical trial, however, rather than the results of independent study.

Anti VEGF injections have also been tested for the treatment of vitreous hemorrhage in the course of PDR. Protocol N study by DRCRnet group showed that intravitreal application of ranibizumab allowed for completion of PRP in a larger number of patients compared to the group that was just observed (44 vs. 31%) [74]. Nevertheless, finally the percentage of required vitrectomies was similar in both groups.

The most important question emerging nowadays is whether the anti-VEFGF treatment can substitute for the PRP in advanced stage of DR. So far results of two large randomized studies comparing efficacy of ranibizumab alone (Protocol S by Diabetic Retinopathy Clinical Research network group (DRCRnet group)) and aflibercept alone (Clarity study) versus PRP in advanced stages of DR (severe NPDR and PDR) are available [75, 76]. In both trials, patients who were subject to anti-VEGF treatment ended up with a better visual field, less often required vitrectomy or developed DME compared with patients after PRP. Nevertheless, for quite a large number of patients in Protocol S, frequent need for intravitreal injections together with high number of follow-up visits sustained a significant burden, that led to a large percentage of lost to follow-up (LTFU) patients at five years (about one third) [77]. In the drop-out group, severe complications, such as progression of neovascularization or tractional retinal detachment were by far more frequent in the anti-VEGF treated group compared to PRP group. In ranibizumab LTFU group retinal detachment was noted in 33% and intensive NVD in 40% versus respectively 2.2% and 9% in the PRP LFTU group [78].

The cost-effectiveness analysis based on Protocol S results and 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. In eyes with PDR without DME, such cost-effectiveness was not found. The use of panretinal photocoagulation in such situations is much cheaper and more economically effective [79].

It is worth noting that panretinal photocoagulation, despite complications such as visual field loss or the risk of macular edema development, is effective in regressing pathological vessels. Moreover, it usually does not need to be repeated many times, which is a feature of anti-VEGF therapy. The results of the Protocol S study after five years show that not all patients are able to tolerate the inconvenience of frequent intravitreal injections (the LTFU group). For this group, PRP seems to be a better solution as it prevents the development of dramatic complications without the need for numerous procedures. The promise of retina sparing laser treatment approaches, such as SML performed in panretinal mode, are that they may offer the durability and effectiveness of conventional LPC, but without adverse treatment effects; and the visual function results of intravitreal drug therapy, but without the cost and

burden of drug injections. Confirmation awaits further study. Application of intravitreal anti-VEGF treatment in advanced PDR is not devoid of serious complications. Contraction of fibrovascular membranes after regression of neovascularization due to VEGF blockage can cause tractional retinal detachment, what is described as "anti-VEGF crunch syndrome". Sudden visual loss is reported between 1 and 6 weeks post injection, 13 days on average. Hence, PDR cases with significant fibrovascascular proliferations are candidates for PPV rather than anti-VEGF treatment alone or in combination with laser [80].

Laser Treatment in DME

Classic Laser Photocoagulation

As it was mentioned at the beginning of this chapter, with the advent of intravitreal therapies, LPC, while still "a" standard of care in patients with DME, has been relegated to the treatment of 2nd or 3rd choice by anti-VEGF therapy. This is for a good reason. Diabetic retinopathy is characterized by chronic neurovascular inflammation and loss of autoregulation. Thus, the limitations of LPC for DME can be easily understood if one uses the histopathologic description of LPC: acute iatrogenic multifocal chorioretinitis. Thus based on our present knowledge, acute multifocal chorioretinitis cannot be advantageous in DME. Anti-VEGF treatment in DME provides significant visual gains without damaging the retina. Of note, only 3% of patients in a milestone ETDRS study from 1985 achieved BCVA gain of three or more ETDRS lines [23]. The scars that occurred after LPC had a tendency for enlargement, what could result in deterioration of visual acuity even years after the laser session. Intense LPC burns may result in choroidal neovascularization, preretinal and subretinal fibrosis that may cause significant permanent visual loss. Nevertheless, LPC performed according to ETDRS protocols is still considered permissible with extrafoveal macular edema and detectable source of the leakage in fluorescein angiography. The European Retinal Society EURETINA recommendation continues to recommend ETDRS-style focal RPC for distinct microaneurysms. Other relative indications include DME with central retinal thickness <300 μm or eyes with persisting vitreomacular adhesion (similar results are obtained with anti-VEGF or RPC) [27]. While LPC has been now largely relegated to rescue therapy, long-term studies of anti-VEGF use for DME show that LPC continues to be necessary in nearly half of all DME eyes to obtain final control and elimination of DME [81, 82] (Fig. 5.11).

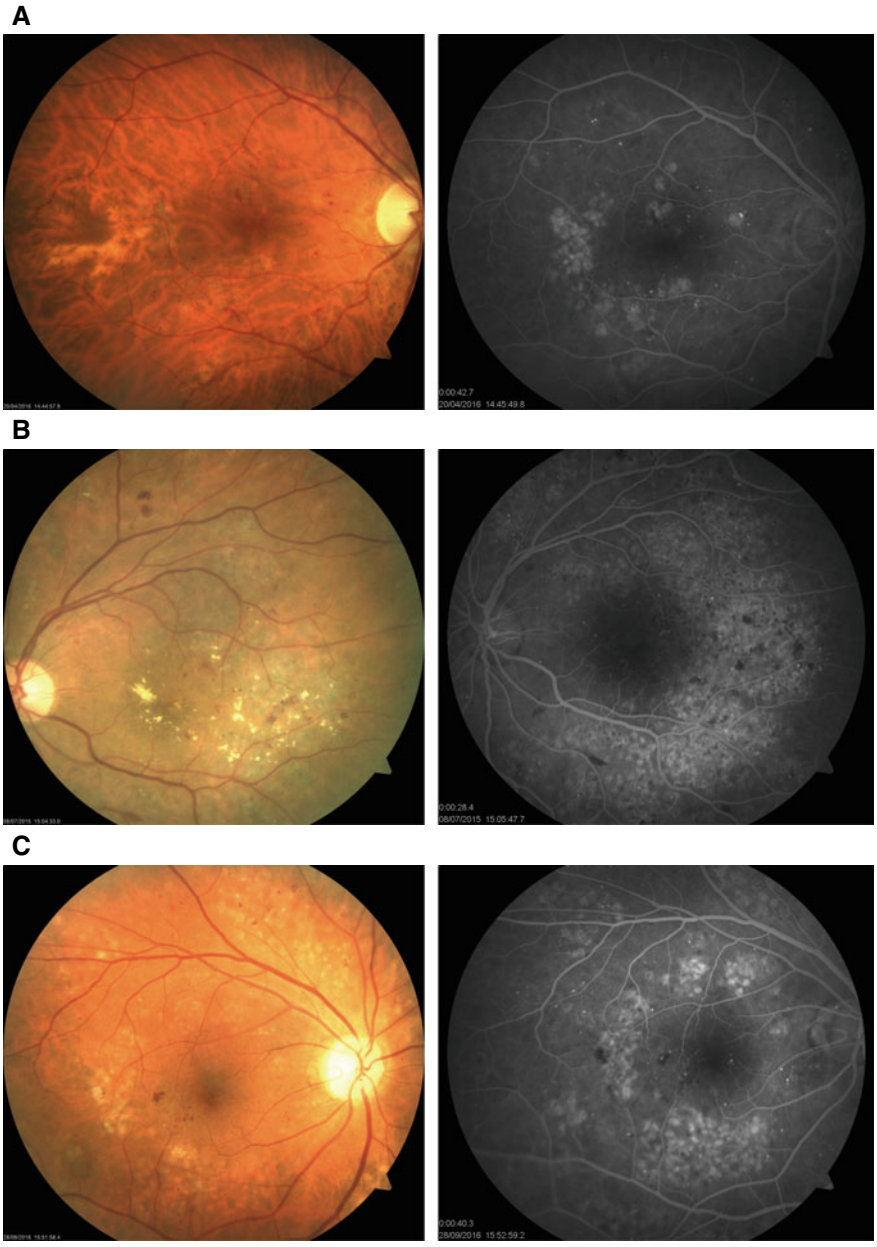

Fig. 5.11 **A**, **B**, **C** Images of the fundus (color photograph and fluorescein angiography) after focal (**A**), grid (**B**) and mixed type (**C**) of laser photocoagulation

Subthreshold Laser Treatment

Over the years there has been a trend toward decreasing treatment intensity and increased treatment density to reduce the adverse effects of retinal laser associated with LPC, and to improve effectiveness [83]. This has been described as "subthreshold" treatment because the laser spots are less visible than those of conventional ETDRS LPC [33]. Subthreshold laser treatments extend from those still clearly producing LPC lesions, to treatment entirely non-damaging to the RPE and neurosensory retina. Thus, absent a qualifier denoting the means of lesion visualization, "subthreshold" has little meaning. Any laser treatment resulting in any degree or frequency of LIRD continues to share all of the adverse effects, potential complications, and limitations of conventional LPC. Only treatment reliably sublethal to the RPE is different, without adverse effects or treatment limitations and working on the retina directly, rather than indirectly to maximize clinical effectiveness [28].

Subthreshold treatment has been attempted by simply reducing the intensity of LPC and by employing short-pulse CW laser modes such as the pattern scanning laser (PASCAL), selective retinal therapy (SRT), and nanosecond laser (2RT). There are just a few clinical reports analyzing PASCAL efficacy in the treatment of DME. Hamada et al. analyzed the outcome of PASCAL applications in 10 eyes with DME [84]. Significant mean reduction of CST was noted at six month's post laser with total resorption of edema in four eyes and stabilization of BCVA. On the other hand, the study comparing effects of treatment of DME with PASCAL laser in suprathreshold versus PASCAL mode in 23 patients proved similar functional and morphological improvements in both modes [85]. Therefore, confirmation of PASCAL efficacy and superiority over classic LPC requires further clinical trials.

The first large clinical trial on efficacy of SRT in DME was conducted in 2010 [86]. Results were analyzed in 60 eyes with CSME. For the treatment of DME Nd:YLF 527 nm laser was used with pulse duration of 1.7 μs and 100 Hz frequency. In each case 30 laser spots were applied of 210 μm diameter and energy at 200–325 μJ, depending on the power titration outcome. Improvement or stabilization of BCVA was noted in 84% of cases 6 months post-treatment, however significant CST reduction or reduction of leakage on FA was not observed. Another study was conducted in Korea on 21 eyes with DME [87]. Authors reported similar results: BCVA improvement by 1–2 ETDRS lines was noted in 41.2% of patients at six months, however again without significant mean reduction of CST [88]. On the other hand, Yamamoto et al. showed significant reduction of CST and stabilization of BCVA in a small group of 22 eyes with DME [89]. As can be seen, scarce clinical material on SRT in DME provides moderately optimistic data. It has to be stressed, that so far commercial lasers of that type are not available, so research has to be conducted in specialized clinical research centers.

Nanosecond lasers, mainly 2RT laser, are applied very seldom in the treatment of DME. That fact limits also the number of published results of clinical trial with the use of that laser in DME. Pelosini et al. analyzed effects of treatment of 28 eyes with the use of 2RT laser (532 nm Q-switched), which generated 3 ns pulse of 1 μJ

energy [90]. Results were similar to those achieved with the SRT laser: significant improvement of BCVA was noted at six months (from 20/44 to 20/27), however without morphological improvement. Moreover, comparison between 2RT laser and classic LPC on a small clinical trial (17 and 18 eyes) did not bring unequivocal results favorizing any of the therapies [91]. In the light of these data, it is so far impossible consider the 2RT laser as an solid option for standard care in DME.

Because the therapeutic range (TR) of LPC and the PASCAL is extremely narrow, only 0.010 W in breadth, reliable non-damaging treatment is not possible, despite use of various titration algorithms such as "endpoint management" (EpM). The target is simply too small. The TR of even shorter pulse SRT is even narrower, and nanosecond laser has no TR as it is simply photodisruptive to the RPE [28]. Each has been shown to be effective for treatment of DME, although generally not as effective as LPC or anti-VEGF drug therapy [92]. The LIRD associated with short pulse CW and nanosecond or microsecond laser necessitates limitation of treatment density and prohibits foveal treatment, limiting potential treatment effectiveness. Because the PASCAL, SRT and 2RT result in ablation of the RPE with little affected and surviving tissue at the margins of the laser spots to mediate the therapeutic effect, the therapeutic effects of these lasers are primarily mediated indirectly by the stress of wound healing accomplished by sliding of the RPE and outer retina to fill the voids left by the laser spots, rather than direct laser stimulation of the RPE for HSP activation. Thus, the therapeutic effects of short pulse lasers are necessarily attenuated [28, 33].

Micropulsed laser have been used extensively for subthreshold treatment of DME as well. Their clinical behavior ranges from LPC, to treatment entirely sublethal to the RPE, depending upon the laser parameters used. Use of visible wavelengths and pulse frequencies ("duty cycles", DC) above 5% narrow the TR and increase the risk or even likelihood of LIRD [17, 28]. Early in the experience with SML high DCs of 15% or more were used because the intent was to cause LIRD, thought at the time to be necessary for effective therapy [93]. It is now known that LIRD is simply an adverse event to be avoided, leading to the preference for a 5% DC to prevent LIRD [33, 94].

There have been many studies of SML for DME. Reviews and meta analyses of SML find it as effective as RPC for DME, but with better visual results [25]. In an LCT comparing high-density SML to conventional LPC and low density SML for DME, Lavinsky and associates found high density SML most effective at reducing macular edema, with visual results comparable to anti-VEGF therapy [95]. No difference in effectiveness has been found based on laser wavelength [96, 97]. A number of studies have shown that the addition of SML to drug therapy can reduce the number of injections needed to manage and eliminate DME [17, 98].

It is key to remember that drugs act quickly, but are short-lived. Thus, even for LPC, the long term benefit of drug therapy over anti-VEGF injections shows little final difference, with LPC being better at reducing macular thickening, while drug therapy produces better visual results. This is attributable to the absence of retinal damage and inflammation with drug therapy. So far published longer term studies of SML and anti-VEGF therapy for DME show no long term advantage to drug

therapy. Thus, anti-VEGF therapy in DME may best be employed in the short term to improve visual acuity, while long-term reduction and eventual elimination of DME can be accomplished with SML. By so doing, the treatment burden, already heavy in diabetics, can be minimized without sacrificing long-term visual results [17, 24, 81, 99].

As noted, the effects of micropulse lasers can range from full-thickness LPC to treatment sublethal to the RPE, depending upon the laser parameters employed. Low-intensity/high density subthreshold micropulse laser is a specific use of micropulse lasers that is designed to be reliably non-damaging to the RPE ("low-intensity") while maximizing the clinically effectiveness of treatment by confluent treatment of large geographic areas of dysfunction retina ("high-density"). Like drug therapy, but unlike all other modes of retinal laser treatment, the safety of SML allows direct laser treatment of the fovea (although it has to be noted that this form of treatment is not directly recommended by the manufacturers of the laser equipment). As the central fovea is commonly involved with DME and the most visually sensitive area, the ability to directly address the fovea is a great potential advantage in disease management. Most significantly, the safety of SML allows early and preventative treatment for DME, allowing treatment before the development of visual loss to preserve, rather than attempt to restore, excellent BCVA. With SML, it is not necessary to wait for DME to worsen sufficiently to justify the risks and adverse effects of either LPC or intravitreal injections. Once this occurs, permanent visual loss may occur. SML can be used to treat eyes with center-involving DME and 20/20–20/40 vision safely to significantly improve both BCVA and macular thickness to avoid visual loss, progression, and the need for subsequent intravitreal injections [34].

The Table 5.7 presents most important of them analyzing at least 30 cases in the SML group.

Apart from general principles of SML action described in the chapter on "Neuroprotection", it is worth mentioning that SML applied in DME not only optimizes the RPE function, but also improves retinal vascularity. Studies by Vujosevic et al. provide reliable data on significant decrease of FAZ area and microaneurysms observed in OCT-angiography measurements [87, 88]. Additionally, improvements are noted in biomarkers of inflammation (hyperreflective foci) and disorganization of retinal inner layers [123, 124]. Interesting study by Ueda et al. proved also decrease in entropy at the level of RPE in DME patients treated with SML, diagnosed with polarized-sensitive optical coherence tomography [125]. These findings may add to understanding of mechanism of SML action on retinal cells in DME (Fig. 5.12).

Despite what is known, areas of controversy remain:

- threshold values of the amount of CST or BCVA for patient' eligibility for SML
- the range of SML treatment—local versus panmacular
- time interval between the SML sessions
- algorithms for combined SML–anti-VEGF treatment
- the choice of laser wavelength (577 or 810 nm).

Research shows that amount of retinal edema measured by CST parameter affects SML efficacy. Mansour et al. report, that SML is effective in cases of DME < 400 μm.

Table 5.7 Major clinical studies on management of diabetic macular edema with SML

Study	No. of eyes	Laser wavelength (nm)	Study design	Results
Luttrull et al. [100]	• SML—95 with CSME	• 810	• 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%
Vujosevic et al. [101]	• SML—32 with CSME • LPC–30 with CSME	• 810	• Comparison of the efficacy of SML versus LPC in CSME at 12 months (BCVA, CST, retinal sensitivity in microperimetry)	• Stabilization of BCVA in both groups • Significant reduction of CST in both groups—no difference between groups • Improvement in retinal sensitivity in the SML group, decrease in retinal sensitivity in the LPC group
Lavinsky et al. [95]	• SML ND—39 • SML HD—42 • LPC—42 (previously untreated patients with BCVA between 20/40 and 20/400)	• 810	• Comparison of BCVA and CST in 3 groups at 12 months	• Highest improvement in BCVA: by mean 0.25 logMAR in the SML HD group compared with mean 0.08 logMAR in the LPC group and mean 0.03 logMAR in the SML ND group • The most significant reduction in CST in the SML HD group (by mean 154 μm) and in the LPC group (by mean 126 μm)—no significant difference between these groups

(continued)

Table 5.7 (continued)

Study	No. of eyes	Laser wavelength (nm)	Study design	Results
Takatsuna et al. [102]	• SML—56 with DME	• 810	• BCVA and CST at 12 months	• Reduction in CST 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)
Othman et al. [103]	• SML in CSME without ischemia—220, of which: 187—first-line therapy (group 1) 33—second-line therapy after LPC (group 2)	• 810	• Treatment effects in 2 groups at 12–19 months • BCVA and CST assessment • DC 15%	• Group 1: significant improvement in BCVA at 4 months, stable in subsequent months (0.21 log-MAR to 0.18 logMAR) • Group 2: stabilisation of BCVA without improvement—significant reduction of CST in both groups
Luttrull et al. [34]	• 39 with CSME and BCVA 20/40 and better	• 810	• Assessment of treatment effects: CST and BCVA at 4–7 months	• Mean improvement in BCVA of 0.03 logMAR • Significant reduction in CST
Mansouri et al. [104]	• 63 with DME	• 810	• Comparison of the effects of SML (BCVA, CST) in group 1 ($n = 33$) with CST $\leq$ 400 μm and in group 2 ($n = 30$) with CST > 400 μm (follow-up time—12 months)	• Group 1: significant improvement of BCVA by mean 0.2 logMAR and significant reduction of CST by mean 55 μm • Group 2: no significant change in BCVA and CST

(continued)

Table 5.7 (continued)

Study	No. of eyes	Laser wavelength (nm)	Study design	Results
Inagaki et al. [105]	• 53 with DME, including: • 24—810 nm SML • 29—577 nm SML	• 810 • 577	• Comparison of treatment effects (CST and BCVA) with 577 nm versus 810 nm laser using SML combined with focal LPC for microaneurysms	• Significant reduction in CST in both groups, no difference between groups • BCVA stable in both groups
Vujosevic et al. [97]	• 53 with CSME < 400 μm, including: • 26—577 nm SML • 27—810 nm SML	• 577 • 810	• Comparison of effects in both groups at 6 months (CST, MV, choroidal thickness, BCVA, retinal sensitivity) • Safety assessment: FAF, FA, integrity of outer retinal layers on OCT	• No significant differences in BCVA, CST, MV and choroidal thickness • Significant improvement in retinal sensitivity in both groups • No scarring in FA, FAF, OCT
Fazel et al. [106]	• 68 with CSME < 450 μm, including: • SML—34 • LPC–34	• 810	• Comparison of the effectiveness of SML versus LPC (BCVA, CST, MV) at 4 months	• Significant reduction of CST in both groups (from mean 357.3 μm to 344.3 μm in the SML group and from mean 354.8 μm to 349.8 μm in the LPC group) • Significant improvement in BCVA only in the SML group (from mean 0.59 to 0.52 logMAR)
Latalska et al. [107]	• 75 eyes with diffuse DME	• 577	• Efficacy of SML at 6 months (improvement of BCVA an reduction of CST)	• BCVA improvement from 0.2 Snellen to 0.3 Snellen (significant) • CST reduction from 500 μm to 346 μm (significant)

(continued)

Table 5.7 (continued)

Study	No. of eyes	Laser wavelength (nm)	Study design	Results
Vesela et al. [108]	• 63 eyes	• 577	• BCVA and CST change at one year	• BCVA improvement in 32% and stabilization in 39% of eyes • Average decrease of CST of 63 μm
Citirik [109]	• 80 eyes with recurrent DME after anti-VEGF treatment	• 577	• Efficacy of SML depending on baseline CST: 250–300 μm (gropu 1), 301–400 μm (group 2) and > 401 μm	• Significant CST reduction and BCVA gain in patient with CST ≤ 300 μm • No change in patients with CST > 300 μm
Vujosevic et al. [110]	• 35 eyes with treatment naïve DME	• 577	• Evaluation of OCTA changes at six months post treatment	• BCVA gain of 4.6 ETDRS letters • Significant decrease of FAZ in DCP • Significant decrease in the number of cysts in SCP • Significant decrease of number of microaneurysms in SCP and DCP
Vujosevic et al. [111]	• 37 eyes with treatment naïve DME	• 577	• Evaluation of change in OCT/OCTA biomarkers at 12 months • Control group consisted of 15 fellow eyes with microaneurysms only	• Significant improvement of BCVA (from 69.4 to 76 ETDRS letters) • Significant decrease in number of microaneurysms and hiperreflective spots, decrease in extension of DRIL

(continued)

Table 5.7 (continued)

Study	No. of eyes	Laser wavelength (nm)	Study design	Results
Bougatsou et al. [112]	• 60 eyes with non-center involved DME	• 532	• Eyes randomized to SML (1) or LPC group (2) • Comparison between SML group and LPC group • Follow-up 6 months	• Significantly better reduction of central macular thickness in G1 • Significant improvement of BCVA in G1 only
Li et al. [113]	• 86 eyes with severe NPDR and central involved DME	• 577: SML plus PRP	• Evaluation of OCTA parameters at 1 day, 1 week 1, 3 and 6 months post treatment • BCVA change	• BCVA stable throughout the study • Decrease in CST at 6 months • Decrease in vascular perfusion at 6 months, increase in FAZ area
Akkaya et al. [114]	• 76 eyes of 47 patients with DME and BCVA $\leq$ 0.15 logMAR	• 577	• Patients randomized to IV group (24 patients) or SML group (23 patients) • Comparison of BCVA and CST at 12 months	• Significantly better in SML group than IV group (0.054 logMAR vs. 0.095 logMAR) • Larger decrease in CST in SML group (39.08 vs. 9.67 μm)
Abdelrahman et al. [115]	• 80 eyes with DME • 40 eyes in control group	• 532	• 40 eyes—SML • 40—eyes IVR • Comparison between the groups and controls at 6 months	• Significantly better BCVA improvement and reduction of CST in IVR group • Improvement of mfERG in IVR group only

(continued)

Table 5.7 (continued)

Study	No. of eyes	Laser wavelength (nm)	Study design	Results
Donati et al. [116]	• 39 eyes with DME	• 577	• Comparison of efficacy of SML with fixed power protocol 250 mW (24 eyes) and titrated power protocol (15 eyes) • Follow—up 12 months	• No improvement of BCVA in both groups, but BCVA stable • Significant CST reduction in both groups • No significant difference in functional and morphological outcome between the groups
Al-Barki et al. [117]	• 44 eyes SML • 54 eyes EpM	• 532 (EpM) • 810	• Comparison between 532 EpM laser (30% and 50% mode) and 810 nm SML at 6 months	• Significant BCVA gain in SML group only • No significant CST reduction in any group
Passos et al. [118]	• 56 eyes with center-involving DME	• 577	• Retrospective analysis of SML efficacy • Mean follow-up time: 14 weeks	• Significant BCVA improvement from 0.59 to 0.43 logMAR • Improvement in SRF in 74% • >10% reduction of CST in 43% of eyes
Valera-Cornejo et al. [119]	• 33 eyes with center-involved DME	• 577	• Efficacy of SML at 3 months • Evaluation of BCVA and CST	• No statistically significant change in BCVA • Significant reduction of CSTby mean 30 μm)
Frizziero et al. [24]	• 134 eyes with center involving DME, treatment naive and CST $\leq$ 400 μm	• 577	• Retrospective analysis of SML efficacy: letter gain and CST • Follow-up 12 months • Fixed power protocol	• Significant improvement of BCVA from 77.3 to 79.4 ETDRS letters • Insignificant reduction of CST

(continued)

Table 5.7 (continued)

Study	No. of eyes	Laser wavelength (nm)	Study design	Results
Lai et al. [120]	• SML 86 eyes • IVA 78 eyes	• 577	• Evaluation of 5 letter gain and 10% CST reduction at 6, 12 and 24 months	• Higher percentage of eyes with 5 letter gain in IVA group at 6 months (56% vs. 38%), but not at 12 months (45% vs. 49%) and 24 months (49% vs. 57%) • Percentage of eyes with at least 10% of CST reduction higher in IVA group at 6 months (73% vs. 49%), but not at 12 months (73% vs. 70%) and 24 months (85% vs. 84%) • Rescue IVA treatment initiated in 24% of eyes
Bonfiglio et al. [121]	• Persistent DME after PPV • 54 eyes SML group • 41 eyes–observation	• 577	• Evaluation of SML efficacy (BCVA gain and CST reduction) at 6 months • Evaluation of OCTA parameters at 6 months	• BCVA improvement in SML group from 51.54 to 57.83 letters, BCVA values higher in SML group • CST reduction significantly larger in SML group • Higher vascular perfusion and density parameters in SML group

(continued)

Table 5.7 (continued)

Study	No. of eyes	Laser wavelength (nm)	Study design	Results
Lois et al. [122]	• 266 eyes • SML versus classic RPC • Center-involved DME < 400 μm • BCVA > 24 ETDRS letters	• 577	• Randomized non-inferiority clinical trial • Comparison of BCVA, CST, visual field, quality of life and cost in SML versus RPC groups at 24 months	• No significant differences in measured parameters between the groups • BCVA improvement was not noted • SML required higher number of treatments

SML—subthreshold micropulse laser, PRP–panretinal photocoagulation, BCVA—best-corrected visual acuity, CST—central subfoveal 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, IVB—intravitreal bevacizumab, FAZ—foveal avascular zone, DCP—deep capillary plexus, SCP—superficial capillary plexus, OCTA—OCT angiography, IVA—intravitreal aflibercept, IVR—intravitreal ranibizumab, EpM—end point management

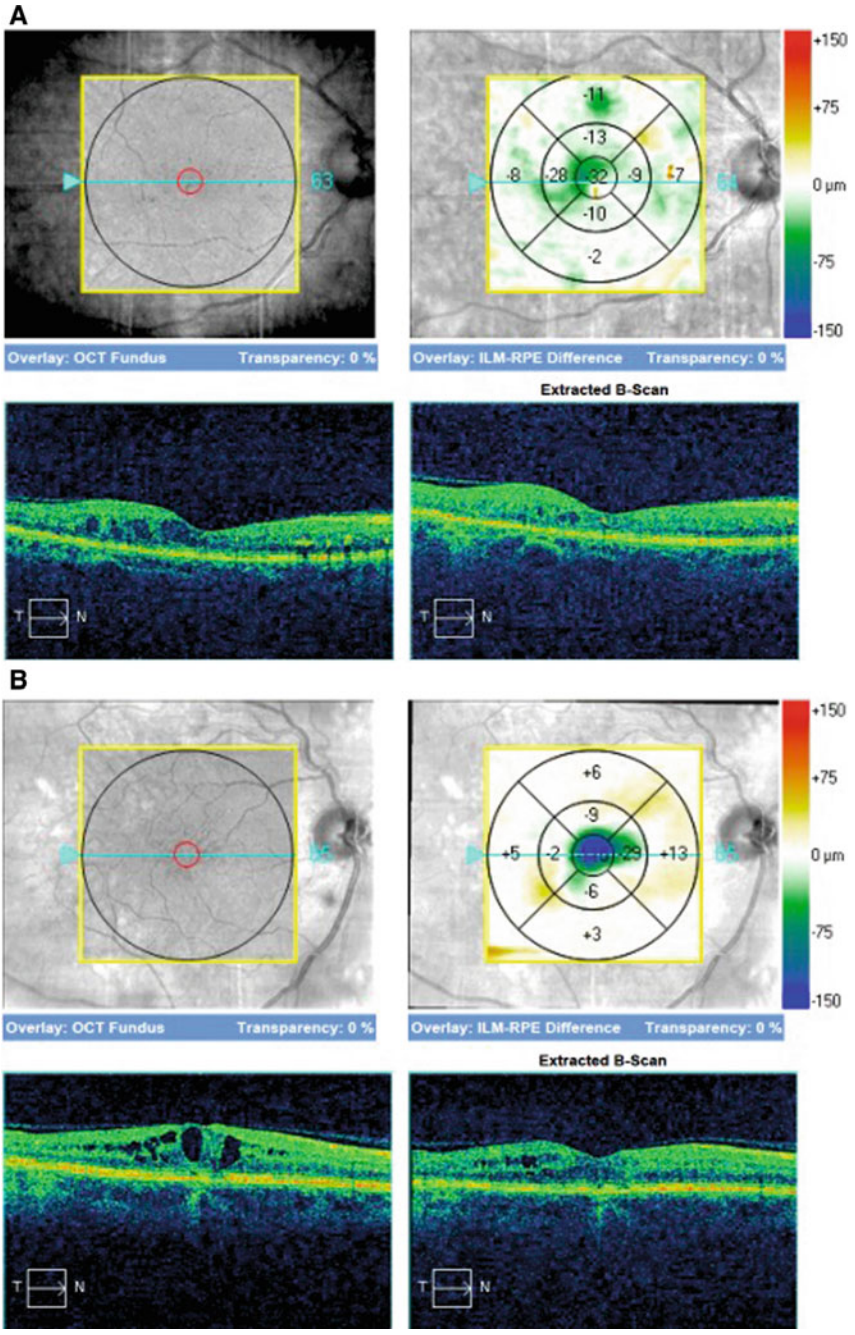

Fig. 5.12 **A**, **B**, **C** Examples of successful SML treatment of DME (SD-OCT images). Significant reduction of central subfoveal thickness and number of intraretinal cysts is noted post-treatment

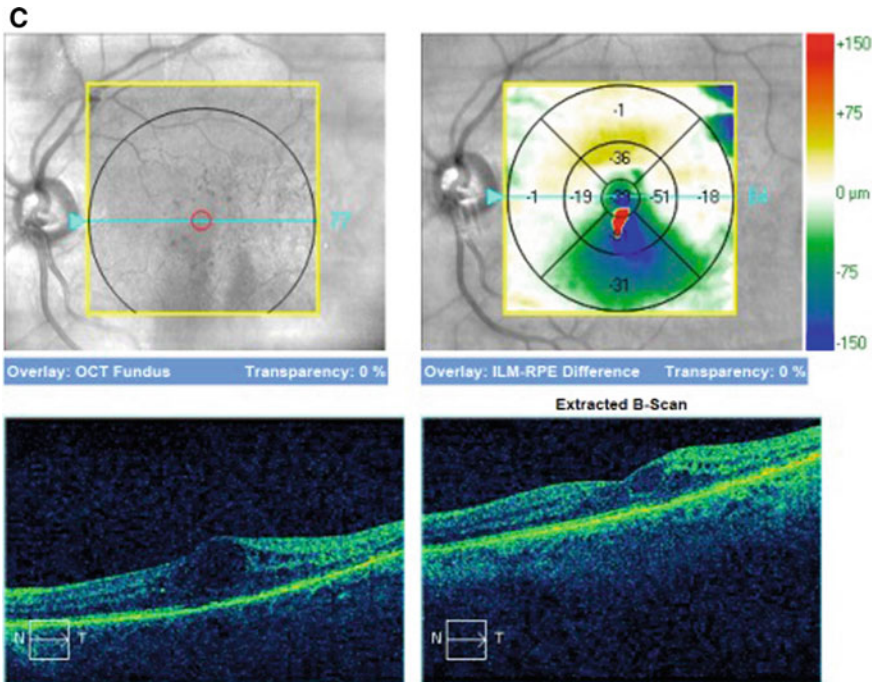

Fig. 5.12 (continued)

Other authors followed that rule in their studies, adopting threshold values of CST below 400 µm to determine eligibility for SML treatment [71, 72, 122]. Citirik reported significant efficacy of 577 nm SML in DME patients with CST $\leq$ 300 µm, however the study analyzed only recurrent DME after anti-VEGF treatment. It can be argued that worse disease is always less responsive to treatment, and takes longer to respond to treatment. Thus, Luttrull et al. use the BCVA criteria to determine patient's eligibility for SML rather than macular thickness to determine whether to start treatment with SML, or anti-VEGF, starting DME treatment with laser in patients with BCVA at 20/50 or better. Only if the BCVA is poor and/or there is a need for rapid visual improvement is treatment started with anti-VEGF. Once BCVA is improved, SML is used to achieve lasting control and elimination of DME [68]. Obviously, as the target of SML always remains the RPE, the RPE condition has to be also taken into consideration when choosing the treatment option for DME as confirmed by the study by Isik et al. [126].

It has to be noted, that SML can provide morphological and functional improvement in patients with good BCVA [34]. As noted above with regard to foveal treatment, this creates a space for SML application within commonly accepted algorithms for DME treatment. According to AAO guidelines, patients with BCVA at > 0.63 (20/25 and better) do not benefit from initial anti-VEGF injection alone versus LPC or observation. Such eyes are thus excellent candidates for SML [127].

Table 5.8 Examples of SML protocols used in published clinical trials. All protocols employ DC of 5%

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	1400	200	0.15	Panmacular
810	1700	500	0.3	Panmacular

Protocols for SML treatment for DME and used in different clinical trials are presented in Table 5.8. All of them employ duty cycle (DC) at 5%. They consent with the guidelines of the LIGHT laser society, which does not recommend power titration for laser power adjustment [94].

In the early days, SML spots were applied in confluent mode at the whole area of retinal edema demonstrated by contact lens examination or OCT. In recognition that DME is simply a local manifestation of a generalized retinopathy, panmacular treatment is now routine. This further recognizes that the key to clinical optimization of SML is treatment area and density. One cannot overtreat, one can only undertreat. Thus, the whole posterior pole area within the vascular arcades is treated. In eyes with significant extramacular retinopathy, consideration should be given to SML peripheral retinal treatment as well, to reverse the retinopathy and reduce production of VEGF, etc., that drive retinopathy and maculopathy worsening—much the same as is accomplished by intravitreal injection [94].

SML (absent LIRD) can be repeated as needed. The time course of response suggests waiting at least 3 months to repeat treatment [99, 128]. If improved, observation can continue as progressive improvement for up to 2 years is not uncommon after a single treatment session.

The most popular wavelength used for SML treatment of DME is 577 nm, with 810 and 532 nm laser used less often. Available comparative studies do not favor any of this modes. Any laser mode or wavelength may be effective, as all share the reset mechanism of action. However, safety strongly favors longer wavelengths. For example, 577 nm is 4 times as energetic as 810 nm and has twice the absorption in the RPE. Thus, the therapeutic (safety) range of 577 nm is 8 times narrower than 810. For 532 nm, the TR narrowing is far more. Narrowing of the TR increases the risk that eye-specific variations such as pigmentation, media opacity, and retinal treatment location may result in treatment that is either damaging (above the TR) or ineffective (below the TR) [17, 28, 94, 96, 97].

Combined SML and Anti VEGF Treatment

As noted, an interesting therapeutic option for the patients with DME emerges while combining the SML with anti-VEGF injections. So far just a few studies analyzing that issue were published. Results are provided in Table 5.9.

Despite various study designs, published results of the studies on combined treatment in DME share some common features. Generally, adding SML to anti-VEGF therapy allows to reduce the number of required intravitreal injections with similar to anti-VEGF monotherapy functional and morphological outcome [139]. Thus, such combination improves patient's comfort and diminishes the financial burden for the health-care system.

Nevertheless, it has to be pointed out that the material on the subject is scarce and conclusions have to be drawn with caution. This is because the treatment approaches and laser parameters in SML studies tend to vary widely, generally reflecting the preference of specific surgeons. So far only 810 nm SML tends to become a first uniform treatment, employing identical laser parameters, treatment field (panmacular), and number of spot applications (400 for a 500 μm spot size) in every eye. In most of the published studies, clinicians start treatment with the loading dose of intravitreal injections followed by the SML.

Complications of PRP and Focal Laser Treatment

1. **Pain**
   Pain symptoms are experienced by a significant percentage of patients undergoing LPC (up to 80%), mainly with panretinal photocoagulation [140, 141]. The source of the pain is probably the posterior ciliary nerves, so it is generally most pronounced in the 3:00 and 9:00 meridians. Continuous wave (CW) 810 nm laser, because it penetrates more deeply, is generally painful even before producing a visible burn. The discomfort is greater when more burns are made, more power is used, and the far periphery where the retina and choroid are thinner are treated. Multispot laser for PRP significantly reduces patient's perception of pain and enables completion of a full PRP at a single session, however by some is regarded as less effective [47, 48].
2. **Subretinal hemorrhage**
   They are rare, but may occur in the presence of significant vascular proliferation. This complication was more common with CW krypton or diode lasers [142, 143].
3. **Visual field constriction**
   The reduction of the field of view is assessed as 40–50% loss after full classical panretinal photocoagulation [144, 145]. In practice, however, this does not mean significant restrictions in everyday functioning (less than 20% of patients lose their driving license for this reason) [146, 147]. In the case of multispot laser

Table 5.9 Results of clinical trials on combining anti-VEGF therapy with SML

Study	Number of eyes	Laser type (nm)	Purpose of the study	Results
Moisseiev et al. [129]	• SML plus ranibizumab—19 • Ranibizumab in monotherapy—19	• 577	• 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 (SML 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)
Akhlaghi et al. [130]	• 42 eyes of 21 patients with refractory DME in both eyes (resistant to intravitreal bevacizumab)	• 810	• One eye randomized to intravitreal bevacizumab only • The other eye received intravitreal bevacizumab plus SML 810 nm • Comparison between the groups at three months	• Significant BCVA improvement in combined treatment group only (from 0.81 to 0.62 logMAR) • Significant reduction of CST in combined group only (from 513 to 408 μm)
Inagaki et al. [131]	• Combined therapy SML plus injections—34	• 577	• Evaluation of BCVA, CST and number of injections at 12 months	• BCVA: improvement from 0.52 logMAR to 0.41 logMAR at 12 months • Stable reduction in CST • Mean number of injections per year: 3,6
Khattab et al. [132]	• Aflibercept—27 (group 1) • Aflibercept plus SML—27 (group 2)	• 577	• 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)

(continued)

Table 5.9 (continued)

Study	Number of eyes	Laser type (nm)	Purpose of the study	Results
Kanar et al. [133]	• Aflibercept in monotherapy—28 • Aflibercept plus SML—28	• 577	• Randomized clinical trial • Evaluation of BCVA, CST and number of necessary injections at 12 months	• Aflibercept group: improvement of BCVA from 0.38 logMAR to 0.20 logMAR, reduction of CST from 451.28 to 328.8 μm • Combination therapy group: improvement of BCVA from 0.40 logMAR to 0.17 logMAR, reduction of CST 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. [134]	• Ranibizumab—7 • Ranibizumab plus 2 sessions of SML—10	• 810	• Prospective, randomized trial • 2 arms • Ranibizumab loading 3 injections and than PRN • Ranibizumab loading 3 iniections and 2 sessions of SML at visit 5 and 6 • Evaluation of BCVA and CST 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 CST: • Ranibizumab alone: –65.25 ± 67.57 versus –117.38 ± 82.71 μm for combined treatment—difference insignificant • Number of injections smaller in the combined treatment group: 7.5 vs. 9.0

(continued)

Table 5.9 (continued)

Study	Number of eyes	Laser type (nm)	Purpose of the study	Results
Abouhussein et al. [135]	• Aflibercept plus SML—20 eyes (A) • Aflibercept—20 eyes (B)	• 577	• Evaluation of number of necessary iniections received after loading dose of 3 monthly injections	Significantly smaller no of necessary injections in group A compared to group B (4.5 vs. 5.4) with similar outcome regarding BCVA and CST
Altinel et al. [136]	• Bevacizumab—40 • Bevacizumab plus SML—40	• 577	• Evaluation of CST, 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. [137]	• Bevacizumab plus SML—49 • Bevacizumab alone—49	• 577	• Loading phase of 3 monthly injections followed by SML 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 CST in both groups, no difference between the groups • Significant difference in no of injections: 4.1 ± 1.5 in the combined treatment group versus 7.2 ± 1.3 in the bevacizumab alone group
Koushan et al. [138]	• Aflibercept • Aflibvercept plus SML	• 532	• Evaluation of BCVA, CST and number of required injections at 48 weeks • Comparison between the groups	• No differences between functional and morphological improvements between the groups • No statistical difference in no of required injections

BCVA—best-corrected visual acuity, CST—central subfoveal thickness, CS—contrast sensitivity, SML—subthreshold micropulse laser PRN—pro re nata

therapy, the changes in the field of view are smaller, if fewer and/or smaller spots are placed [55].

4. **Disturbances in the quality of vision**
   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 photo-coagulation spot located too close to the fovea. Other visual quality disturbances include reduction of the range of accommodation due to damage to the long posterior ciliary nerves. Moreover, patients may experience transient photophobia, moderate nyctalopia and disturbances in color vision in the blue spectrum [148– 150].
5. **Secondary choroidal neovascularization (CNV)**
   A less common that occurs after photocoagulation in the macular area using small burns, such as 50 μm, and too much laser power. Bruch's membrane ruptures occur and the neovascularization from the choroid follows. Treatment of such CNV may require anti-VEGF therapy [151, 152]. Damage to Bruch's membrane during photocoagulation may also cause subretinal fibrosis, without obvious features of CNV [153].
6. **The occurrence or worsening of macular edema**
   Conventional panretinal photocoagulation may cause or aggravate macular edema. For this reason, treatment of diabetic maculopathy should be planned prior to peripheral photocoagulation or in parallel. The anti-VEGF/PRP combination therapy is effective in preventing DME in patients undergoing panretinal photocoagulation. Sometimes anti-VEGF therapy is used before intensive photocoagulation is performed [154, 155].
7. **Preretinal fibrosis**
   Glial proliferation in the epiretinal membranes (ERM) happens 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 [156].
8. **Deterioration of vision related to the enlargement of scars after photocoagulation**
   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 deterioration of vision: decrease in BCVA and permanent scotoma formation [157] (Fig. 5.13).
9. **Choroidal detachment**
   This occurs rarely, after very intense photocoagulation [158].

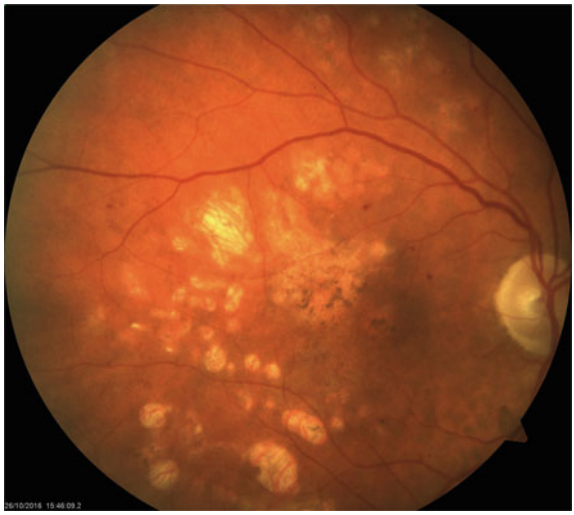

Fig. 5.13 Signifcant enlargement of scars post RPC performed in the macular area

Complications of SML Treatment

Note that all of the above complications of conventional LPC are precluded with SML. Correctly done, SML peripheral retinal treatment has no known adverse treatment effects and improves, rather that worsens, retinal and visual function [159]. Complications of SML thus follow the divergence of treatment from SML standards toward those used for LPC.

References

1. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35(3):556–64.
2. Bertelsen G, Peto T, Lindekleiv H, Schirmer H, Solbu MD, Toft I, et al. Tromso eye study: prevalence and risk factors of diabetic retinopathy. Acta Ophthalmol. 2013;91(8):716–21.
3. Thomas RL, Dunstan FD, Luzio SD, Chowdhury SR, North RV, Hale SL, et al. Prevalence of diabetic retinopathy within a national diabetic retinopathy screening service. Br J Ophthalmol. 2015;99(1):64–8.
4. Wang W, Lo ACY. Diabetic retinopathy: pathophysiology and treatments. Int J Mol Sci. 2018;19(6):1816.
5. Beltramo E, Porta M. Pericyte loss in diabetic retinopathy: mechanisms and consequences. Curr Med Chem. 2013;20(26):3218–25.
6. Romero-Aroca P, Baget-Bernaldiz M, Pareja-Rios A, Lopez-Galvez M, Navarro-Gil R, Verges R. Diabetic macular edema pathophysiology: vasogenic versus inflammatory. J Diabetes Res. 2016;2016:2156273.
7. Joussen AM, Poulaki V, Le ML, et al. A central role for inflammation in the pathogenesis of diabetic retinopathy. FASEB J. 2004;18(12):1450–2.
8. Arroba AI, Valverde AM. Modulation of microglia in the retina: new insights into diabetic retinopathy. Acta Diabetol. 2017;54:527–33.

9. Park SH, Park JW, Park SJ, et al. Apoptotic death of photoreceptors in the streptozotocin-induced diabetic rat retina. Diabetologia. 2003;46(9):1260–8.
10. Barber AJ. A new view of diabetic retinopathy: a neurodegenerative disease of the eye. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27(2):283–90.
11. van Dijk HW, Verbraak FD, Kok PH, Stehouwer M, Garvin MK, Sonka M, DeVries JH, Schlingemann RO, Abràmoff MD. Early neurodegeneration in the retina of type 2 diabetic patients. Invest Ophthalmol Vis Sci. 2012;53(6):2715–9.
12. Alistair J, Lieth E, Khin SA, Antonetti DA et al. Neural apoptosis in the retina during experimental and human diabetes early onset and effect of insulin. J Clin Invest. 1998;102:783–91.
13. van Dijk HW, Verbraak FD, Kok PH, Garvin MK, Sonka M, Lee K, Devries JH, Michels RP, van Velthoven ME, Schlingemann RO, Abràmoff MD. Decreased retinal ganglion cell layer thickness in patients with type 1 diabetes. Invest Ophthalmol Vis Sci. 2010;51(7):3660–5.
14. Stefánsson E. The therapeutic effects of retinal laser treatment and vitrectomy. A theory based on oxygen and vascular physiology. Acta Ophthalmol Scand. 2001;79(5):435–40.
15. Luttrull JK, Chang DB, Margolis BWL, Dorin G, Luttrull DK. Laser re-sensitization of medically unresponsive neovascular age-related macular degeneration: efficacy and implications. Retina. 2015;35(6):1184–94.
16. Lavinsky D, Wang J, Huie P, Dalal R, Lee SJ, Lee DY, Palanker D. Nondamaging retinal laser therapy: rationale and applications to the macula. Invest Ophthalmol Vis Sci. 2016; 57(6):2488±500.
17. Luttrull JK, Sramek C, Palanker D, Spink CJ, Musch DC. Long-term safety, high-resolution imaging, and tissue temperature modeling of subvisible diode micropulse photocoagulation for retinovascular macular edema. Retina. 2012;32(2):375–86.
18. Luttrull JK, Margolis BWL. Functionally guided retinal protective therapy as prophylaxis for age-related and inherited retinal degenerations. A pilot study. Invest Ophthalmol Vis Sci. 2016;5 7(1):265–75.
19. Beere HM, Wolf BB, Cain K, Mosser DD, Mahboubi A, Kuwana T, Tailor P, Morimoto RI, Cohen GM, Green DR. Heat-shock protein 70 inhibits apoptosis by preventing recruitment of procaspase-9 to the Apaf-1 apoptosome. Nat Cell Biol. 2000;2(8):469–75.
20. Furukawa A, Koriyama Y. A role of heat shock protein 70 in photoreceptor cell death: potential as a novel therapeutic target in retinal degeneration. CNS Neurosci Ther. 2016;22(1):7–14.
21. Wilkinson CP, Ferris FLIII, Klein RE et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1679.
22. Four risk factors for severe visual loss in diabetic retinopathy. The third report from the Diabetic Retinopathy Study. The Diabetic Retinopathy Study Research Group. Arch Ophthalmol. 1979;97(4):654–5.
23. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic edema. Arch Ophthalmol. 1985;103:1796–806.
24. Frizziero L, Calciati A, Torresin T, Midena G, Parrozzani R, Pilotto E, Midena E. Diabetic macular edema treated with 577-nm subthreshold micropulse laser: a real-life, long-term study. J Pers Med. 2021;11(5):405.
25. Chen G, Tzekov R, Li W, Jiang F, Mao S, Tong Y. Subthreshold micropulse diode laser versus conventional laser photocoagulation for diabetic macular edema: a meta-analysis of randomized controlled trials. Retina. 2016;36(11):2059–65.
26. Wilkinson CP, Ferris FL 3rd, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003;110(9):1677–82.
27. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, Jonas J, Larsen M, Tadayoni R, Loewenstein A. Guidelines for the management of diabetic macular edema by the European society of retina specialists (EURETINA). Ophthalmologica. 2017;237(4):185–222.
28. Chhablani J, Roh YJ, Jobling AI, Fletcher EL, Lek JJ, Bansal P, Guymer R, Luttrull JK. Restorative retinal laser therapy: present state and future directions. Surv Ophthalmol. 2018;63(3):307–28.

29. Hwang TS, Gao SS, Liu L, Lauer AK, Bailey ST, Flaxel CJ, et al. Automated quantification of capillary nonperfusion using optical coherence tomography angiography in diabetic retinopathy. JAMA Ophthalmol. 2016;134:367–73.
30. Al-Sheikh M, Tepelus TC, Nazikyan T, Sadda SR. Repeatability of automated vessel density measurements using optical coherence tomography angiography. Br J Ophthalmol. 2017;101:449–52.
31. Sikorski BL, Malukiewicz G, Stafiej J, Lesiewska-Junk H, Raczynska D. The diagnostic function of OCT in diabetic maculopathy. Mediators Inflamm. 2013;2013: 434560.
32. Bressler NM, Beaulieu WT, Glassman AR, Blinder KJ, Bressler SB, Jampol LM, Melia M, Wells JA 3rd; Diabetic Retinopathy Clinical Research Network. Persistent macular thickening following intravitreous aflibercept, bevacizumab, or ranibizumab for central-involved DME with vision impairment: a secondary analysis of a randomized clinical trial. JAMA Ophthalmol. 2018;136(3):257–69.
33. Luttrull JK, Dorin G. Subthreshold diode micropulse photocoagulation as invisible retinal phototherapy for diabetic macular edema. A review. Current Diabetes Rev. 2012;8:274–84.
34. Luttrull JK, Sinclair SD. Safety of transfoveal subthreshold diode micropulse laser for intrafoveal diabetic macular edema in eyes with good visual acuity. Retina. 2014;34(10):2010–20.
35. Price LD, Au S, Chong NV. Optomap ultrawide field imaging identifies additional retinal abnormalities in patients with diabetic retinopathy. Clin Ophthalmol. 2015;24(9):527–31.
36. Silva PS, Horton MB, Clary D, Lewis DG, Sun JK, Cavallerano JD, Aiello LP. Identification of diabetic retinopathy and ungradable image rate with ultrawide field imaging in a national teleophthalmology program. Ophthalmology. 2016;123(6):1360–7.
37. Ghasemi Falavarjani K, Wang K, Khadamy J, Sadda SR. Ultra-wide-field imaging in diabetic retinopathy; an overview. J Curr Ophthalmol. 2016;28(2):57–60.
38. Silva PS, Cavallerano JD, Haddad NM, Kwak H, Dyer KH, Omar AF, Shikari H, Aiello LM, Sun JK, Aiello LP. Peripheral lesions identified on ultrawide field imaging predict increased risk of diabetic retinopathy progression over 4 years. Ophthalmology. 2015;122(5):949–56.
39. Wessel MM, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S. Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema. Br J Ophthalmol. 2012;96(5):694–8.
40. Talks SJ, Manjunath V, Steel DH, Peto T, Taylor R. New vessels detected on wide-field imaging compared to two-field and seven-field imaging: implications for diabetic retinopathy screening image analysis. Br J Ophthalmol. 2015;99(12):1606–9.
41. Soliman AZ, Silva PS, Aiello LP, Sun JK. Ultra-wide field retinal imaging in detection, classification, and management of diabetic retinopathy. Semin Ophthalmol. 2012;27(5–6):221–7.
42. Pellegrini M, Cozzi M, Staurenghi G, Corvi F. Comparison of wide field optical coherence tomography angiography with extended field imaging and fluorescein angiography in retinal vascular disorders. PLoS ONE. 2019;14(4): e0214892.
43. Couturier A, Rey PA, Erginay A, et al. Widefield OCT-angiography and fluorescein angiography assessments of nonperfusion in diabetic retinopathy and edema treated with anti-vascular endothelial growth factor. Ophthalmology. 2019;126(12):1685–94.
44. https://www.aao.org Diabetic Retinopathy, Preferred Practice Pattern 2019.
45. Royal College of Ophthalmologists Guidelines 2013. www.rcophth.ac.uk
46. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes. 1995;44(8):968–83.
47. Zoungas S, Arima H, Gerstein HC, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol. 2017;5(6):431–7. https://doi.org/10.1016/S2213-8587(17)30104-3.
48. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837–53.
49. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ. 1998;317(7160):703–13.

50. Gæde P, Vedel P, Parving HH, et al. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet. 1999;353(9153):617–22.
51. Diabetic Retinopathy Study Research Group. Indications for photocoagulation treatment of diabetic retinopathy: diabetic retinopathy study report 14. Int Ophthalmol Clin. 1987;27:239–53.
52. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98:766–85.
53. Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of diabetic retinopathy study (DRS) findings, DRS report number 8. Ophthalmology. 1981;88(7):583–600.
54. Nagpal M, Marlecha S, Nagpal K. Comparison of laser photocoagulation for diabetic retinopathy using 532-nm standard laser versus multispot pattern scan laser. Retina. 2010;30(3):452–8.
55. Subash M, Comyn O, Samy A, et al. The effect of multispot laser panretinal photocoagulation on retinal sensitivity and driving eligibility in patients with diabetic retinopathy. JAMA Ophthalmol. 2016;134(6):666–72.
56. Muqit MM, Marcellino GR, Gray JC, et al. Pain responses of Pascal 20 ms multi-spot and 100 ms single-spot panretinal photocoagulation: manchester pascal study, MAPASS report 2. Br J Ophthalmol. 2010;94(11):1493–8.
57. Muqit MM, Marcellino GR, Henson DB, et al. Single-session vs multiple-session pattern scanning laser panretinal photocoagulation in proliferative diabetic retinopathy: the manchester pascal study. Arch Ophthalmol. 2010;128(5):525–33.
58. Seymenoğlu RG, Ulusoy MO. Başer EF: safety and efficacy of panretinal photocoagulation in patients with high-risk proliferative diabetic retinopathy using pattern scan laser versus conventional YAG laser. Kaohsiung J Med Sci. 2016;32(1):22–6.
59. Nemcansky J, Stepanov A, Nemcanska S, et al. Single session of pattern scanning laser versus multiple sessions of conventional laser for panretinal photocoagulation in diabetic retinopathy. Efficacy, safety and painfulness. PLoS One 2019;14(7):e0219282.
60. Muraly P, Limbad P, Srinivasan K, et al. Single session of Pascal versus multiple sessions of conventional laser for panretinal photocoagulation in proliferative diabetic retinopathy: a comparative study. Retina. 2011;31(7):1359–65.
61. Muqit MM, Marcellino GR, Henson DB, et al. Randomized clinical trial to evaluate the effects of Pascal panretinal photocoagulation on macular nerve fiber layer: manchester Pascal study report 3. Retina. 2011;31(8):1699–707.
62. Bailey CC, Sparrow JM, Grey RH, et al. The national diabetic retinopathy laser treatment audit II. Proliferative retinopathy. Eye (Lond). 1998;12(Pt1):77–84.
63. Muqit MM, Marcellino GR, Henson DB, et al. Pascal panretinal laser ablation and regression analysis in proliferative diabetic retinopathy: manchester Pascal study report 4. Eye (Lond). 2011;25(11):1447–56.
64. Bandello F, Brancato R, Menchini U, et al. Light panretinal photocoagulation (LPRP) versus classic panretinal photocoagulation (CPRP) in proliferative diabetic retinopathy. Semin Ophthalmol. 2001;16(1):12–8.
65. Luttrull JK, Musch DC, Spink CA. Subthreshold diode micropulse panretinal photocoagulation for proliferative diabetic retinopathy. Eye. 2008;22(5):607–12.
66. Jhingan M, Goud A, Peguda HK, et al. Subthreshold micropulse laser for proliferative diabetic retinopathy: a randomized pilot study. Clin Ophthalmol. 2018;12:141–5.
67. Arevalo JF, Maia M, Flynn HW Jr, Saravia M, Avery RL, Wu L, Eid Farah M, Pieramici DJ, Berrocal MH, Sanchez JG. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. Br J Ophthalmol. 2008;92(2):213–6.
68. Berrocal MH, Acaba-Berrocal L. Early pars plana vitrectomy for proliferative diabetic retinopathy: update and review of current literature. Curr Opin Ophthalmol. 2021;32(3):203–8.

69. Cho WB, Moon JW, Kim HC. Intravitreal triamcinolone and bevacizumab as adjunctive treatments to panretinal photocoagulation in diabetic retinopathy. Br J Ophthalmol. 2010;94:858–63.
70. Mason JO, Yunker JJ, Vail R, McGwin G Jr. Intravitreal bevacizumab (Avastin) prevention of panretinal photocoagulation-induced complications in patients with severe proliferative diabetic retinopathy. Retina. 2008;28:1319–24.
71. Figueira J, Fletcher E, Massin P, Silva R, Bandello F, Midena E, Varano M, Sivaprasad S, Eleftheriadis H, Menon G, Amaro M, Ayello Scheer S, Creuzot-Garcher C, Nascimento J, Alves D, Nunes S, Lobo C, Cunha-Vaz J; EVICR.net Study Group. Ranibizumab plus panretinal photocoagulation versus panretinal photocoagulation alone for high-risk proliferative diabetic retinopathy (PROTEUS study). Ophthalmology. 2018;125(5):691–700.
72. Tonello M, Costa RA, Almeida FP, Barbosa JC, Scott IU, Jorge R. Panretinal photocoagulation versus PRP plus intravitreal bevacizumab for high-risk proliferative diabetic retinopathy (IBeHi study). Acta Ophthalmol. 2008;86(4):385–9. https://doi.org/10.1111/j.1600-0420.2007.01056.x. Epub 2007 Nov 7 PMID: 17995982.
73. Jorge R, Costa RA, Calucci D, Cintra LP, Scott IU. Intravitreal bevacizumab (Avastin) for persistent new vessels in diabetic retinopathy (IBEPE study) Retina. 2006;26(9):1006–13.
74. Bhavsar AR, Torres K, Beck RW, et al. Randomized clinical trial evaluating intravitreal ranibizumab or saline for vitreous hemorrhage from proliferative diabetic retinopathy. JAMA Ophthalmol. 2013;131(3):283–93.
75. Writing Committee for the Diabetic Retinopathy Clinical Research Network, Gross JG, Glassman AR, Jampol LM, Inusah S, Aiello LP, Antoszyk AN, Baker CW, Berger BB, Bressler NM, Browning D, Elman MJ, Ferris FL 3rd, Friedman SM, Marcus DM, Melia M, Stockdale CR, Sun JK, Beck RW. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA. 2015;314(20):2137–46.
76. Sivaprasad S, Prevost AT, Vasconcelos JC, et al. CLARITY Study Group. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. Lancet Lond Engl. 2017;389(10085):2193–203.
77. Gross J, Glassman AR, Liu D, et al. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy. JAMA Ophthalmol. 2018;136(10):1138–48.
78. Maguire MG, Liu D, Bressler SB, Friedman SM, Melia M, Stockdale CR, Glassman AR, Sun JK; DRCR Retina Network. Lapses in care among patients assigned to ranibizumab for proliferative diabetic retinopathy: a post hoc analysis of a randomized clinical trial. JAMA Ophthalmol. 2021;139(12):1266–73.
79. Hutton DW, Stein JD, Glassman AR, Bressler NM, Jampol LM, Sun JK; DRCR Retina Network. Five-year cost-effectiveness of intravitreous ranibizumab therapy vs panretinal photocoagulation for treating proliferative diabetic retinopathy: a secondary analysis of a randomized clinical trial. JAMA Ophthalmol. 2019;137(12):1–9.
80. Tan Y, Fukutomi A, Sun MT, Durkin S, Gilhotra J, Chan WO. Anti-VEGF crunch syndrome inproliferative diabetic retinopathy: A review. Surv Ophthalmol. 2021 Nov-Dec;66(6):926–932.
81. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, Gibson A, Sy J, Rundle AC, Hopkins JJ, Rubio RG, Ehrlich JS; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012;119(4):789–801.
82. Brown DM, Schmidt-Erfurth U, Do DV, Holz FG, Boyer DS, Midena E, Heier JS, Terasaki H, Kaiser PK, Marcus DM, Nguyen QD, Jaffe GJ, Slakter JS, Simader C, Soo Y, Schmelter T, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Zeitz O, Metzig C, Korobelnik JF. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. Ophthalmology. 2015;122(10):2044–52.

83. Mainster MA. Decreasing retinal photocoagulation damage: principles and techniques. Semin Ophthalmol. 1999;14:200e9.
84. Hamada M, Ohkoshi K, Inagaki K, Ebihara N, Murakami A. Subthreshold photocoagulation using endpoint management in the PASCAL® system for diffuse diabetic macular edema. J Ophthalmol. 2018;31(2018):7465794.
85. Pei-Pei W, Shi-Zhou H, Zhen T, Lin L, Ying L, Jiexiong O, Wen-Bo Z, Chen-Jin J. Randomised clinical trial evaluating best-corrected visual acuity and central macular thickness after 532-nm subthreshold laser grid photocoagulation treatment in diabetic macular oedema. Eye (Lond). 2015;29(3):313–21; quiz 322.
86. Roider J, Liew SH, Klatt C, Elsner H, Poerksen E, Hillenkamp J, Brinkmann R, Birngruber R. Selective retina therapy (SRT) for clinically significant diabetic macular edema. Graefes Arch Clin Exp Ophthalmol. 2010;248(9):1263–72.
87. Park YG, Kim JR, Kang S, Seifert E, Theisen-Kunde D, Brinkmann R, Roh YJ. Safety and efficacy of selective retina therapy (SRT) for the treatment of diabetic macular edema in Korean patients. Graefes Arch Clin Exp Ophthalmol. 2016;254(9):1703–13.
88. Kim M, Park YG, Jeon SH, Choi SY, Roh YJ. The efficacy of selective retina therapy for diabetic macular edema based on pretreatment central foveal thickness. Lasers Med Sci. 2020;35(8):1781–90.
89. Yamamoto M, Miura Y, Hirayama K, Kohno T, Kabata D, Theisen-Kunde D, Brinkmann R, Honda S. Predictive factors of outcome of selective retina therapy for diabetic macular edema. Int Ophthalmol. 2020;40(5):1221–32.
90. Gaca-Wysocka M, Grzybowski A. Application of 2RT nanopulse retinal laser in the treatment of diabetic macular edema. Ophthatherapy [Internet]. 2017 June 30 [cited 2020 Nov 5];4(2):81–4.
91. Casson RJ, Raymond G, Newland HS, Gilhotra JS, Gray TL. Pilot randomized trial of a nanopulse retinal laser versus conventional photocoagulation for the treatment of diabetic macular oedema. Clin Exp Ophthalmol. 2012;40(6):604–10.
92. Moisseiev E, Loewenstein A. Diabetic macular edema: emerging strategies and treatment algorithms. Dev Ophthalmol. 2017;60:165–74. https://doi.org/10.1159/000459706. Epub 2017 Apr 20 PMID: 28427075.
93. Figueira J, Khan J, Nunes S, Sivaprasad S, Rosa A, de Abreu AF, Cunha-VAz JG, Chong NV. Prospective randomised controlled trial comparing sub-threshold micropulse diode laser photocoagulation and conventional green laser for clinically significant diabetic macular oedema. Br J Ophthalmol. 2009;93:1341–4.
94. Keunen JEE, Battaglia-Parodi M, Vujosevic S, Luttrull JK. International retinal laser society guidelines for subthreshold laser treatment. Transl Vis Sci Technol. 2020;9(9):15.
95. Lavinsky D, Cardillo JA, Melo LA Jr, et al. Randomized clinical trial evaluating mETDRS versus normal or high-density micropulse photocoagulation for diabetic macular edema. Invest Ophthalmol Vis Sci. 2011;52(7):4314–23.
96. Chang DB, Luttrull JK. Comparison of subthreshold 577 and 810 nm micropulse laser effects on heat-shock protein activation kinetics: implications for treatment efficacy and safety. Transl Vis Sci Technol. 2020;9(5):23.
97. Vujosevic S, Martini F, Longhin E, Convento E, Cavarzeran F, Midena E. Subthreshold micropulse yellow laser versus Subthreshold micropulse infrared laser in center-involving diabetic macular edema: Morphologic and Functional Safety. Retina. 2015;35:1594–6031.
98. Battaglia Parodi M, Bandello F. Is laser still important in diabetic macular edema as primary or deferral therapy? Dev Ophthalmol. 2017;60:125–30.
99. Sivaprasad S, Sandhu R, Tandon A, Sayed-Ahmed K, McHugh DA. Subthreshold micropulse diode laser photocoagulation for clinically significant diabetic macular oedema: a three-year follow up. Clin Exp Ophthalmol. 2007;35:640e4.
100. Luttrull JK, Musch DC, Mainster MA. Subthreshold diode micropulse photocoagulation for the treatment of clinically significant diabetic macular oedema. Br J Ophthalmol. 2005;89(1):74–80.

101. Vujosevic S, Bottega E, Casciano M, et al. Microperimetry and fundus autofluorescence in diabetic macular edema: subthreshold micropulse diode laser versus modified early treatment diabetic retinopathy study laser photocoagulation. Retina. 2010;30(6):908–16.
102. Takatsuna Y, Yamamoto S, Nakamura Y, et al. Long-term therapeutic efficacy of the subthreshold micropulse diode laser photocoagulation for diabetic macular edema. Jpn J Ophthalmol. 2011;55(4):365–9.
103. Othman IS, Eissa SA, Kotb MS, et al. Subthreshold diode-laser micropulse photocoagulation as a primary and secondary line of treatment in management of diabetic macular edema. Clin Ophthalmol. 2014;8:653–9.
104. Mansouri A, Sampat KM, Malik KJ, et al. Efficacy of subthreshold micropulse laser in the treatment of diabetic macular edema is influenced by pre-treatment central foveal thickness. Eye (Lond). 2014;28(12):1418–24.
105. Inagaki K, Ohkoshi K, Ohde S, et al. Comparative efficacy of pure yellow (577-nm) and 810-nm subthreshold micropulse laser photo-coagulation combined with yellow (561–577-nm) direct photocoagulation for diabetic macular edema. JPN J Ophthalmol. 2015;59(1):21–8.
106. Fazel F, Bagheri M, Golabchi K, et al. Comparison of subthreshold diode laser micropulse therapy versus conventional photocoagulation laser therapy as primary treatment of diabetic macular edema. J Curr Ophthalmol. 2016;28(4):206–11.
107. Latalska M, Prokopiuk A, Wróbel-Dudzińska D, Mackiewicz J. Subthreshold micropulse yellow 577 nm laser therapy of diabetic macular oedema in rural and urban patients of south-eastern Poland. Ann Agric Environ Med. 2017;24(1):96–9.
108. Veselá Š, Hejsek L, Stepanov A, Dusová J, Marak J, Jirásková N, Studnička J. The use of micropulse laser in patients with diabetic macular edema at the Department of Ophthalmology, Faculty Hospital Hradec Králové. Cesk Slov Oftalmol. 2018 Summer;74(2):53-58. English. https://doi.org/10.31348/2018/1/2-2-2018. PMID: 30441950.
109. Citirik M. The impact of central foveal thickness on the efficacy of subthreshold micropulse yellow laser photocoagulation in diabetic macular edema. Lasers Med Sci. 2019;34(5):907–12.
110. Vujosevic S, Gatti V, Muraca A, Brambilla M, Villani E, Nucci P, Rossetti L, De Cilla' S. Optical coherence tomography angiography changes after subthreshold micropulse yellow laser in diabetic macular edema. Retina. 2020;40(2):312–21.
111. Vujosevic S, Toma C, Villani E, Brambilla M, Torti E, Leporati F, Muraca A, Nucci P, De Cilla S. Subthreshold micropulse laser in diabetic macular edema: 1-year improvement in OCT/OCT-angiography biomarkers. Transl Vis Sci Technol. 2020;9(10):31.
112. Bougatsou P, Panagiotopoulou EK, Gkika M, Dardabounis D, Konstantinidis A, Sideroudi H, Perente I, Labiris G. Comparison of subthreshold 532 nm diode micropulse laser with conventional laser photocoagulation in the treatment of non-centre involved clinically significant diabetic macular edema. Acta Medica (Hradec Kralove). 2020;63(1):25–30.
113. Li ZJ, Xiao JH, Zeng P, Zeng R, Gao X, Zhang YC, Lan YQ. Optical coherence tomography angiography assessment of 577 nm laser effect on severe non-proliferative diabetic retinopathy with diabetic macular edema. Int J Ophthalmol. 2020;13(8):1257–65.
114. Akkaya S, Açıkalın B, Doğan YE, Çoban F. Subthreshold micropulse laser versus intravitreal anti-VEGF for diabetic macular edema patients with relatively better visual acuity. Int J Ophthalmol. 2020;13(10):1606–11.
115. Abdelrahman A, Massoud W, Elshafei AMK, Genidy M, Abdallah RMA. Anatomical and functional outcomes of subthreshold micropulse laser versus intravitreal ranibizumab injection in treatment of diabetic macular edema. Int J Retina Vitreous. 2020;6(1):63.
116. Donati MC, Murro V, Mucciolo DP, Giorgio D, Cinotti G, Virgili G, Rizzo S. Subthreshold yellow micropulse laser for treatment of diabetic macular edema: comparison between fixed and variable treatment regimen. Eur J Ophthalmol. 2021;31(3):1254–60.
117. Al-Barki A, Al-Hijji L, High R, Schatz P, Do D, Nguyen QD, Luttrull JK, Kozak I. Comparison of short-pulse subthreshold (532 nm) and infrared micropulse (810 nm) macular laser for diabetic macular edema. Sci Rep. 2021;11(1):14.

118. Passos RM, Malerbi FK, Rocha M, Maia M, Farah ME. Real-life outcomes of subthreshold laser therapy for diabetic macular edema. Int J Retina Vitreous. 2021;7(1):4.
119. Valera-Cornejo DA, García-Roa M, Quiroz-Mendoza J, Arias-Gómez A, Ramírez-Neria P, Villalpando-Gómez Y, Romero-Morales V, García-Franco R. Micropulse laser in patients with refractory and treatment-naïve center-involved diabetic macular edema: short terms visual and anatomic outcomes. Ther Adv Ophthalmol. 2021;19(13):2515841420979112.
120. Lai FHP, Chan RPS, Lai ACH, Tsang S, Woo TTY, Lam RF, Yuen CYF. Comparison of two-year treatment outcomes between subthreshold micropulse (577 nm) laser and aflibercept for diabetic macular edema. Jpn J Ophthalmol. 2021;65(5):680–8.
121. Bonfiglio V, Rejdak R, Nowomiejska K, Zweifel SA, Justus Wiest MR, Romano GL, Bucolo C, Gozzo L, Castellino N, Patane C, Pizzo C, Reibaldi M, Russo A, Longo A, Fallico M, Macchi I, Vadalà M, Avitabile T, Costagliola C, Jonak K, Toro MD. Efficacy and safety of subthreshold micropulse yellow laser for persistent diabetic macular edema after vitrectomy: a pilot study. Front Pharmacol. 2022;6(13): 832448.
122. Lois N, Gardner E, Waugh N, Azuara-Blanco A, Mistry H, McAuley D, Acharya N, Aslam TM, Bailey C, Chong V, Downey L, Eleftheriadis H, Fatum S, George S, Ghanchi F, Groppe M, Hamilton R, Menon G, Saad A, Sivaprasad S, Shiew M, Steel DH, Talks JS, Adams C, Campbell C, Mills M, Clarke M; DIAMONDS Study Group. Diabetic macular oedema and diode subthreshold micropulse laser (DIAMONDS): study protocol for a randomised controlled trial. Trials. 2019;20(1):122.
123. Frizziero L, Calciati A, Midena G, Torresin T, Parrozzani R, Pilotto E, Midena E. Subthreshold micropulse laser modulates retinal neuroinflammatory biomarkers in diabetic macular edema. J Clin Med. 2021;10(14):3134.
124. Midena E, Bini S, Martini F, Enrica C, Pilotto E, Micera A, Esposito G, Vujosevic S. Changes of aqueous humor müller cells' biomarkers in human patients affected by diabetic macular edema after subthreshold micropulse laser treatment. Retina. 2020;40(1):126–34.
125. Ueda K, Shiraya T, Araki F, Hashimoto Y, Yamamoto M, Yamanari M, Ueta T, Minami T, Aoki N, Sugiyama S, Zhou HP, Totsuka K, Toyama T, Sugimoto K, Obata R, Kato S. Changes in entropy on polarized-sensitive optical coherence tomography images after therapeutic subthreshold micropulse laser for diabetic macular edema: a pilot study. PLoS ONE. 2021;16(9): e0257000.
126. Işık MU, Değirmenci MFK, Sağlık A. Factors affecting the response to subthreshold micropulse laser therapy used in center-involved diabetic macular edema. Lasers Med Sci. 2022;37(3):1865–71.
127. Baker CW, Glassman AR, Beaulieu WT, Antoszyk AN, Browning DJ, Chalam KV, Grover S, Jampol LM, Jhaveri CD, Melia M, Stockdale CR, Martin DF, Sun JK; DRCR Retina Network. Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. JAMA. 2019;321(19):1880–94.
128. Luttrull JK, Spink CJ. Serial optical coherence tomography of subthreshold diode laser micropulse photocoagulation for diabetic macular edema. Ophthalmic Surg Lasers Imaging. 2006;37:370–7.
129. Moisseiev E, Abbassi S, Thinda S, et al. Subthreshold micropulse laser reduces anti-VEGF injection burden in patients with diabetic macular edema. Eur J Ophthalmol. 2018;28(1):68–73.
130. Akhlaghi M, Dehghani A, Pourmohammadi R, Asadpour L, Pourazizi M. Effects of subthreshold diode micropulse laser photocoagulation on treating patients with refractory diabetic macular edema. J Curr Ophthalmol. 2018;31(2):157–60.
131. Inagaki K, Hamada M, Ohkoshi K. Minimally invasive laser treatment combined with intravitreal injection of anti-vascular endothelial growth factor for diabetic macular oedema. Sci Rep. 2019;9(1):7585.
132. Khattab AM, Hagras SM, AbdElhamid A, et al. Aflibercept with adjuvant micropulsed yellow laser versus aflibercept monotherapy in diabetic macular edema. Graef Arch Clin Exp Ophthalmol. 2019;257(7):1373–80.

133. Kanar HS, Arsan A, Altun A, et al. Can subthreshold micropulse yellow laser treatment change the anti-vascular endothelial growth factor algorithm in diabetic macular edema? A randomized clinical trial. Indian J Ophthalmol. 2020;68(1):145–51.
134. Furashova O, Strassburger P, Becker KA, Engelmann K. Efficacy of combining intravitreal injections of ranibizumab with micropulse diode laser versus intravitreal injections of ranibizumab alone in diabetic macular edema (ReCaLL): a single center, randomised, controlled, non-inferiority clinical trial. BMC Ophthalmol. 2020;20(1):308.
135. Abouhussein MA, Gomaa AR. Aflibercept plus micropulse laser versus aflibercept monotherapy for diabetic macular edema: 1-year results of a randomized clinical trial. Int Ophthalmol. 2020;40(5):1147–54.
136. Altınel MG, Acikalin B, Alis MG, Demir G, Mutibayraktaroglu KM, Totuk OMG, Ardagil A. Comparison of the efficacy and safety of anti-VEGF monotherapy versus anti-VEGF therapy combined with subthreshold micropulse laser therapy for diabetic macular edema. Lasers Med Sci. 2021;36(7):1545–53.
137. El Matri L, Chebil A, El Matri K, Falfoul Y, Chebbi Z. Subthreshold micropulse laser adjuvant to bevacizumab versus bevacizumab monotherapy in treating diabetic macular edema: one-year-follow-up. Ther Adv Ophthalmol. 2021;2(13):25158414211040890.
138. Koushan K, Eshtiaghi A, Fung P, Berger AR, Chow DR. Treatment of diabetic macular edema with aflibercept and micropulse laser (DAM study). Clin Ophthalmol. 2022;8(16):1109–15.
139. Gawęcki M. Subthreshold diode micropulse laser combined with intravitreal therapy for macular edema-A systematized review and critical approach. J Clin Med. 2021;10(7):1394.
140. Richardson C, Waterman H. Pain relief during panretinal photo-coagulation for diabetic retinopathy: a national survey. Eye (Lond). 2009;23(12):2233–7.
141. Wu WC, Hsu KH, Chen TL, et al. Interventions for relieving pain associated with panretinal photocoagulation: a prospective randomized trial. Eye (Lond). 2006;20(6):712–9.
142. Blankenship GW, Gerke E, Batlle JF. Red krypton and blue-green argon laser diabetic panretinal photocoagulation. Graefes Arch Clin Exp Ophthalmol. 1989;227(4):364–8.
143. Sebag J, Buzney SM, Belyea DA, et al. Posterior vitreous detachment following panretinal laser photocoagulation. Graefes Arch Clin Exp Ophthalmol. 1990;228(1):5–8.
144. Buckley SA, Jenkins L, Benjamin L. Fields, DVLC and panretinal photocoagulation. Eye (Lond). 1992;6(Pt6):623–5.
145. Pahor D. Visual field loss after argon laser panretinal photocoagulation in diabetic retinopathy: full- versus mild-scatter coagulation. Int Ophthalmol. 1998;22(5):313–9.
146. Muqit MM, Wakely L, Stanga PE, et al. Effects of conventional argon panretinal laser photocoagulation on retinal nerve fibre layer and driving visual fields in diabetic retinopathy. Eye (Lond). 2010;24(7):1136–42.
147. Pearson AR, Tanner V, Keightley SJ, et al. What effect does laser photocoagulation have on driving visual fields in diabetics? Eye (Lond). 1998;12(Pt1):64–8.
148. Preti RC, Ramirez LM, Monteiro ML, et al. Contrast sensitivity evaluation in high risk proliferative diabetic retinopathy treated with panretinal photocoagulation associated or not with intravitreal bevacizumab injections: a randomised clinical trial. Br J Ophthalmol. 2013;97(7):885–9.
149. Lövestam-Adrian M, Svendenius N, Agardh E. Contrast sensitivity and visual recovery time in diabetic patients treated with panretinal photocoagulation. Acta Ophthalmol Scand. 2000;78(6):672–6.
150. Khosla PK, Rao V, Tewari HK, et al. Contrast sensitivity in diabetic retinopathy after panretinal photocoagulation. Ophthalmic Surg. 1994;25(8):516–20.
151. Simon P, Glacet-Bernard A, Binaghi M, et al. Exérèse de néovaisseaux choroïdiens compliquant le traitement de la choriorétinopathie séreuse centrale [Choroidal neovascularization as a complication following laser treatment of central serous chorioretinopathy]. J Fr Ophtalmol. 2001;24(1):64–8.
152. Koenig F, Soubrane G, Coscas G. Déchirures de l'épithélium pigmentaire après photocoagulation au cours de la dégénérescence maculaire liée à l'âge [Retinal pigment epithelial tears after photocoagulation in age-related macular degeneration]. J Fr Ophtalmol. 1989;12(11):775–80.

153. Guyer DR, D'Amico DJ, Smith CW. Subretinal fibrosis after laser photocoagulation for diabetic macular edema. Am J Ophthalmol. 1992;113(6):652–6.
154. Shimura M, Yasuda K, Nakazawa T, et al. Panretinal photocoagulation induces pro-inflammatory cytokines and macular thickening in high-risk proliferative diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2009;247(12):1617–24.
155. Krick TW, Bressler NM. Recent clinically relevant highlights from the diabetic retinopathy clinical research network. Curr Opin Ophthalmol. 2018;29(3):199–205.
156. Rema M, Sujatha P, Pradeepa R. Visual outcomes of pan-retinal photocoagulation in diabetic retinopathy at one-year follow-up and associated risk factors. Indian J Ophthalmol. 2005;53(2):93–9.
157. Schatz H, Madeira D, McDonald HR, et al. Progressive enlargement of laser scars following grid laser photocoagulation for diffuse diabetic macular edema. Arch Ophthalmol. 1991;109(11):1549–51.
158. Mori K, Yoneya S, Gehlbach PL. Choroidal perfusion delay and hyperpermeability in exudative retinal detachment induced by panretinal scatter photocoagulation. Retin Cases Brief Rep. 2007;1(2):68–9.
159. Gawęcki M. Increase in central retinal edema after subthreshold diode micropulse laser treatment of chronic central serous chorioretinopathy. Case Rep Ophthalmol Med. 2015;2015:813414.

Chapter 6
Lasers in the Treatment of Central Serous Chorioretinopathy

Maciej Gawęcki and Andrzej Grzybowski

Abstract Central serous chorioretinopathy (CSCR) is a clinical entity that has been well described in medical literature, however its etiology and pathophysiology still remains a medical mystery. Recent advances in retinal and choroidal diagnostics have changed approach to CSCR pathogenesis with the choroid perceived as the origin this disorder and retinal pigment abnormalities as secondary. CSCR is nowadays placed within the spectrum of pachychoroid diseases characterized by the increased choroidal thickness. Moreover, the advent of OCT-angiography has enabled to assess the potential complications of CSCR such as choroidal neovascularization, which is detected frequently with this imaging. All these facts had an impact on therapeutic strategies applied in CSCR. Typically CSCR is treated with different forms of laser, starting from classic photocoagulation (LPC), through subthreshold micropulse laser (SMPLT) and ending at photodynamic therapy (PDT). The therapeutic target of each of these procedures is different, thus the stage and type of CSCR has to be considered before initiation of therapy. LPC is nowadays used in selected cases with single extrafoveal leak. SMPLT as a cheap and safe form of treatment is used commonly in simple CSCR cases, while PDT is preferred in complex and long-standing forms of CSCR. The timing of application of treatment is still a question of debate, however there is a rising body of evidence that early treatment provides better functional results. The chapter contains analysis of available diagnostic and therapeutic modalities used for CSCR with the emphasis on its efficacy in real life studies. Therapeutic questions and dilemmas are presented and discussed, together with the proposed parameters for laser techniques in that entity.

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_6

Central serous chorioretinopathy (CSCR) is a relatively common clinical entity that has been quite well described in medical literature. Nevertheless, CSCR etiology and pathomechanism still remains a medical mystery with new pathogenic theories constantly proposed by the researchers.

Incidence

It has been proven that CSCR affects predominantly males, what has been reported in many studies. Kitzmann et al. reported annual incidence of CSCR at 9.9 per 10,000 individuals for men and 1.7 per 100,000 for women [1]. Less apparent dominance of males in that group was reported by Spaide [2] (2.6:1) and Tittl [3] (2.7:1). For many years it was believed that CSCR affects very young people. Today the average age of CSCR patients is slightly higher than previously thought. In mentioned Spaide study it was reported at 51 years and Tittl provides the number of 49.8 years. CSCR is also reported in number of older individuals, what implies the need for differential diagnosis with neovascular form of AMD (nAMD) [4].

Risk Factors

There has been large genetic research on predispositions for incidence of CSCR, however results are not yet clear and conclusive. Some reports show relevance of occurrence of CSCR to different variants of complement factor H gene [5, 6] or C4B gene [7]. For many years CSCR was associated with specific type of personality (type A), characterized as highly ambitious, anxious, proactive and rigidly organized [8]. Modern studies however not always find such relationship [9]. Occurrence of CSCR was commonly connected to high level of chronic stress or single stressful episodes as well as sleeping disorders and working on shifts [10–12]. Spahn et al. report higher level of stress a few weeks before the onset CSCR [13]. Controlled studies of CSCR patients show the higher levels of psychological problems and chronic anxiety when compared to healthy individuals [14–16]. Generally, results of most of the studies on CSCR indicate the connection between the level of stress and occurrence of CSCR, however still there is a lack of research that would quantify that.

The best recognized external factor triggering CSCR is the intake of steroids, especially systemic. Haimovici et al. report odds to ratio for occurrence of CSCR in patients taking systemic steroids at 37:1 [17]. There are also numerous reports on CSCR diagnosed after topical use of steroids ex in inhalation, intraarticular injections or dermatological ointments [18–20].

Disturbances in the level of endogenous corticosteroids may also play part in CSCR etiopathogenesis. There are a few facts that support that theory. Patients with chronic active form of CSCR were reported to have higher levels of endogenous corticoids: androsterone, estron, etiocholanolone and androstenedione [21].

(Interestingly, some research show that A type personalities have upraised levels of endogenous corticoids in plasma [22].) A developed hypercortisolemia i.e. Cushing syndrome is associated with the risk of CSCR episode [23, 24]. Alterations in the levels of endogenous corticoids are also most likely to cause CSCR episodes in third trimester of pregnancy [25, 26]. Analysis of those reports resulted in a proposal of "mineralocorticoid pathway" theory of CSCR pathogenesis, which is discussed further [27]. Risk factors of CSCR brought up less frequently are cardiovascular diseases (arterial hypertension or coronary disease) or the presence of Helicobacter Pylori in digestive tract [28–30].

Different Concepts of CSCR Pathomechanism

It is important to perceive different theories of CSCR pathogenesis as their understanding determines the rationale in application of different therapeutic strategies, including different forms of laser treatment.

Retinal Pigment Epithelium (RPE) Dysfunction

First concepts of pathomechanism of CSCR referred to impairment of the function of the RPE as the main source of fluid accumulation under the sensory retina (subretinal fluid—SRF). Altered metabolism of the RPE cell resulted in deficiencies in the active transport through the RPE and poor elimination of the SRF [31–33]. Modern pathogenetic concepts concentrate rather on the alterations in the choroid and treat lesions of the RPE as secondary.

Choroidal Dysfunction

Introduction of indocyanine green angiography (ICGA) into diagnostics of CSCR shed a new light into its pathology. ICGA performed in patients with CSCR revealed increased choroidal vessels permeability visible as areas of hyperfluorescence starting from intermediate phase of the angiogram [34]. Later on, visualization of the choroid with enhanced depth of imaging OCT (EDI-OCT) or swept source OCT (SS-OCT) enabled to assess various choroidal alterations, such as increased choroidal thickness, widening of choroidal vessels in Haller layer and defects in the inner choroid [35]. On the other hand OCT-angiography (OCTA) showed impaired perfusion on the level of choriocapillaris [36, 37]. Loss of choriocapillaris in the course of chronic CSCR explains the morphological and functional retinal impairment [38]. Deficits in the nutrition of outer retinal layers in the long-term results in the loss of the RPE cells and photoreceptors.

Choroid Morphology Abnormalities

Modern approach situates CSCR within the spectrum of diseases in which increased choroidal thickness is noted and described as pachychoroid. Other clinical entities belonging to that group include pachychoroid pigment epitheliopathy (PPE), pachychoroid neovasculopathy (PNV), polypoidal choroidal vasculopathy (PCV), focal choroidal excavation (FCE) and peripapillary pachychoroid syndrome (PPS). Common features of that disorders include focal or generalized increase in choroidal thickness, widening of large vessels in Haller's layer, thinning of overlying medium-sized vessels of Sattler's layer and thinning of choriocapillaris, sometimes accompanied by deficits in neighboring RPE cells. Theoretical scenario of evolution of morphological changes in CSCR could be described as follows: dilation of large choroidal vessels—pressure on medium size choroidal vessels and choriocapillaris—loss of small vessels and impairment of perfusion—loss of RPE cells and photoreceptors and/or neovascularization as a result of ischemia. In case of CSCR this sequence is accompanied by increased permeability od choriocapillaris (visualized on ICGA), excavation of fluid outside the vessel lumen and its penetration to subretinal space (well visualized on SD-OCT scans) (Fig. 6.1).

Mineralocorticoid Pathway

Analysis of the relationship between the occurrence of CSCR and intake of steroids resulted in research on alterations of the levels of endogenous corticoids in patients affected by CSCR. The "mineralocorticoid pathway" theory assumed upregulation of receptors for mineralocorticoids, also present in the choroid, in patients with CSCR. In consequence of hyperactivation of these receptors, retention of water in the choroid occurs, resulting in the increase of hydrostatic pressure in choroidal vessels. Subsequently, fluid leaks from choroidal vessels and penetrates under sensory retina. This concept remains in consent with the description of symptoms in pachychoroid spectrum of diseases, where significant widening of the vessels in Haller's layer is observed [39]. The theory explains also the presence of symptoms from other organs that express mineralocorticoid receptors (cardiovascular system, brain, kidneys) that are noted in CSCR patients. Patients in whom CSCR occurs are at higher risk of cardiovascular events, hypertension and personality disorders [29, 40, 41]. Therapeutic consequences of accepting such pathomechanism of CSCR could be the use of mineralocorticoid receptors inhibitors, which will be discussed further in that chapter.

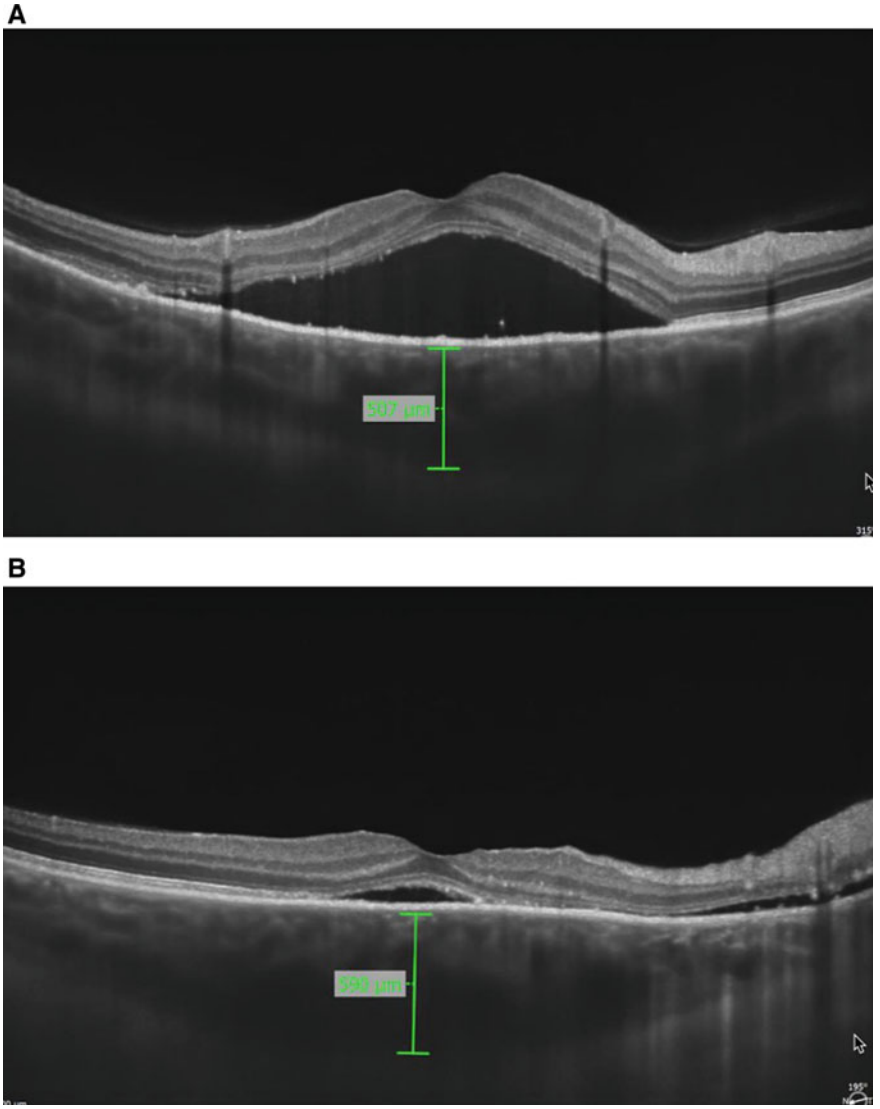

Fig. 6.1 Increase in choroidal thickness in the course of CSCR

Clinical Picture, Diagnostics and Classification

Typical episodes of CSCR result in moderate decrease in best corrected visual acuity (BCVA) and decrease in the quality of vision, including metamorhopsias, scotomas, lower contrast sensitivity and hypermetropisation. In long-standing or recurrent cases

significant visual impairment might be noted, with low BCVA and permanent deficits in visual field.

Classification

Classification of CSCR is evolving constantly with emerging modern knowledge on that clinical entity. Traditionally CSCR has been divided into acute and chronic cases, depending on its duration. Usually, the threshold of 4–6 months was adopted to classify acute and chronic cases. More complex classification system was proposed by Daruich et al. [42]:

- Acute CSCR—self-resolving serous retinal detachment (SRD) within 4 months from the onset.
- Non-resolving or persistent—acute CSCR with duration longer than 4 months.
- Recurrent CSCR—acute CSCR after previous episode with total resolution of SRD.
- Chronic CSCR—widespread RPE alterations with or without SRD and with or without active leakage sites.
- Inactive CSCR—history of acute CSCR but without SRD on examination.

The most recent classification of CSCR as well as its diagnostic criteria were proposed by Central Serous Chorioretinopathy International Group in 2020 [43]. It combines presentation of CSCR on multimodal imaging with duration and presence of recurrences of the disease as well as complication by choroidal neovascularization (CNV) (nowadays sometimes term macular neovascularization - MNV is used).

Detailed classification of Central Serous Chorioretinopathy International Group is presented at Fig. 6.2.

The main two criteria for recognition of CSCR (both necessary) are as follows [43]:

(1) the presence or documented evidence of previous SRD involving the posterior pole unrelated to other diseases or drug intake, tractional maculopathy, retinal vascular disorders, optic pit, choroidal nevus or macular neovascularization due to other causes and
(2) at least one RPE alteration on fundus autofluorescence (FAF), SOCT or infrared imaging.

Minor criteria (at least one necessary) include:

(1) mid-phase areas of hyperfluorescence on indocyanine green angiography (ICGA);
(2) 1 or more focal leaks on fluorescein angiography (FA);
(3) subfoveal choroidal thickness (SFCT) $\geq$400 μm.

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<table>
<tr><td rowspan="3">Simple
Total area of RPE alteration ≤2 DA</td><td>Primary
First known episode of SRF</td><td rowspan="3">± Persistent
SRF >6months</td><td rowspan="3">± with outer retinal atrophy
ONL thinning and/or ELM disruption and/or EZ attenuation</td><td rowspan="5">± with CNV</td></tr>
<tr><td>Recurrent
Presence of SRF with history or signs of resolved episode(s)</td></tr>
<tr><td>Resolved
Absence of SRF</td></tr>
<tr><td rowspan="3">Complex
Total area of RPE alteration >2 DA or multifocal</td><td>Primary
First known episode of SRF</td><td rowspan="2">± Persistent
SRF >6months</td><td rowspan="2">± with outer retinal atrophy
ONL thinning and/or ELM disruption and/or EZ attenuation</td></tr>
<tr><td>Recurrent
Presence of SRF with history or signs of resolved episode(s)</td></tr>
<tr><td>Resolved
Absence of subretinal fluid</td><td></td><td>± with intraretinal fluid</td></tr>
<tr><td>Atypical</td><td>Bullous variant, RPE tear, association with other retinal diseases</td><td></td><td></td></tr>
</table>

+ if fovea is involved (SRF, outer retinal atrophy, PED)

Fig. 6.2 New proposed classification of central serous chorioretinopathy using multimodal imaging. CNV—choroidal neovascularization; DA—disc area; ELM—external limiting membrane; EZ—ellipsoid zone; ONL—outer nuclear layer; PED—pigment epithelial detachment; RPE—retinal pigment epithelium; SRF—subretinal fluid

The major novelty of recent classification of CSCR is a division into simple and complex cases, basing on the extent of RPE alterations. In case they are larger than 2 disc areas (DA) the CSCR is classified as complex [43]. Further divisions include the primary, recurrent or resolved subtypes. The persistent cases are recognized if SRF is present for more than 6 months [43].

This modern division abandons older classification into acute and chronic cases, as it does not reflect complexity of this disease and does not evaluate the possible morphological impairment visible sometimes at the beginning of the course of CSCR.

Diagnostics

As can be seen from the principles of the recent classification, CSCR is a clinical entity that requires multimodal diagnostic approach. Proper diagnostics is also important if referred to different forms of laser treatment applied in that disease.

Fundus Autofluorescence

FAF together with SD-OCT is a simple and non-invasive diagnostic test performed in CSCR at the beginning of diagnostic process. It bases on the autofluorescence of photopigments and lipofuscin detected at the eye fundus. Acute and simple forms

of CSCR with active leakage on FAF present with areas of hypofluorescence in the place corresponding to SRD. After SRD resolution FAF pattern may return to normal or, in chronic forms, present a very characteristic picture. In such cases FAF image reflects RPE alterations and accumulation of not metabolized fluorophores of photoreceptors both at the level of RPE and sensory retina. Such images show areas of hypoautofluorescence referring to RPE deficits, geographic in shape areas of hyperautofluorescence referring to the actual or past presence of SRF ("gravitational tracks") and areas of punctate hyperautofluorescence. In resolved cases devoid of SRF, typical pattern of "gravitational tracks" enables to differentiate CSCR with other retinal disorders, such as dry AMD (Fig. 6.3).

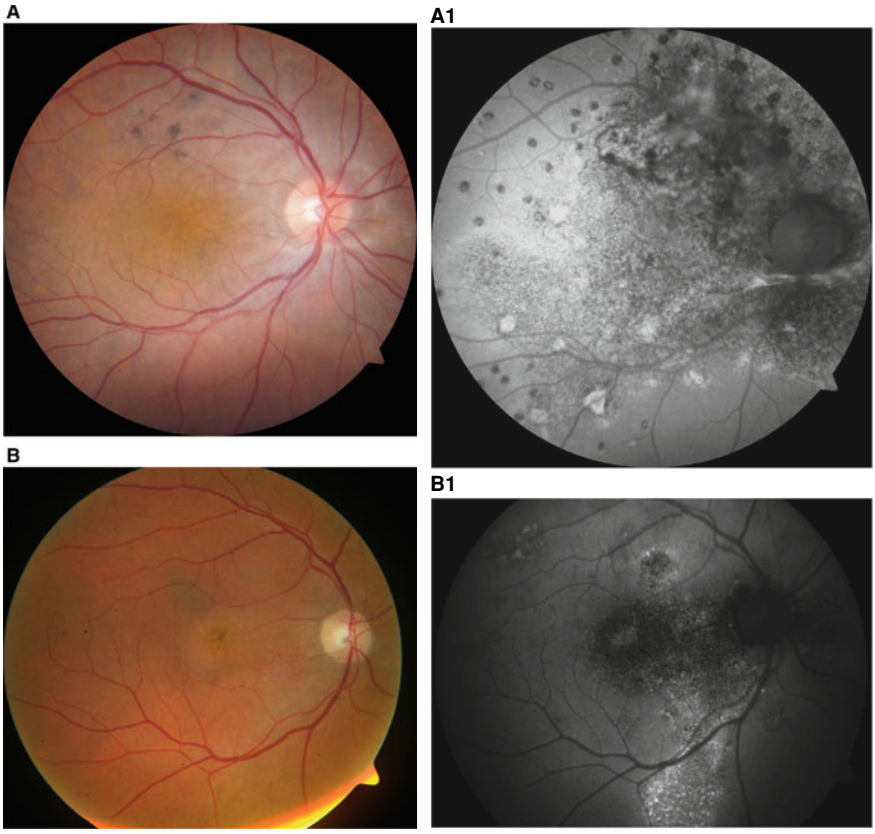

Fig. 6.3 **A**, **B** Color fundus photographs and FAF images of "gravitational tracks" observed in chronic CSCR

SD-OCT/SS-OCT

SD-OCT is a main tool for assessing activity of CSCR in the form of SRF. Typically, the fluid is located under the sensory retina, however in long-standing cases intraretinal cysts are also noted. SRF is a hallmark of active process and is found in both acute and persistent cases.

SD-OCT provides also information on the duration of the disease as well as amount of retinal impairment. Acute cases are characterized by elongation of photoreceptors detached from the RPE and visible at the roof of fluid cavity. In persistent cases photoreceptors are shed and phagoticised by macrophages and visible as debris in the form of hyperreflective granules on the inner side of the fluid cavity. This hyperreflective dots refer to hyperautofluorescent foci on FAF images. In long-standing cases retinal thinning is also typical. That is especially apparent in resolved forms of CSCR, where measurements of the thickness of individual retinal layers are much easier and provide consistent values. Alterations of the RPE present in the form of hyperreflective pigmentary foci in the sensory retina and deficits in the outer retinal layers including the RPE.

The retinal pigment epithelial detachment (PED) is also a quite common finding in CSCR, especially in chronic cases. It can be localized within the SRD or outside the SRD area [44]. Numerous PEDs are characteristic for complicated and atypical forms of CSCR formerly named as diffuse decompensation of the RPE. Cases complicated by CNV present with symptoms typical for different forms of CNV with the predominance of type 1 and mixed type. The SD-OCT maps reflecting the areas of the presence of SRF can be used as guidance for performing subthreshold micropulse laser treatment.

SD-OCT with enhanced depth imaging (EDI) or Swept Source SOCT (SS-SOCT) provide images of the choroid and enable assessment of its thickness and morphology of vascular layers. Increased subfoveal choroidal thickness (SFCT) is a hallmark of pachychoroid disease, including CSCR. Additionally widening of vessels at Haller layer can be observed, as well as pressure of dilated large vessels on the medium size vessels and choriocapillaries [45]. Changes in vascular morphology of the choroid after treatment correspond to efficacy of applied therapy. It has to be remembered though, that choroidal thickness varies according to age, gender and axial length (refractive error). These facts have to be taken into account while assessing potential SFCT increase (Fig. 6.4).

Angio-OCT (OCTA)

Introduction of OCTA to diagnostics of CSCR provided additional information on two important subjects: the presence of macular neovasacularization and disturbance in choroidal perfusion. CNV (MNV) occurs in CSCR as its complication and OCTA

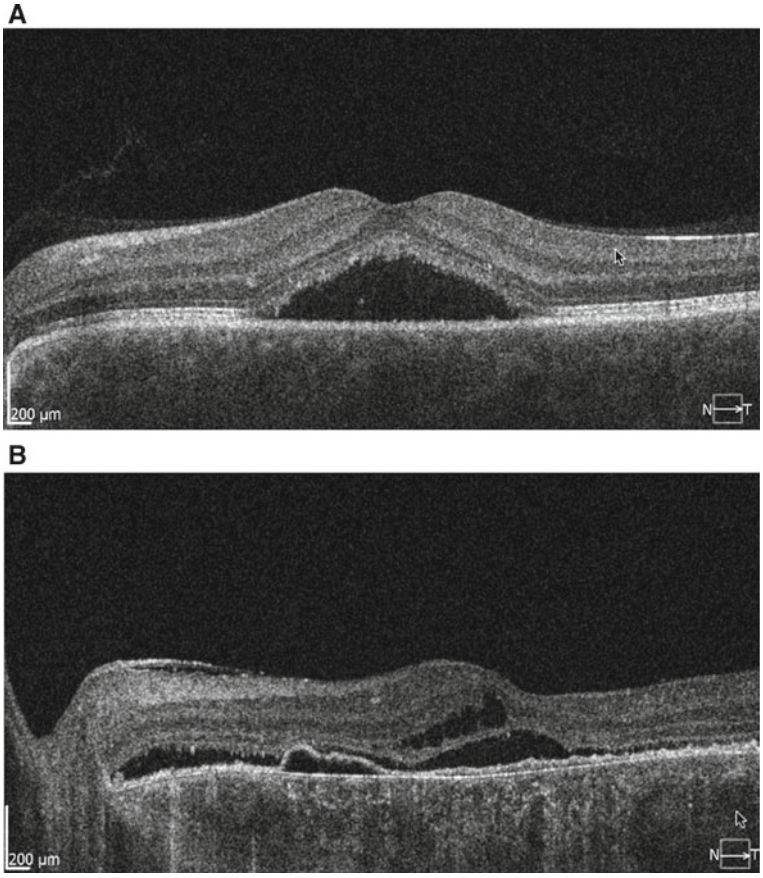

Fig. 6.4 **A**, **B** SD-OCT in acute (**A**) and chronic (**B**) variant of CSCR. Picture **A** presents elongation of photoreceptors and increased retinal thickness. Case on picture **B** shows small amounts of SRF, hyperreflective granules within the fluid cavity, retinal thinning, and cystoid changes in neurosensory retina

proved that this event is not rare (the subject is discussed in detail further on). Angio-OCT shows details of vascular network of CNV and makes diagnosis simpler [46]. CNV occurs in complex cases of CSCR, where the fluorescein angiography images present a variety of symptoms overlapping each other [47]. That hinders the recognition of the leakage and visualization of CNV. Disturbances of perfusion at the level of choriocapillaris are also visible on OCTA images in the course of CSCR. Angio-OCT detects areas of signal void that correspond to impairment of blood flow [48, 49]. Extent of that finding can be referred to visual impairment noted in the course of CSCR (Fig. 6.5).

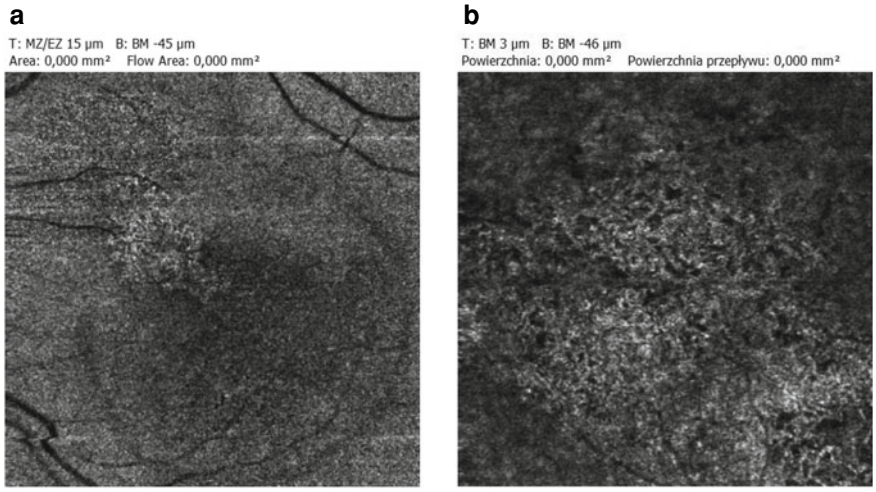

Fig. 6.5 **A**, **B** OCT-angiography of MNV in the course of CSCR (**A**) and in resolved case of CSCR (**B**). Scan **A** presents small CNV located under the RPE at the edge of subretinal detachment. Scan **B** visualizes area of signal void at the level of choriocapillaris referring to impaired perfusion after the episode of CSCR

Fluorescein Angiography (FA)

FA has been a main diagnostic tool for CSCR for a few decades, however nowadays it should be accompanied by other modalities. Simple forms of CSCR on FA present typically as single or several leakage points with just minor changes in the RPE, visible usually as "window defects". Normally leakage sites on FA are visible as pin-point spots of hyperfluorescence that increase in size and intensity with time to adopt the "ink-blot" pattern. However, in around 14% of cases leakage adopts the shape of "smokestack" [50]. In mid- and late phases of angiogram the dye accumulates in the SRD space, what is visible as a diffuse circular hyperfluorescence (pooling). The areas of PED present as sites of intensive dye pooling with round or oval shape. They are clearly visible from the early phases of the angiography and their hyperfluorescence increase in intensity in later phases. Complex variant of CSCR is characterized by multiple leakage points, sometimes very indistinct and similar to symptoms of staining rather than leakage, areas of PED and extensive defects in the RPE of variable depth. The actual activity of the disease has to be evaluated with the help of SD-OCT as on FA the presence of clear leakage and SRF is sometimes difficult to be stated. FA for many years was the most important landmark for qualification of CSCR for classic laser photocoagulation. It is also helpful in diagnosis of choroidal neovascularization that complicates CSCR in solid percentage of cases (Fig. 6.6).

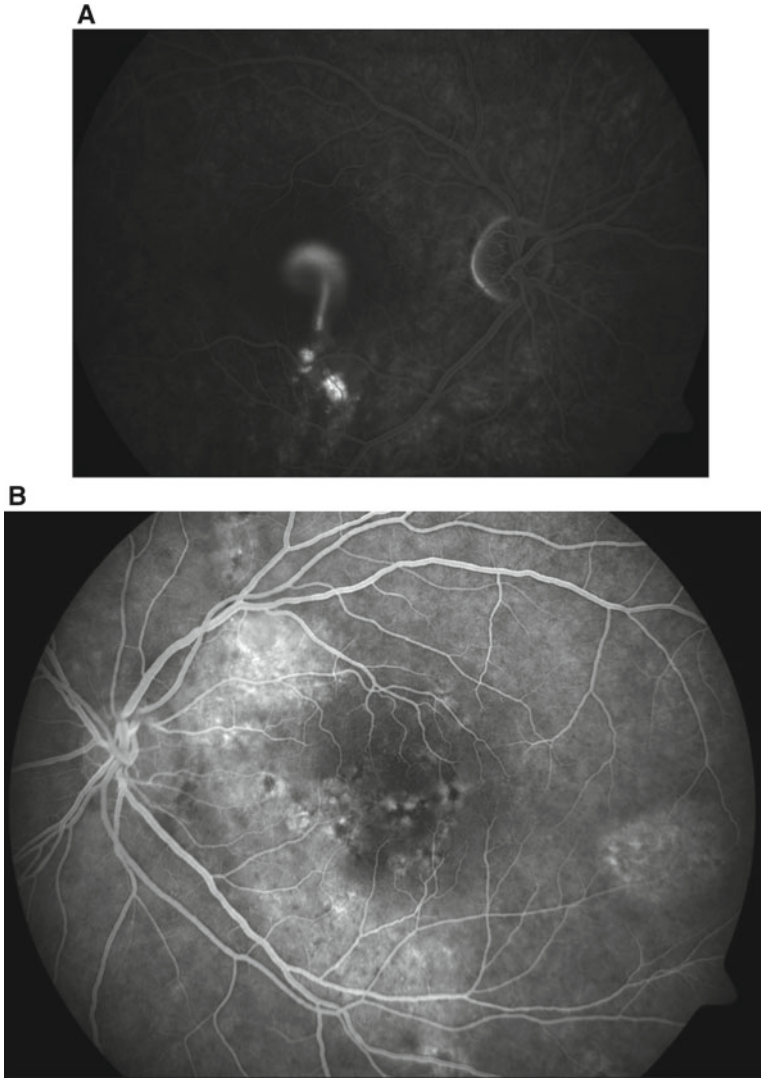

Fig. 6.6 **A**, **B** Fluorescein angiography in acute (**A**) and chronic case of CSCR (**B**). At the photograph **A** a clear leakage in the form of smokestack is visualized. In picture **B** FA reveals a variety of symptoms including areas of minor leakage, staining and window defects. The activity of the disease is difficult to assess without the SD-OCT

Indocyanine Green Angiography (ICGA)

Indocyanine green angiography is not performed in CSCR on standard basis, nevertheless it visualizes choroid, where the source of pathology is located [51]. There are a few features of the ICGA characteristic for CSCR. In early phase altered filling of

choriocapillaris often persisting to late phase is noted. In mid-phase, typical ICGA image shows placoid areas of hyperfluorescence, which represent increased permeability of the choriocapillaris and subsequent leakage of the dye outside the vessel lumen [52]. That symptom might persist in the late phase or vanish due to dye washout. In the mid-phase phase dilatation of large choroidal vessels, which is typical for the pachychoroid spectrum of disorders, is also visible. Visualization of areas of choroidal pathology with the ICGA helps in planning of treatment, especially photodynamic therapy (PDT) performed in chronic cases [53, 54]. In cases complicated by the CNV, ICGA enables to detect and assess the size of neovascular membrane in the form of hyperfluorescent plaque. Nowadays diagnosis of secondary CNV in the course of CSCR is confirmed more often by the OCTA than ICGA, however ICGA still remains the most reliable diagnostic modality in controversial cases (Fig. 6.7).

Differential Diagnosis

Basic variants of CSCR have to be distinguished from clinical entities that present with SRF sometimes with accompanying PED or retinal edema/retinal cystoid changes [55]. CSCR complicated by CNV has to be distinguished from the entities presenting with subretinal neovascularization. Below we present the most important clinical entities that should be distinguished from CSCR with basic indications for diagnostic tests required for such differentiation.

Polipoidal Choroidal Vasculopathy (PCV)

PCV is nowadays considered a form of subretinal neovascularization with branching vascular network originating from the choroid. Generally, it occurs in older age than CSCR and its incidence rate is the same in males and females. PCV usually presents with variety of symptoms, one of which being SRF, but also subretinal hemorrhages, serous or sero-sangineous PEDs and subretinal orange nodules. SD-OCT often shows dome-shaped PED with underlying hyperreflective accumulation with hyporeflective lumen (the polyp). ICGA reveals abnormal vascular network with characteristic hyperfluorescent nodules referred to as polyps. CSCR rarely presents with such flourishing image with intraretinal cysts, hemorrhagic PED or intraretinal lipid deposits [56]. Usually ICGA determines the diagnosis, sometimes with the help of OCTA which also presents anomalous vascular network (Fig. 6.8).

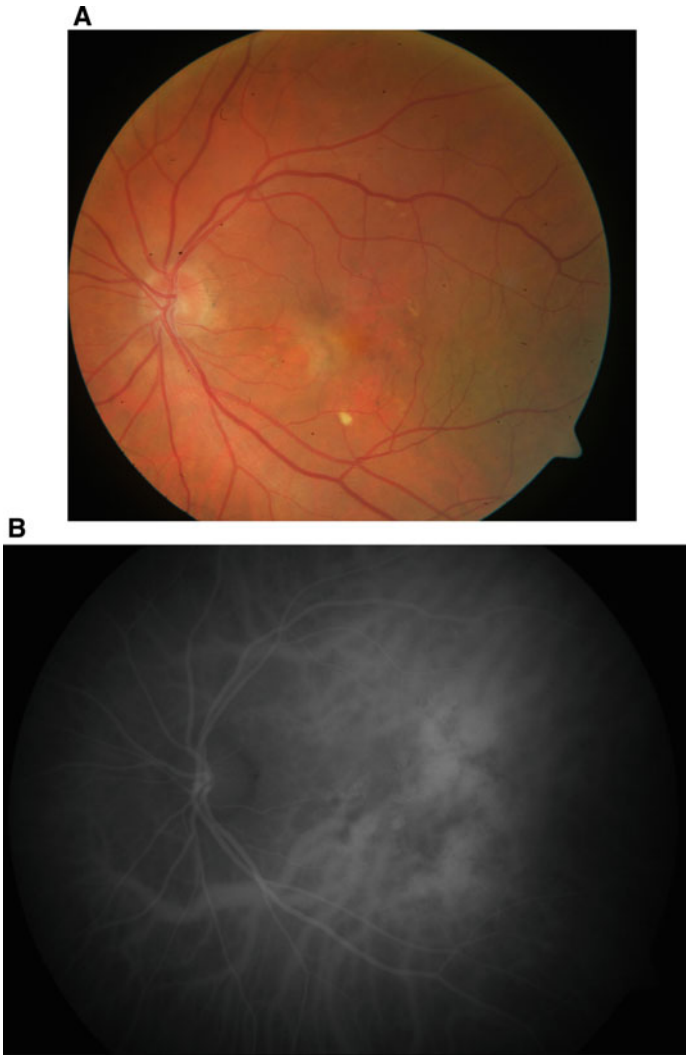

Fig. 6.7 Increase in choroidal permeability in the course of CSCR on ICGA. Color photograph shows chronic form of CSCR with yellowish fibrin deposits. ICGA image presents hyperfluorescent areas corresponding to areas of leakage from choriocapillaris in mid-phase of angiogram

Pachychoroid Neovasculopathy

Pachychoroid neovasculopathy is characterized by the development of choroidal neovascularization over the area of choroidal thickening with dilated vessels of Haller's layer. It was classified as MNV-1 [57]. From definition MNV is not preceded by any episode of CSCR. Final diagnosis is often a question of exclusion of other

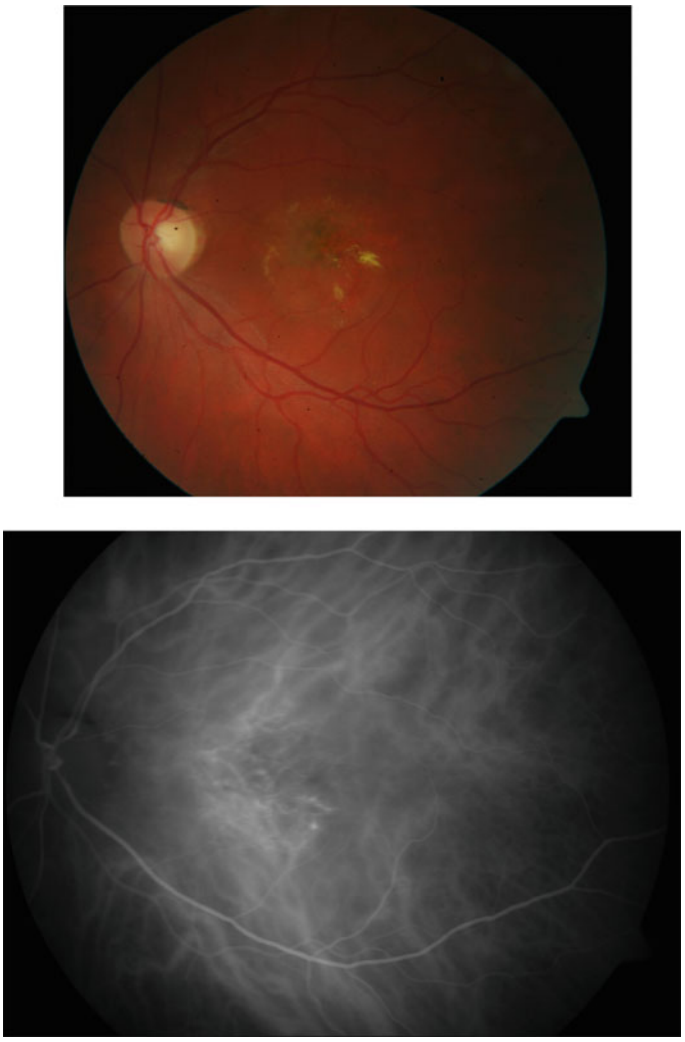

Fig. 6.8 PCV at the ICGA. Mid-phase shows typical hyperfluorescent foci referring to "polyps" as well as branching vascular network

possible entities, especially other diseases presenting with MNV, including AMD, myopia, angioid streaks, PCV etc. Differential diagnosis has to include available diagnostic modalities, such as FA, ICGA, SD-OCT and OCTA [58]. Evaluation of choroidal thickness can provide some indication and narrow search for possible entities.

Age Related Macular Degeneration AMD

Neovascular AMD (nAMD)

SRF is a hallmark of active neovascular AMD and it is also characterized by the presence of MNV. It has to be differentiated from basic variants of CSCR and CSCR complicated by the MNV. Typical forms of CSCR are usually easily distinguished from nAMD as diagnostic tests do not reveal any presence of subretinal neovascularization (SD-OCT, OCTA, FA, ICGA). Nowadays OCTA becomes the first choice, as non-invasive procedure for exclusion of MNV in CSCR cases. Cases of CSCR complicated by MNV are more challenging and usually require more diagnostic tests including angiographies (FA, ICGA). MNV in AMD occurs usually in older patients than MNV in CSCR: mean 75 years versus 57 years, respectively [59, 60]. MNV in nAMD has usually more rapid progression and more complex presentation on FA and SD-OCT, with subretinal hemorrhages, large areas of dye leakage and profound disturbances of retinal architecture. NAMD patients often present with poorer baseline visual acuity compared to CSCR patients. Presence of drusen in the fellow eye indicates AMD. On the other hand, increased choroidal thickness on SD-OCT (SS-OCT) and presence of typical alterations on FAF (gravitational tracks) suggest CSCR as primary disorder.

Non-exudative Form

Non-exudative or dry from of AMD has to be distinguished from resolved forms of CSCR. Both entities present with RPE alterations, such as foci of hyperpigmentation and areas of RPE atrophy, however drusen are the hallmark of AMD. Resolved cases of CSCR present with typical FAF images corresponding to the areas of fluid presence in previous episodes. As with nAMD, the age of CSCR patients is usually significantly lower compared to AMD patients.

High Myopia

High myopia can be complicated by subretinal neovascularization in up to 10% of cases [61]. CSCR complicated by the MNV has to be distinguished from these cases as well. Patients with myopic MNV present with other features typical for that disorder, such as lesser density of the RPE and lacker cracks. Neovascularization in high myopia has usually subacute course and takes limited area. FA reveals moderate leakage without significant enlargement in late phases and SD-OCT rarely shows PEDs or significant amount of SRF [62]. Moreover, choroidal thickness in high myopia is usually significantly lower than in typical CSCR patient.

Angioid Streaks

Angioid streaks are defects in Bruch's membrane typically associated with systemic diseases such as pseudoxathoma elasticum, Paget's disease Ehlers-Danlos syndrome and others [63]. They can be complicated by the CNV and as such have to be differentiated from CSCR [64]. The differential diagnosis is based on fundoscopy, which reveals cracks in Bruch's membrane in a form of bilateral orange-brown bands. FAF helps to visualize RPE defects associated with the presence of Bruch's membrane cracks. The CNV in angioid streaks is located in the projection of the cracks.

Dome Shaped Macula (DSM)

DSM affects patients with high myopia, in whom a large forward macular bulge is observed on SD-OCT. Many of those patients develop neurosensory detachment in the posterior pole, which has to be differentiated from CSCR [65]. Specific accompanying features of SRF in DSM include high myopia, forward protrusion of the macula, subfoveal choroidal thickening with the thinning of remaining choroid [66]. It has to be emphasized that the incidence of CSCR in myopic patients is low due to thin choroid (Fig. 6.9).

Optic Disc Pit (ODP)

ODP is developmental congenital anomaly presenting as focal excavation in the optic disc (typically in inferotemporal aspect). As a consequence of connection between vitreous cavity, subretinal space and subarachnoid space, accumulation of fluid in the retina and under the retina occurs, nevertheless the exact mechanism is not yet determined [67]. Frequently ODP manifests as maculopathy that resembles CSCR [68]. SD-OCT reveals subretinal or/and intraretinal fluid typically on the optic disc side of posterior pole. FA present with the undefined leakage under the retina without focal leaks typical for CSCR. Moreover, grayish pit is observed on fundoscopic examination at the disc, what determines the diagnosis (Fig. 6.10).

Ocular Tumors

Choroidal hemangioma is a benign hamartoma that in circumscribed form presents as subretinal orange lesion with serous retinal detachment. It can be mistaken for CSCR with flat lesions, that do not elevate the RPE much, however typically SD-OCT shows such clear elevation [69–71]. FA does not show a focal leakage typical

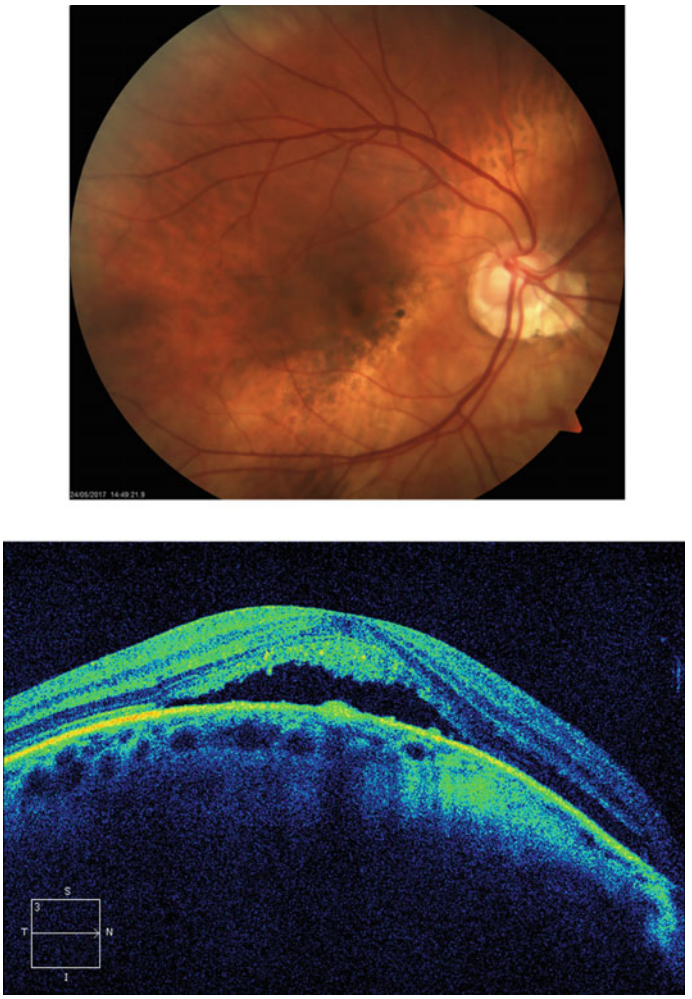

Fig. 6.9 Color fundus photograph and SD-OCT in dome shaped macula. The presence of SRF is observed. Forward protrusion of the posterior pole and retinal thinning typical for high myopia should be noted

for CSCR, but very indistinct leakage over the area of hemangioma. The picture obtained with the ICGA determines diagnosis as it shows vascularity of the tumor in the early phases with characteristic wash-out in later phases. SD-OCT with enhanced depth imaging or SS-OCT show a very significant increase in choroidal thickness, usually at the level of 1000–2000 μm, which is much higher value compared to such measurements in CSCR. The mass of the hemangioma can be also assessed by ocular ultrasonography, which shows acoustic solidity in B-scan.

Choroidal nevi or melanomas can present with subretinal fluid overlying the mass of the tumor and such cases, especially with the light tumor pigmentation,

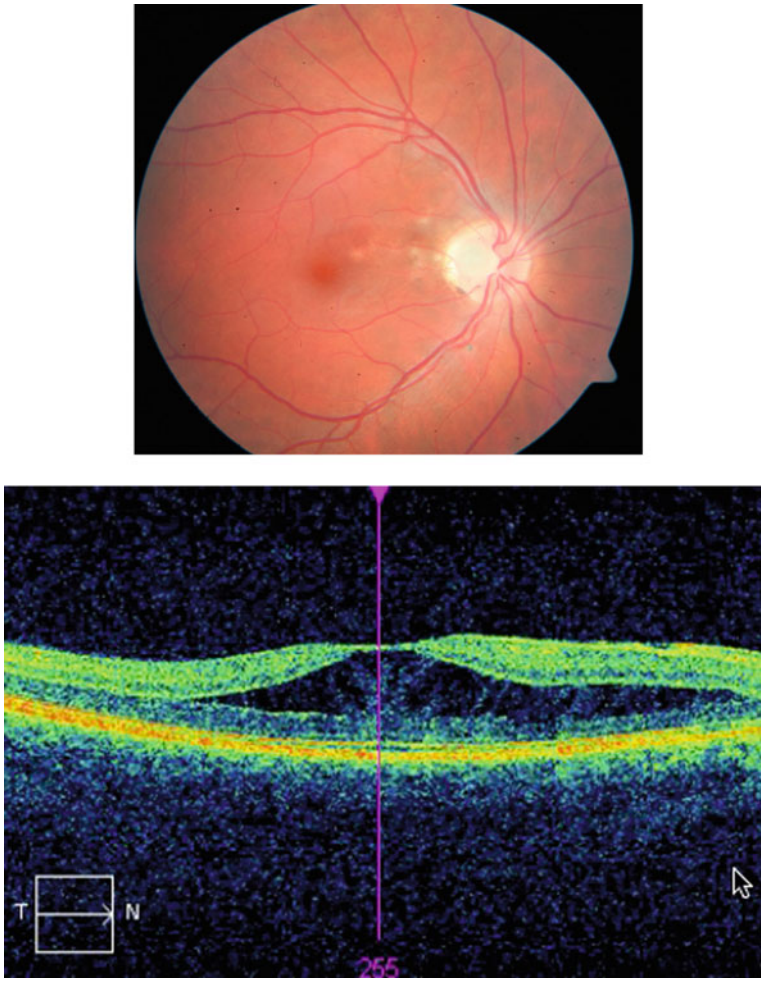

Fig. 6.10 Optic nerve pit. Color fundus photograph shows pale whitening at the temporal part of the optic nerve head corresponding to pit cavity. SD-OCT reveals fluid localized within, not under the sensory retina

can be mistaken for CSCR [72, 73]. In typical cases a pigmentary mass is visible on ophthalmic examination, which triggers the need for prompt diagnostics. SRF is visible on the SD-OCT with characteristic elevation of the RPE [74]. FA does not present focal leakages as in CSCR but "pin-point" leakage in case of melanoma or blockade of fluorescence in the case of nevus [75]. Additionally, ICGA in melanoma is characterized by a mixed pattern of fluorescence in contrary to ink-blot pattern in CSCR. Finally, B-scan ultrasonography reveals low-internal reflectivity of choroidal melanoma and nevus, contrary to lack of echogenicity in CSCR.

Posterior Scleritis

Posterior scleritis is an inflammatory condition which presents as idiopathic entity or accompanies other disorders, such as herpes zoster, herpes simplex, syphilis, tuberculosis, rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, ulcerative colitis or Crohn's disease. Typically, posterior scleritis occurs with SRF, which can be confusing if only local signs are evaluated. However usually the condition is painful, contrary to CSCR. Images of FA and SD-OCT can be similar as in CSCR (focal leaks, SRF, increased choroidal thickness). The diagnosis is determined by evaluation of accompanying symptoms such as proptosis, hyperemia and pain and ultrasound examination with typical T-sign [76, 77].

Vogt-Koyanagi-Harada (VKH) Disease

VKH disease is a granulomatous panuveitis that might be mistaken for CSCR due to a few common features, including increased choroidal thickness, exudative retinal detachment and local leaks on FA [78]. Nevertheless usually the presence of inflammatory symptoms, including anterior chamber and vitreous cells, and optic nerve edema, never noted in classic CSCR, decide on diagnosis. Additionally, some of results of multimodal imaging can be helpful in differential diagnosis. These refer to RPE alterations seen on SD-OCT, such as RPE undulation and folds together with internal limiting membrane (ILM) fluctuation typical for VKH disease while PEDs and RPE hyperplasia occur rather with CSCR [79, 80]. Choroidal hyperpermeability on ICGA is of greater extent in VKH disease compared to CSCR.

Inflammatory Diseases

CSCR is frequently misdiagnosed as posterior uveitis, what leads to use of steroids and exacerbation of the condition [81, 82]. That includes CSCR cases with fibrin in SRF posing as foci of inflammation or complex CSCR cases presenting with subacute multifocal leaks and staining on FA, which is also characteristic for choroiditis. In these patients careful examination in search for the inflammatory symptoms is necessary. The presence of optic nerve leak, vasculitis and vitritis incline to direct diagnostics towards inflammatory diseases [83]. The absence of such features should prevent clinician from hasty administering steroids that worsen the course of CSCR.

Vitelliform Lesions

Vitelliform lesions of genetic background such as Best vitelliform macular dystrophy (BVMD) or adult onset vitelliform macular dystrophy (AVMD), as well as vitelliform lesions observed in the course of AMD, can present with neurosensory detachment involving the macula [84, 85]. Additionally their appearance with yellowish subretinal deposits visible at the fundus may masquerade for CSCR presenting with fibrin in subretinal fluid. Nevertheless, the differential diagnosis is usually quite straightforward. Vitelliform lesions do not present with focal leaks on FA, but typically block fluorescence. Additionally, they present with characteristic hyperautofluorescence on FAF. Moreover, if clear SRF is present in the course of vitelliform lesion, usually hyperreflective subretinal material is also located there, which helps in diagnosis. Challenging cases should also be diagnosed with EOG, which shows decreased Arden ratio in BVMD. The age of the patient should also be taken into consideration, especially in AVMD, which occurs in older individuals [86] (Fig. 6.11).

Macular Edema (ME) Due to Vascular Retinal Diseases

Vascular retinal diseases are rarely mistaken with the CSCR, nevertheless some forms of diabetic macular edema or macular edema secondary to retinal vein occlusion may produce diagnostic difficulties [87, 88]. This ME variants include cases with subretinal fluid, visible on SD-OCT [89]. Usually cystic changes in neurosensory retina are also observed. Diagnosis is based on the presence of characteristic lesions visible in the retinal vascular disorders, including microaneurysm, hard and soft exudates, and hemorrhages.

The Course of CSCR

Most of the cases of CSCR resolve spontaneously within a few months from disease onset. Daruich et al. report 84% of cases resolving without significant deficit by 6 months [90]. This type of scenario is typical for acute or simple cases, characterized by just one or two leakage points on FA and minor RPE alterations visible on FAF. To the contrary, complex cases that present with multiple leakage points on FA, areas of PED, significant deficits in the RPE and often retinal thinning, persist and sustain a therapeutic problem. Progressing atrophy of the outer retinal layers leads to significant visual impairment noted in cases lasting for years rather than months.

Breukink et al. report mean deficit in BCVA as 0.16 logMAR after mean 10 years of the persisting CSCR [91]. Gawęcki et al. noted BCVA drop to the level of 0.63 Snellen after mean 1.5 years of persisting CSCR [37]. Mrejen et al. analyzed a large sample of 217 eyes with CSCR and the mean follow up of 11 years. In that group

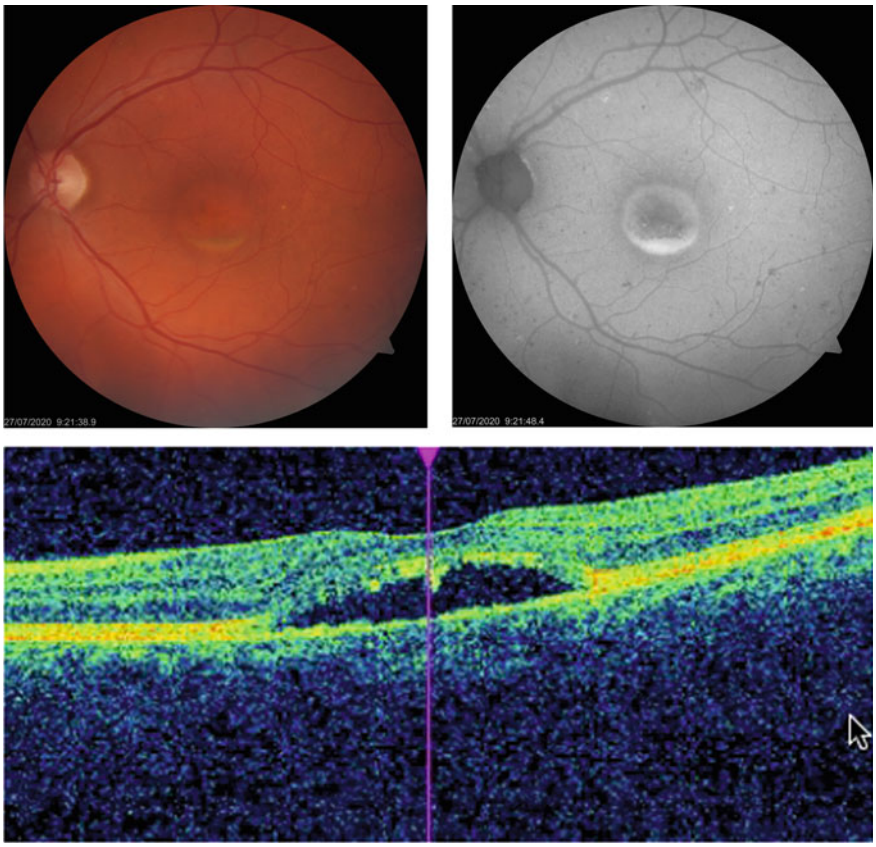

Fig. 6.11 Color photograph, fundus autofluorescence and SD-OCT image of the patients diagnosed with AVMD after a few years of observation and resorption of subretinal deposits. The case might be mistaken for CSCR

as much as 12.8% had BCVA $\leq$ 20/200 in both eyes, what equals a legal blindness [92]. The course of such long-standing cases usually involves temporal remissions and recurrences. These occur in CSCR in as much as 50% of cases [93]. So far there has not been determined what causes a relapse of that disease and what could possible prevent that.

Long-standing cases have more chances to be complicated by the MNV, that occurs usually in patients later in the sixth decade of life [59]. The reports from the studies assessing the incidence of MNV in CSCR vary significantly in numbers and depend very much on the diagnostic method used for detection of subretinal neovascularization. Using angio-OCT as a diagnostic method led to detection of CNV in as much as 39.2% of chronic cases [94]. With the use of classic methods, such as FA and SD-OCT, reported numbers are between 2 and 9% [2, 95]. Presence of MNV in the course of CSCR requires differential diagnostics with other diseases

complicated by subretinal neovascularization, mainly with nAMD and PCV. It has to be remembered that nAMD and PCV usually affects older patients. The mean age of occurrence of MNV in that disease is estimated at 75 years [60].

Laser Treatment of CSCR

Laser Retinal Photocoagulation - LPC

Classic laser photocoagulation has been used in the treatment of CSCR for many years, however mechanism of its action was not fully understood. It was speculated, that laser photocoagulation stimulates healing responses in the RPE and improves its function as a pump, thus leading to elimination of SRF [96].

Nevertheless, recommendations for LPC in CSCR are not always clear and vary among researchers. They have been discussed constantly since the late 1960-ties with first recommendations formulated by Gass in 1974 [97]. Generally, LPC was recommended for the selected cases with a clear leakage point located in a safe distance from the foveal center—minimum of 375–500 μm [98, 99]. Additionally, as the endpoint of classic LPC is a retinal scar that can result in functional scotoma, such treatment was not undertaken in cases, where spontaneous remission of symptoms was expected. That referred to first episodes of CSCR, when observation was recommended for at least 3 months after disease onset. If the leakage point was located within 500 μm from the fovea center, 6 months of observation was recommended [100]. Prompt treatment was indicated only in patients who wanted to speed up resolution of symptoms due to occupational reasons or in case of vision loss in the other eye [100]. A few months waiting time was also abandoned or limited in recurrent cases, especially if the visual impairment was noted after previous episodes. It has been proved though, that application of the LPC shortens the course of the disease but does not influence the final visual acuity, which is the same in patients treated and observed [101]. Similar conclusions were drawn with application of classic continuous wave laser for the leakage point the subthreshold mode, but in acute cases [102].

Relevance of application of the LPC to location of the leakage point significantly narrowed the number of cases eligible for that procedure. In fact, using modern CSCR classification, we could say that only simple cases where eligible for LPC. The location of the leakage had to be determined by FA, which was a basic mandatory diagnostic test before performing that treatment. Large number of patients with the central location of the leakage spot had to be excluded. Approach to complex cases with multiple subacute leakage, numerous areas of PED and RPE alterations varied among the clinicians. Some authors treated such clinical picture as indication for LPC [100]. Nowadays complex and usually longstanding cases are more often treated with PDT or non-damaging lasers rather than photocoagulated (Fig. 6.12).

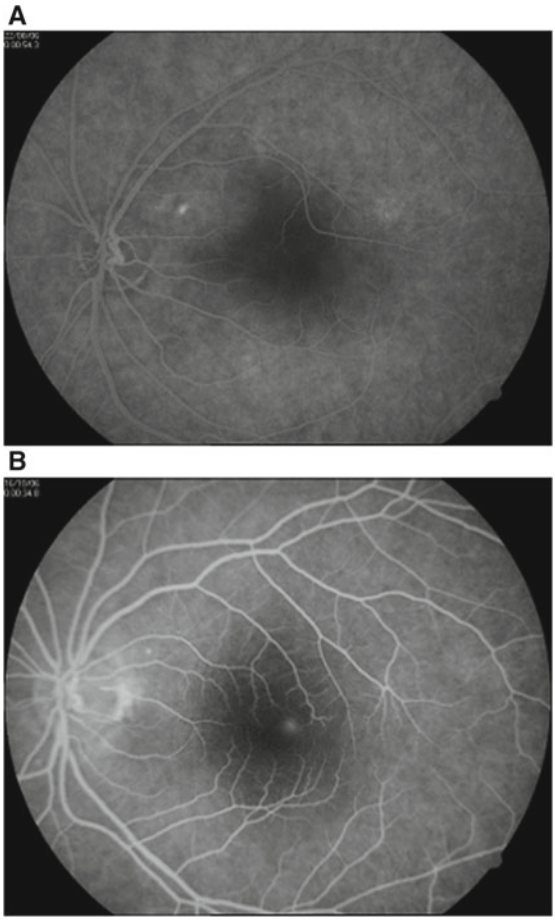

Fig. 6.12 A leakage point in CSCR at photograph **A** and **B** from fluorescein angiography. Patient from the photograph **A** is eligible for LPC as the leakage point is distant from the foveal center. At the photo **B** the leakage point is located in the center of the macula, so LPC is not possible

Technique

Ciardella et al. suggest the spot size slightly larger than the leaking point, usually 200 μm. In most cases several spots are needed to achieve the effect [100]. Laser power titration is recommended (typically starting from 100 mW) to obtain slight gray discoloration of the retina, but not the clear white reaction. Impact duration is usually set at 0.2–0.3 s.

Conventional LPC for the leakage spot is carried out with the use of contact lasers lenses for the posterior pole, such as Area Centralis by Volk or Reicher-Mainster focal-grid by Ocular.

Complications

Complications of the LPC results from the use of inadequate laser parameters or placement of the laser spot too close to the fovea. Using high laser power parameters and relatively small spot diameter, ex. 50 μm, may result in damage to the Bruch's membrane and subsequent development of subretinal neovascularization. This complication, although not frequent, leads to a significant visual impairment. As it was emphasized before, the endpoint of the conventional laser treatment is retinal scar. Typically, those scars enlarge with time, thus producing larger scotomas in the visual field. If additionally, laser burn is placed close to the foveal center, (ex. within 500 μm), the enlarged scar might cause not only visual field defect, but also decrease in visual acuity.

Current Position of LPC in the Treatment of CSCR

LPC is still in use for the treatment of CSCR today, however we have to keep our reservation to patients' eligibility for the treatment. With the accessibility to non-damaging retinal therapies, it is usually not a first choice for clinicians. Besides, many CSCR cases with central location of the leakage are not candidates for such treatment. Another group of patients who can hardly benefit from such treatment are individuals with complex forms of CSCR involving large areas of posterior pole and presenting without clear leakage points. In such cases usually treatment modalities, which enable to cover the whole area of detected pathology are chosen. In the PDT procedure usually the whole area of increased permeability of choriocapillaris (detected at ICGA) is covered with one wide round spot. On the other hand, with the use of subthreshold micropulse laser (SML) treatment we try to mobilize the large number of RPE cells thus the panmacular protocol is employed. Interestingly, before the onset of PDT and SMPLT, some authors suggested covering the whole area of RPE decompensation with the spots of GRID LPC, despite lack of proof for efficacy of such treatment in clinical trials [100].

Non-damaging Laser Treatment in CSCR

Subthreshold Micropulse Laser (SML) Treatment

SML is truly subthreshold and truly non-damaging laser therapy that does not leave any traces in the retina. Due to its low cost and wide safety margin, it is frequently used to treat CSCR as the first line modality both in acute and chronic cases (simple/complex).

Laser Wavelengths

SML is a form of laser application that can be employed with different laser wavelengths. Nowadays the most popular is 577 nm, but 810 nm is used with success also and less often 532 nm. So far there are no studies that compare directly the efficacy of application of different laser wavelengths in CSCR. Theoretical background backs both 577 and 810 nm with 810 nm having wider safety margin [103].

Technique

The procedure is conducted under topical anesthesia, which is required as it is conducted through the contact laser lens. Otherwise, the anesthetic is not necessary due to the lack of any painful reaction from the retina. The lenses used for the procedure are typical laser contact lenses used for focal or GRID photocoagulation, including Area Centralis by Volk or Reichert-Mainster focal-grid from Ocular. As in the other clinical entities involving retinal edema, SML is applied to the retina in confluent way without spacing between laser spots. Nevertheless, the preferred extend of treatment differs between the clinicians.

The extent of SML in the treatment of CSCR is applied in three different ways:

1. **Minimal Treatment**
   The form of laser application based on angiographical image (FA or ICGA). Areas of dye leakage are treated as active sites and covered with laser spots. This form of treatment involves the smallest number of laser impacts.
2. **SD-OCT based treatment**
   The form of laser application based on the SD-OCT imaging. The whole area of SRF presence is treated. The number of spots is usually between minimal and panmacular treatment.
3. **Panmacular treatment**
   The idea of this form of therapy is mobilization of the large number of RPE cells. The laser session includes the whole area of posterior pole within temporal vascular arcades. This form of treatment requires the largest number of laser spots and is preferred for the chronic/complex variants of the disease.

Possible treatment protocols have been provided by the LIGHT society [104] (Table 6.1).

Adjusting SML power parameters remains a subject of controversy. LIGHT society recommends treatment with fixed low power parameters, while other researchers and equipment providers recommend power titration. It has to be stated though, that subthreshold micropulse laser procedures are generally safe with both approaches and cases of overtreatment are reported very seldom. SML can be repeated without any damage to the retina. The schedule of retreatment in CSCR is still discussed. Sometimes the retreatment schedule is adapted from the old ETDRS protocols and in case of insufficient response, the following laser session is performed after the period of 3 months. Other researchers recommend patient's evaluation in

Table 6.1 Presents examples of SML 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	1400	200	0.15	Panmacular
810	1700	500	0.3	Panmacular

SD-OCT at 6 weeks after treatment. In case of lack of response or worsening, the second session of SML is to be performed at this control visit. In case of partial response (reduction of SRF and CRT) the following control visit with assessment with SD-OCT is scheduled at another 6 weeks' time and decision of supplementary treatment is made than [105].

SML in Chronic CSCR (cCSCR)

Typically, chronic forms of CSCR are treated with SML. Numerous research studies provide good morphological results with moderate functional improvement. Most of the published studies employ 577 nm SML, less 810 nm and just a few 532 nm laser [106] (Table 6.2).

Evaluation of effects of SML in cCSCR has to take into account resorption of SRF and BCVA improvement. Most of the studies report relatively high percentages of SRF resorption, usually between 40 and 80%, but only moderate BCVA improvement of about one line on the Snellen chart [112–115]. Complete treatment failure of SML in CSCR is reported quite seldom. For example, study by Sousa et al. with 532 micropulse did not show any significant improvement in mean values of BCVA or SD-OCT [116]. Nevertheless, even in that study some patients showed SRF resolution or visual gain.

Metaanalysis of effects of clinical trials with SML in cCSCR performed by Scholz et al. in 2017 provides the mean number of ETDRS letters improvement at 6.34 (range −15 to +20) [117]. This relatively low number and wide range of visual gains reported in different studies, naturally incline to consider the timing of SML application, expecting better functional results with early treatment (Fig. 6.13).

SML in Acute CSCR (aCSCR)

SML is rarely reported in short-standing and simple variants of CSCR, nevertheless if applied, provides usually better results than in chronic forms. The results of the

Table 6.2 Provides results of SML treatment of cCSCR in studies involving at least 30 cases

Study	Laser wavelength	Mean follow up	Duration of CSCR	No of patients	% of cases with complete SRF resolution	BCVA improvement (logMAR)	No of treatments
Scholz et al. [107]	577	5 months	Longer than 6 weeks	38	24	Mean 0.06	–
Gawęcki et al. [108]	577	6 months	Longer than 4 months	51	70,6	Mean 0.08	1–2
Arsan et al. [109]	577	Minimum 12 months Median follow-up: 17.82	Longer than 3 months	39	92.3	Median: 0.4	1–4
Altinel et al. [110]	577	12 months	Minimum 4 months	39	35.9	Improvement by ≥2 lines in 25.6% of patients; no significant improvement in mean BCVA value for the whole group	Median 3
Isik et al. [111]	577	11.4	Longer than 3 months	58	67.2	Mean 0.29–0.38 at the last follow up	Not reported

studies on application of SML in acute CSCR with the number of patients exceeding 30 are presented in Table 6.3.

Gawecki et al. showed better BCVA improvement with early application of SML in CSCR (128). Arora et al. proved superiority of SML treatment in simple acute cases of CSCR over observation referring to BCVA and contrast sensitivity [125]. On the other hand, Zhou et al. did not confirm superiority of SML over conventional laser in respect to BCVA and morphological outcome, however the study included only the cases with the active leakage distant from the foveal center [127]. Authors conclude that non-damaging character of SML makes it an important therapeutic option for acute CSCR. Similar conclusions are provided by Sun et al. who proved non-inferiority of SML to conventional subthreshold laser [128]. Authors emphasize, that SML should be a choice for patients with central location of leak on FA.

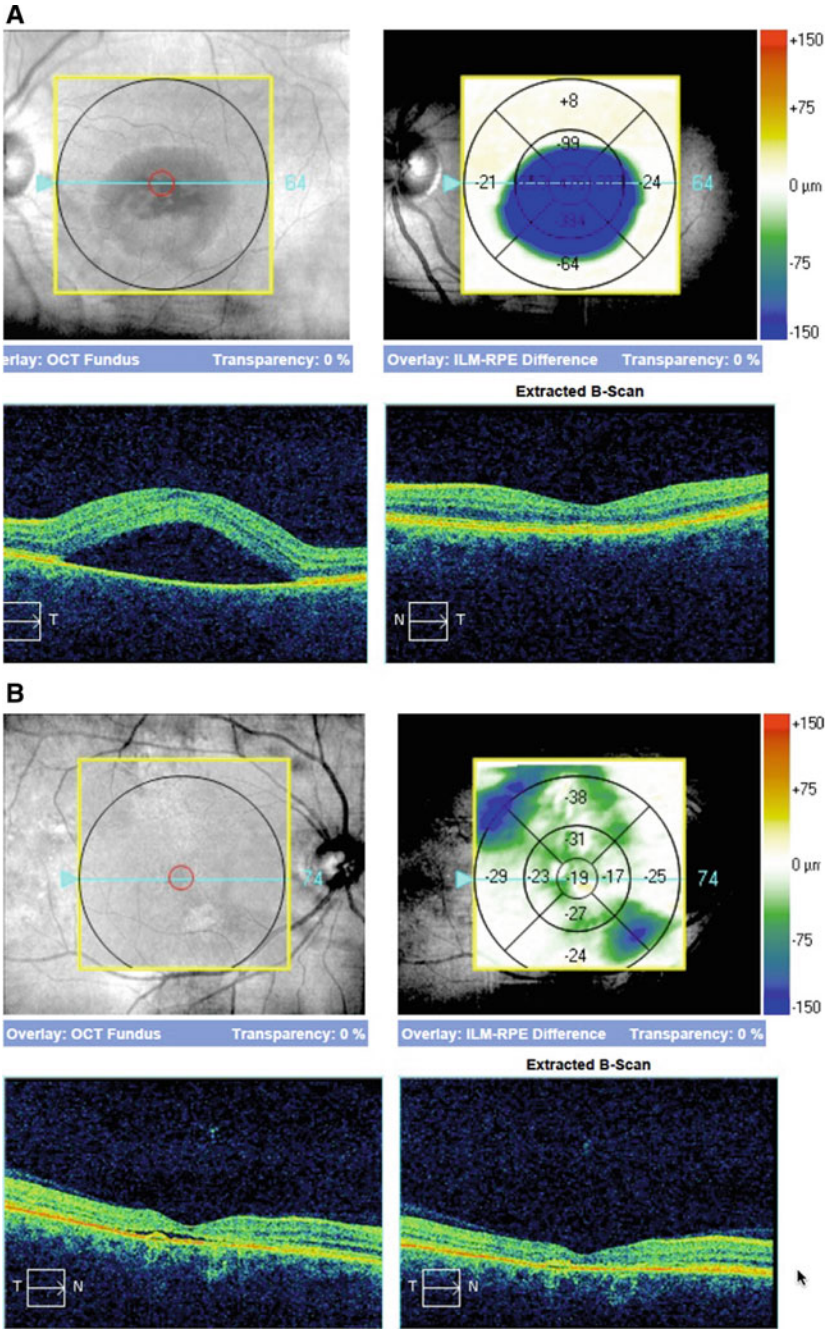

Fig. 6.13 Effective SML treatment in chronic form of CSCR on SD-OCT scans. Scan **A** shows complete resorption of SRF in short-standing form of CSCR. No apparent disturbances in retinal morphology are observed after resorption of fluid. Scan **B** presents successful treatment in chronic form of CSCR lasting for a few years. Significant retinal thinning can be observed

Table 6.3 SMPLT treatment of acute CSCR in the studies of at least 30 eyes

Study	Laser wavelength/design	Duration of CSCR	Follow up	No of patients	% of SRF resolution/reduction	BCVA improvement (logMAR)/letters	No of treatments
Gawecki et al. [118]	SMPLT 577	3 weeks–6 months	3–6 months	32	81.25	Mean 0.15 Better improvement with early application of SML	1–2
Arora et al. [119]	SMPLT 810	Less than 2 months, single leak on FA	6 months	34	Mean Height of SRF at the follow up: 15.76 μm	Mean 0.56	1
	Observation			34	Mean Height of SRF at the follow up: 71.65 μm	Mean 0.46	
Zhou et al. [120]	SML 577	Less than 6 months, active leakage distant from the foveal center—more than 300 μm	6 months	55	85.5	0.32	1–2
	577—Continuous wave			55	92.7	0.39	1–2

(continued)

Table 6.3 (continued)

Study	Laser wavelength/design	Duration of CSCR	Follow up	No of patients	% of SRF resolution/reduction	BCVA improvement (logMAR)/letters	No of treatments
Zhou et al. [121]	SML 577 50% threshold power		3 months	30	83.3	0.32	1
	SML 577 25% threshold power			24	54.2	0.13	1
Sun et al. [122]	SML 577	Less than 6 months, limited leakage point in ETDRS ring 2 or 3 (outside the center)	3 months	44	63.63	6.23 ETDRS letters	1
	Conventional threshold 577			44	81.82	6.61 ETDRS letters	1
Long et al. [123]	SML 577 nm	Less than 3 months	6 months	16	NS	Change from 0.48 to 0.01	Mean 2
	Observation			18	NS	Change from 0.56 to 0.09	0

Local Complications

So far there are no reports that would indicate retinal damage after properly performed SML. Single reports refer to overtreatment due to the use of too high laser power parameters and resulting in increase in the amount of SRF and defects in the RPE visible in FA [124].

SML Position in the Treatment of CSCR

The position of SML in the treatment of CSCR is yet to be determined. Its low cost and favorable results places it in the front of other treatments, especially in simple variants of the disease. Its superiority over PDT in the treatment of complex cases is questionable and needs to be analyzed in the further studies.

Other Subthreshold Lasers

Similar philosophy of laser application as in SML but with different pulse duration (15 ms) is employed in PASCAL laser with end-point management software (EpM). So far there are just two available studies analyzing efficacy of that form of treatment in CSCR of duration longer than 4 months [125, 126].

Authors employed the following parameters: spot diameter 200 μm, spacing 0.25, pulse duration 15 ms and 30% of titration resulting power. Mean BCVA improvement at 6 months was 12 ETDRS letters and total resorption of SRF was noted in 75% of patients; 44% of eyes required second EpM session at 3 months. The second study reported resolution of SRF in 53.8% at 12 months and mean BCVA improvement by 4.9 ETDRS letters.

Microsecond and nanosecond lasers were also tried in the treatment of CSCR, however so far published reports are very scarce. It has to be emphasized, that both of these treatments target melanosomes of the RPE causing microbubble formation at these granula and subsequent selective cell disruption. The healing process stimulates proliferation and migration of new RPE cells, which substitute the damaged ones and provide better metabolism at the irradiated sites [127, 128]. The whole process is often called retinal rejuvenation.

Selective retina therapy (SRT) involves Q-switched neodymium-doped yttrium lithium fluoride 527 nm microsecond laser. Results of this form of treatment of CSCR were reported in several papers, with larger trials emerging just recently. Results of the studies with more than 20 eyes are presented in Table 6.4.

Table 6.4 Studies on PDT in chronic CSCR including more than 50 patients and at least 12 months of the follow up

Study	PDT strategy	No of patients	BCVA improvement (logMAR)	% of SRF resolution	No of recurrences	No of treatments
Ruiz-Del-Tiempo et al. [145]	Standard	75	+0.23	93.7	0	1–2
Noh et al. [146]	Standard	52	Not reported	100	0	1
Moreno et al. [147]	Half dose	72	+0.16	100	2	1
Fujita et al. [148]	Half dose	204	+0.12	89.2	12 (5%)	1–2
Haga et al. [149]	Half dose	79	+0.13	98–100	10 (12%)	1–2
Lai et al. [150]	Half dose	136	+0.21	97.1	9 (6.6%)	1–2
Tseng et al. [151]	Half dose	56	+0.23	100	4 (6%)	1–2

Study	Duration of CSCR	No of eyes	Morphological results	Functional results (mean values)
Elsner et al. [129]	Acute cases <3 months	27	Total resorption of SRF in 100% at 3 months	Significant BCVA improvement from 20/40 to 20/20 at 3 months
Park et al. [130]	Longer than 3 months	50	Total resorption of SRF in 74% at 3 months. Mean reduction of CRT from 341.4 μm to 236 μm, significant	Significant Improvement of BCVA from 0.44 logMAR to 0.37 logMAR at 3 months
Kyo et al. [131]	Acute and chronic	77	Significant CRT reduction from 316 to 218 μm and complete resolution of SRF in 59.7% at six months	Significant BCVA improvement from 0.08 to 0.04 logMAR at 6 months
Lee et al. [132]	3 months and longer	44, 22—SRT group and 22 control group	Total resolution of SRF at 3 months in 70.3% of eyes. Significantly higher percentage of SRF resolution in SRT group at 6 weeks (63.6% vs. 23.8%)	Insignificant improvement of BCVA at 6 weeks in both groups, but significant improvement of contrast sensitivity in SRT group

(continued)

(continued)

Study	Duration of CSCR	No of eyes	Morphological results	Functional results (mean values)
Jeon et al. [133]	Chronic, resistant to bevacizumab	22	Complete resorption of SRF in 81.8% eyes at 12 months; significant CRT reduction from 323 to 221.5 μm	Insignificant BCVA improvement from 0.49 to 0.43 logMAR at 12 months
Kim et al. [134]	3 months and longer	137	Complete resolution of SRF in 52.6% at 3 months and 90.5% at 6 months; CRT reduction from 347.67 to 173.42 μm at 6 months	BCVA significant improvement from 0.41 logMAR to 0.33 logMAR at 6 months

As can be seen from the above table, application of SRT in chronic type of CSCR provides results similar to those observed after SMPLT. Morphological improvement is noted in majority of cases, but functional gains are either statistically insignificant or just moderate in numbers.

It has to be emphasized that neodymium-doped yttrium lithium fluoride (Nd:YLF) laser is not yet commercially available in many countries, what limits its use.

Similar problems emerge with evaluation of efficacy of nanosecond lasers in the treatment of CSCR. The Ellex 2RT nanosecond laser device is a Q-switched, green Nd:YAG laser (532 nm) with a pulse duration of 3 ns and a spot size of 400 μm with a speckled-beam profile. Its mechanism of action is similar to SRT with shorter pulse duration. 2-RT laser is performed in the private sector of ophthalmological medicine only. This fact resulted in just a couple of papers analyzing that subject. Large study of Kaymak et al. (56 eyes) analyzed effects of 2-RT laser treatment in CSCR with different RPE extent of damage [135]. Resolution of SRF at 12 months was observed in 100% of eyes with minor RPE damage at baseline, but only 42.9% of eyes with significant RPE impairment. Functional effect with improvement of contrast sensitivity was also better in eyes with mild and moderate RPE alterations. The second study by Funk et al. reported 91% efficacy of resolution after application of 2-RT laser in patients without RPE atrophy [136]. Nevertheless, these results need to be confirmed in randomized and controlled studies.

Photodynamic Therapy

Photodynamic therapy has quite long history in the treatment of CSCR, however it was first applied in the treatment of nAMD. The main principle of that therapy is the employment of photosensitizer, in this case verteporfin, which after long irradiation with low power laser light of 689 nm produces reactive oxygen species (ROS) that react with blood vessel endothelial cells. As a result of anti-inflammatory response, temporary thrombosis of choriocapillaris occurs, what reduces choriocapillaries congestion and vascular hyperpermeability. Nassisi et al. with the use of angio-OCT showed the significant reduction in the density of choriocapillaris at 1 week after half-dose PDT procedure in CSCR, returning to normal at 1 month after treatment [137]. Similar transient effect in choroidal vasculature but with significant reduction in choroidal thickness at 1 month were also noted by Alovisi et al. [138]. Longer observation by Flores-Moreno et al. showed significant decrease in the choroidal thickness, particularly in the choriocapillaris plus Sattler layer at 3 and 6 months after half fluence PDT [139]. Standard parameters used in PDT in nAMD treatment include dose of 50 J/cm^2, irradiance of 600 mW/cm^2 of 689 nm light over 83 s. These original parameters were first tried with success for the treatment of CSCR but due to rare, but significant complications that developed, were reduced by half. As PDT is available at the medical market for about 20 years now, many studies on its efficacy in the treatment of CSCR have been conducted. Most of them include chronic or long-lasting cases however PDT was also tried with acute forms of CSCR.

PDT in the Treatment of Chronic CSCR

Results of this treatment can be analyzed according to BCVA improvement, resorption of SRF and percentage of recurrences. Results of the studies for cCSCR involving more than 50 patients and at least 12-months of the follow up are provided in the Table 6.4. Morphological improvement defined as resorption of SRF is reported in majority of cases of chronic CSCR. In fact, all of the studies reported resorption of SRF in more than 70% of cases with most of the studies declaring such efficacy between 90 and 100%. Again, these numbers are given in each of the treatment strategies applied. It has to be noted though, that consequently only moderate BCVA improvement is reported, usually between 0.1 and 0.2 logMAR. Available studies analyzing the strategy with half-fluence PDT for chronic CSCR involved lesser number of participants, but provided similar results as with the other two strategies [140–143]. Interesting comparative analysis of results of PDT with different fluence values (30% vs. 40% vs. 50%) was provided recently by Park et al. [144]. The largest BCVA improvement (+0.21 logMAR), highest percentage of SRF resolution (100%) and lack of recurrences during 12 months observation period was achieved with 50%

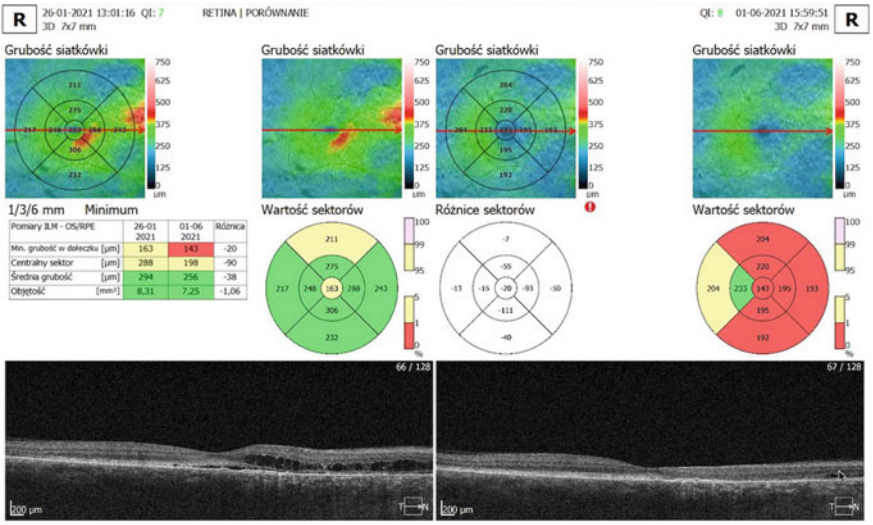

Fig. 6.14 Effects of PDT treatment in chronic case of CSCR lasting 2 years (SD-OCT scans). Despite full resolution of SRF and retinal edema, significant retinal thinning is noted

fluence. Example of successful PDT treatment of chronic CSCR is presented in (Fig. 6.14).

PDT in the Treatment of Acute CSCR

Acute CSCR is not treated with PDT as frequently as chronic form of that disease. Recent randomized clinical trial by Misotten et al. analyzed effects of prompt PDT applied within a week after presentation versus 3 months observation [152]. Patients with persistent leak at any 3 months during 12 months of the follow up, were the subject to PDT. The BCVA at 12 months in both groups were not different with less PDT treatments in observation group. Nevertheless, BCVA improvement was faster in the prompt PDT cohort. Other studies analyzing effects of half-dose PDT versus placebo for CSCR lasting <3 months favor therapeutic intervention [153–155]. Metanalysis of results of these 3 studies proves better morphological and functional results of treated patients at 12 months [156].

Technique

Infusion of the desired dose of verteporfin is performed over 10 min. About 15 min after start of infusion the laser is delivered through a Reichert-Mainster PDT contact

lens, that enables maximum diameter of irradiated area at around 8000 μm. Laser application time is the same for all PDT procedures: 83 s. The procedure is conducted in a dim slit lamp light and does not produce any pain. The extent of PDT in CSCR (the irradiation area) is planned on the basis of angiographic examinations, preferable ICGA, rarely only FA [157].

Nowadays two strategies are preferred for the treatment of CSCR: half dose (3 mg/m^2) or half fluence (25 J/cm^2) with the same duration of exposure.

Complications

Complications after PDT are rare and occur with the employment of any treatment protocol: standard protocol as used in the treatment of nAMD or protocols with reduced laser parameters or reduced verteporfin dose. These include consequently two main types of lesions: RPE alterations (usually atrophy, sometimes hyperplasia or RPE rip) [146, 150, 158] and development of CNV [147, 151, 159]. Listed complications are reported in just a few studies and with minor frequency. The largest percentage of complications was reported by Moreno et al. with the use of standard protocol and Lai et al. for half dose PDT. The first study referred to 2 cases of CNV and 9 cases of RPE hyperplasia noted in the cohort of 72 patients. The other one reported 5 cases of RPE atrophy and 1 case of RPE rip in the group of 136 treated patients. For half fluence PDT complications included just one case of CNV for a group of 32 individuals [160].

The main side effect of PDT is increased photosensitivity of the skin due to administration of verteporfin. That is why patients after this procedure are advised to wear clothes with full skin coverage, hats and sunglasses for 3–5 days. Other side effects occurring with minor frequency include irritation of eyelids, headache, nausea or back/joint pain. Transient decrease in visual acuity is reported in 1–4% and is less frequent with reduced exposure parameters.

PDT Versus SML in the Treatment of CSCR

Most of the published studies comparing efficacy of PDT versus SML in the treatment of CSCR, based mostly on chronic cases, do not find statistically significant difference neither in morphological or functional outcome. Just one large PLACE trial favors PDT, especially in SRF resolution, however not in quality-of-life improvement.

The Table 6.5 provides a list of comparative studies on PDT versus SML in the treatment of chronic CSCR including at least 30 patients.

We believe, that further research is needed to determine which treatment modality is more suitable for CSCR variants according to a classification based on multimodal imaging and baseline RPE deficits. Poor BCVA improvements in chronic cases

Table 6.5 A list of comparative studies on PDT versus SML in the treatment of chronic CSCR including at least 30 patients

Study	Design	No of patients	Follow up	BCVA improvement (logMAR)	% of SRF resolution	No of recurrences	No of treatments
Van Dijk et al. (PLACE trial) [161]	Half dose-PDT	67	7–8 months	+1.39 (ETDRS letters)	67.2	5%	1–2
	SML 810	66		+4.48 (ETDRS letters)	28.8	1.3%	1–2
Scholz et al. [162]	Half dose-PDT	58	6 weeks	+0.04 logMAR	21	NR	1–2
	SML 577	42		+0.08 logMAR	36	NR	1–2
Roca et al. [163]	Half dose-PDT	67	17.4 months	+0.03 logMAR	95.5	NR	1–3
	SML 577	92	15.8 months	+0.21 LogMAR	92.4	NR	1–4

with all treatment modalities incline also to early initiation of invasive therapies, nevertheless the possible benefit of such approach is yet to be determined.

PDT Position in the Treatment of CSCR

PDT is frequently used in the treatment of CSCR, mainly in chronic cases. The most commonly protocol employs half—dose verteporfin, less often half-fluence. As those two approaches provide good results, the standard nAMD protocol is practically out of use for CSCR nowadays. According to available data, PDT provides instant satisfactory morphological results in overwhelming majority of cases. Also, minor number of recurrencies is worth noting. Moreover, theoretically, it is the PDT that answers directly to modern pathophysiological concept of CSCR with the source of pathology located in the vascularity of the choroid.

On the other hand, the procedure is costly and involves intravenous application of the drug, which has potential to evoke photosensitivity reactions. These properties of PDT might be perceived as a burden, especially if compared to cheap and simple SML. Comparative studies SML versus PDT rarely favor any of these therapies and need to be continued to assess objectively the value of both strategies in different forms of CSCR, especially in the light of a new simple—complex classification. Nevertheless, in simple cases cheap SML seems to be reasonable first choice for treatment, with PDT usually favored for complex ones.

Other Treatments in CSCR

Different oral and topical medications are constantly tried for CSCR, most of them without background of randomized controlled research [164]. Among drugs administered for that disorder are carbonic anhydrase inhibitors, beta blockers, antibiotics such as amoxycillin, claritomycin, metronidazole, proton pump inhibitors, anticoagulants like aspirin, cytostatics (methotrexate) or non-steroid anti-inflammatory drugs in eye-drops (nepafenac, ketorolac or bromfenac). Those medications are still occasionally used in the treatment of CSCR, however this form of management does not have any back-up of clinical trials. So far reports on efficacy of these drugs in the treatment of CSCR are anecdotal and there are no convincing clinical data to justify their routine use.

Mineralocorticoid Inhibitors

Among oral pharmacological therapies for cCSCR the exception is the application of inhibitors to mineralocorticoid receptors, primarily Eplerenone, which has gained a lot of attention and clinical trials [165–168]. This form of treatment is justified in the light of the mineralocorticoid receptors activation and up-regulation observed in CSCR depicted at the beginning of this chapter. Blockage of the mineralocorticoid receptors should directly inhibit retention of water in the choroid and diminish the leak. Therapy with Eplerenone involves oral intake of 50 mg of this drug per day for the minimum of 3–6 months. Results of studies with Eplerenone are unequivocal. Some of the research reports its efficacy [169–171], but most recent studies, including randomized trials do not [172–175]. What is common in results from the studies that report success after application of Eplerenone in chronic CSCR, is relatively satisfactory morphological outcome and just minor improvement of BCVA. That is also similar to results of other treatment modalities, like PDT or SML.

Evolution of Treatment Strategies for CSCR

Timing of Treatment

There is no consensus on timing of initiation of treatment in CSCR. Still, some research recommend observation for the first 3–4 months after disease onset in expectance of spontaneous resolution of SRF [176]. This recommendation dates back to 70-ties of twentieth century, when the only available treatment option in selected cases of CSCR was laser photocoagulation. As the end-point of that treatment was a retinal scar and in consequence possible defect in central visual field,

spontaneous resolution of SRF in a few months' time was considered a more beneficial option. Nowadays, this approach is questioned by other clinicians [112, 118]. There are some data that suggest the damage to photoreceptors during first weeks of the disease [177, 178]. Moreover, some research suggests that early initiation of treatment could provide better functional results [118, 119]. That concept, together with availability of non-damaging retinal therapies, like SML, might result in modification of recommendations for the treatment of CSCR towards its initiation soon after onset.

The utilization of the new morphological classification of CSCR (simple versus complex cases) into clinical practice can possible also modify these recommendations. With complex cases involving a lot of the RPE alterations at baseline, the delay in application of treatment does not seem to make any sense. Simple cases, logically, have better prognosis, however still retinal thinning is possible to occur despite full resolution of SRF within a few months. That is why some ophthalmologists treat all patients with CSCR at presentation or after a short period of one month observation.

The question which therapy should be a first line in the treatment of CSCR remains under discussion among clinicians. As we noted earlier, SML compared to PDT is cheap and does not involve invasive application of a drug, neither results in potential systemic reactions. On the other hand, not all the cases respond to this modality, especially not all the complex ones. So far, a prospective study that would link the treatment modality used in CSCR to the variant of the disease has not yet been conducted. That is why, clinical approach in choosing the treatment option has to base on theoretical speculations, treatment availability, cost calculation and surgeons experience and discretion. We believe, that simple cases of CSCR can be successfully treated with SML both in its acute and chronic forms. On the other hand, management of complex cases may be started with either SML or PDT, however in lack of response to SML, switch to PDT should be prompt. In such cases ICGA guidance for the PDT is recommended [53, 179].

Summary

Available evidence shows that every form of CSCR poses a potential threat to visual system and can lead to some degree of visual impairment even in cases of short duration. Laser procedures stand as the main form of treatment of CSCR in modern ophthalmology. We believe that deferral of treatment can reduce retinal potential for improvement, so we suggest early initiation of therapy. The choice of the procedure should involve case classification according to its complexity, duration and recurrencies. Simple cases might be a good subject to SML, however in complex longstanding cases with many RPE alterations, PDT should be considered as the first choice of treatment.

References

1. Kitzmann AS, Pulido JS, Diehl NN, Hodge DO, Burke JP. The incidence of central serous chorioretinopathy in Olmsted County, Minnesota, 1980–2002. Ophthalmology. 2008;115(1):169–73.
2. Spaide RF, Campeas L, Haas A, Yannuzzi LA, Fisher YL, Guyer DR, Slakter JS, Sorenson JA, Orlock DA. Central serous chorioretinopathy in younger and older adults. Ophthalmology. 1996;103(12):2070–9.
3. Tittl MK, Spaide RF, Wong D, Pilotto E, Yannuzzi LA, Fisher YL, Freund B, Guyer DR, Slakter JS, Sorenson JA. Systemic findings associated with central serous chorioretinopathy. Am J Ophthalmol. 1999;128(1):63–8.
4. Tsai DC, Chen SJ, Huang CC, Chou P, Chung CM, Huang PH, Lin SJ, Chen JW, Chen TJ, Leu HB, Chan WL. Epidemiology of idiopathic central serous chorioretinopathy in Taiwan, 2001–2006: a population-based study. PLoS ONE. 2013;8(6):e66858.
5. Schellevis RL, van Dijk EHC, Breukink MB, Altay L, Bakker B, Koeleman BPC, Kiemeney LA, Swinkels DW, Keunen JEE, Fauser S, Hoyng CB, den Hollander AI, Boon CJF, de Jong EK. Role of the complement system in chronic central serous chorioretinopathy: a genome-wide association study. JAMA Ophthalmol. 2018;136(10):1128–36.
6. Mohabati D, Schellevis RL, van Dijk EHC, Altay L, Fauser S, Hoyng CB, De Jong EK, Boon CJF, Yzer S. Genetic risk factors in acute central serous chorioretinopathy. Retina. 2019;39(12):2303–10.
7. Mohabati D, Schellevis RL, van Dijk EHC, Fauser S, den Hollander AI, Hoyng CB, De Jong EK, Yzer S, Boon CJF. Genetic risk factors in severe, nonsevere and acute phenotypes of central serous chorioretinopathy. Retina. 2020;40(9):1734–41.
8. Yannuzzi LA. Type-A behavior and central serous chorioretinopathy. Retina. 1987;7(2):111–31.
9. van Haalen FM, van Dijk EHC, Andela CD, Dijkman G, Biermasz NR, Pereira AM, Boon CJF. Maladaptive personality traits, psychological morbidity and coping strategies in chronic central serous chorioretinopathy. Acta Ophthalmol. 2019;97(4):e572–9.
10. Bousquet E, Dhundass M, Lehmann M, Rothschild PR, Bayon V, Leger D, Bergin C, Dirani A, Beydoun T, Behar-Cohen F. Shift work: a risk factor for central serous chorioretinopathy. Am J Ophthalmol. 2016;165:23–8.
11. Gelber GS, Schatz H. Loss of vision due to central serous chorioretinopathy following psychological stress. Am J Psychiatry. 1987;144(1):46–50.
12. Ji Y, Li M, Zhang X, Peng Y, Wen F. Poor sleep quality is the risk factor for central serous chorioretinopathy. J Ophthalmol. 2018;1(2018):9450297.
13. Spahn C, Wiek J, Burger T, Hansen L. Psychosomatic aspects in patients with central serous chorioretinopathy. Br J Ophthalmol. 2003;87(6):704–8.
14. Bazzazi N, Ahmadpanah M, Akbarzadeh S, Seif Rabiei MA, Holsboer-Trachsler E, Brand S. In patients suffering from idiopathic central serous chorioretinopathy, anxiety scores are higher than in healthy controls, but do not vary according to sex or repeated central serous chorioretinopathy. Neuropsychiatr Dis Treat. 2015;28(11):1131–6.
15. Sahin A, Bez Y, Kaya MC, Türkcü FM, Sahin M, Yüksel H. Psychological distress and poor quality of life in patients with central serous chorioretinopathy. Semin Ophthalmol. 2014;29(2):73–6.
16. Genovese G, Meduri A, Muscatello MRA, Gangemi S, Cedro C, Bruno A, Aragona P, Pandolfo G. Central serous chorioretinopathy and personality characteristics: a systematic review of scientific evidence over the last 10 years (2010 to 2020). Medicina (Kaunas). 2021;57(6):628.
17. Haimovici R, Koh S, Gagnon DR, Lehrfeld T, Wellik S, Central Serous Chorioretinopathy Case-Control Study Group. Risk factors for central serous chorioretinopathy: a case-control study. Ophthalmology. 2004;111(2):244–9.
18. Fardin B, Weissgold DJ. Central serous chorioretinopathy after inhaled steroid use for post-mycoplasmal bronchospasm. Br J Ophthalmol. 2002;86(9):1065–6.

19. Chan LY, Adam RS, Adam DN. Localized topical steroid use and central serous retinopathy. J Dermatolog Treat. 2016;27(5):425–6.
20. Balakrishnan S, Apsingi S, Manjure SB. Sudden loss of visual acuity following intra-articular steroid injection in to the knee joint: a case report. Cases J. 2008;1(1):428.
21. Schellevis RL, Altay L, Kalisingh A, Mulders TWF, Sitnilska V, Hoyng CB, Boon CJF, Groenewoud JMM, de Jong EK, den Hollander AI. Elevated steroid hormone levels in active chronic central serous chorioretinopathy. Invest Ophthalmol Vis Sci. 2019;60(10):3407–13.
22. Zakir SM, Shukla M, Simi ZU, Ahmad J, Sajid M. Serum cortisol and testosterone levels in idiopathic central serous chorioretinopathy. Indian J Ophthalmol. 2009;57(6):419–22.
23. van Haalen FM, van Dijk EHC, Dekkers OM, Bizino MB, Dijkman G, Biermasz NR, Boon CJF, Pereira AM. Cushing's syndrome and hypothalamic-pituitary-adrenal axis hyperactivity in chronic central serous chorioretinopathy. Front Endocrinol (Lausanne). 2018;20(9):39.
24. van Dijk EH, Dijkman G, Biermasz NR, van Haalen FM, Pereira AM, Boon CJ. Chronic central serous chorioretinopathy as a presenting symptom of Cushing syndrome. Eur J Ophthalmol. 2016;26(5):442–8.
25. Sunness JS, Haller JA, Fine SL. Central serous chorioretinopathy and pregnancy. Arch Ophthalmol. 1993;111(3):360–4.
26. Gawecki M, Groszewska E. Central serous chorioretinopathy during pregnancy complicated by systemic hypertension—a case report. Klin Oczna. 2016;117(4):256–9.
27. Behar-Cohen F, Zhao M. Corticosteroids and the retina: a role for the mineralocorticoid receptor. Curr Opin Neurol. 2016;29(1):49–54.
28. Eom Y, Oh J, Kim SW, Huh K. Systemic factors associated with central serous chorioretinopathy in Koreans. Korean J Ophthalmol. 2012;26(4):260–4.
29. Chen SN, Lian I. Increased risk of coronary heart disease in male patients with central serous chorioretinopathy: results of a population-based cohort study. Br J Ophthalmol. 2014;98(7):997.
30. Rahbani-Nobar MB, Javadzadeh A, Ghojazadeh L, Rafeey M, Ghorbanihaghjo A. The effect of Helicobacter pylori treatment on remission of idiopathic central serous chorioretinopathy. Mol Vis. 2011;11(17):99–103.
31. Spitznas M. Pathogenesis of central serous retinopathy: a new working hypothesis. Graefes Arch Clin Exp Ophthalmol. 1986;224(4):321–4.
32. Marmor MF. New hypotheses on the pathogenesis and treatment of serous retinal detachment. Graefes Arch Clin Exp Ophthalmol. 1988;226(6):548–52.
33. Marmor MF. Control of subretinal fluid: experimental and clinical studies. Eye (Lond). 1990;4(Pt 2):340–4.
34. Spaide RF, Hall L, Haas A, Campeas L, Yannuzzi LA, Fisher YL, Guyer DR, Slakter JS, Sorenson JA, Orlock DA. Indocyanine green videoangiography of older patients with central serous chorioretinopathy. Retina. 1996;16(3):203–13.
35. Imamura Y, Fujiwara T, Margolis R, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. Retina. 2009;29(10):1469–73.
36. Agrawal R, Chhablani J, Tan KA, Shah S, Sarvaiya C, Banker A. Choroidal vascularity index in central serous chorioretinopathy. Retina. 2016;36(9):1646–51.
37. Gawęcki M, Jaszczuk-Maciejewska A, Jurska-Jaśko A, Kneba M, Grzybowski A. Impairment of visual acuity and retinal morphology following resolved chronic central serous chorioretinopathy. BMC Ophthalmol. 2019;19(1):160.
38. Teussink MM, Breukink MB, van Grinsven MJ, Hoyng CB, Klevering BJ, Boon CJ, de Jong EK, Theelen T. OCT angiography compared to fluorescein and indocyanine green angiography in chronic central serous chorioretinopathy. Invest Ophthalmol Vis Sci. 2015;56(9):5229–37.
39. Yang L, Jonas JB, Wei W. Choroidal vessel diameter in central serous chorioretinopathy. Acta Ophthalmol. 2013;91:e358–66.
40. Piskunowicz M, Jaracz M, Lesiewska H, Malukiewicz G, Brozek-Pestka M, Borkowska A. Temperament profile in patients with central serous chorioretinopathy: a case-control study. Eur J Ophthalmol. 2014;24(3):392–5.

41. Carlesimo SC, Piazzi G, Leone C, Di Santo L, Coccanari dè Fornari MA. Corioretinopatia sierosa centrale (C.R.S.C.) di Masuda quale investimento somatico nel Narcisismo: nostra rifl essione sulla nuova nosografi a psichiatrica [Masuda's Central Serous Chorioretinopathy (C.S.C.R.) and its somatic investment in Narcissism: our observations on new psychiatric nosography]. Clin Ter. 2014;165(1):27–30. Italian.
42. Daruich A, Matet A, Dirani A, Bousquet E, Zhao M, Farman N, Jaisser F, Behar-Cohen F. Central serous chorioretinopathy: recent findings and new physiopathology hypothesis. Prog Retin Eye Res. 2015;48:82–118.
43. Chhablani J, Cohen FB; Central Serous Chorioretinopathy International Group. Multimodal imaging-based central serous chorioretinopathy classification. Ophthalmol Retina. 2020;4(11):1043–46.
44. van Velthoven ME, Verbraak FD, Garcia PM, Schlingemann RO, Rosen RB, de Smet MD. Evaluation of central serous retinopathy with en face optical coherence tomography. Br J Ophthalmol. 2005;89(11):1483–8.
45. Yang L, Jonas JB, Wei W. Choroidal vessel diameter in central serous chorioretinopathy. Acta Ophthalmol. 2013;91(5):e358–62.
46. Sacconi R, Tomasso L, Corbelli E, Carnevali A, Querques L, Casati S, Bandello F, Querques G. Early response to the treatment of choroidal neovascularization complicating central serous chorioretinopathy: a OCT-angiography study. Eye (Lond). 2019;33(11):1809–17.
47. Yeo JH, Oh R, Kim YJ, Kim JG, Yoon YH, Lee JY. Choroidal neovascularization secondary to central serous chorioretinopathy: OCT angiography findings and risk factors. J Ophthalmol. 2020;7(2020):7217906.
48. Matet A, Daruich A, Hardy S, Behar-Cohen F. Patterns of choriocapillaris flow signal voids in central serous chorioretinopathy: an optical coherence tomography angiography study. Retina. 2019;39(11):2178–88.
49. Rochepeau C, Kodjikian L, Garcia MA, Coulon C, Burillon C, Denis P, Delaunay B, Mathis T. Optical coherence tomography angiography quantitative assessment of choriocapillaris blood flow in central serous chorioretinopathy. Am J Ophthalmol. 2018;194:26–34.
50. Bujarborua D, Nagpal PN, Deka M. Smokestack leak in central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol. 2010;248(3):339–51.
51. Hu J, Qu J, Piao Z, Yao Y, Sun G, Li M, Zhao M. Optical coherence tomography angiography compared with indocyanine green angiography in central serous chorioretinopathy. Sci Rep. 2019;9(1):6149.
52. Hua R, Yao K, Xia F, Li J, Guo L, Yang G, Tao J. The hyper-fluorescent transitional bands in ultra-late phase of indocyanine green angiography in chronic central serous chorioretinopathy. Lasers Surg Med. 2016;48(3):260–3.
53. van Dijk EHC, van Rijssen TJ, Subhi Y, Boon CJF. Photodynamic therapy for chorioretinal diseases: a practical approach. Ophthalmol Ther. 2020;9(2):329–42.
54. Hayashida M, Miki A, Honda S, Nakamura M. Comparison between the outcomes of fluorescein angiography-guided and indocyanine green angiography-guided half-time photodynamic therapy for central serous chorioretinopathy. Photodiagnosis Photodyn Ther. 2020;31:101955.
55. van Dijk EHC, Boon CJF. Serous business: delineating the broad spectrum of diseases with subretinal fluid in the macula. Prog Retin Eye Res. 2021;84:100955.
56. Ooto S, Tsujikawa A, Mori S, Tamura H, Yamashiro K, Otani A, Yoshimura N. Retinal microstructural abnormalities in central serous chorioretinopathy and polypoidal choroidal vasculopathy. Retina (Phila. Pa.). 2011;31:527e534.
57. Sagar P, Sodhi PS, Roy S, Takkar B, Azad SV. Pachychoroid neovasculopathy: a comparative review on pathology, clinical features, and therapy. Eur J Ophthalmol. 2021;29:11206721211036290.
58. Lee GW, Roh HC, Kang SW, Kim AY, Noh H, Choi KJ. The implications of subretinal fluid in pachychoroid neovasculopathy. Sci Rep. 2021;11(1):4066.
59. Chhablani J, Kozak I, Pichi F, Chenworth M, Berrocal MH, Bedi R, Singh RP, Wu L, Meyerle C, Casella AM, Mansour A, Bashshur Z, Scorza A, Carrai P, Nucci P, Arevalo JF; King Khaled Eye Specialist Hospital International Collaborative Retina Study Group. Outcomes

of treatment of choroidal neovascularization associated with central serous chorioretinopathy with intravitreal antiangiogenic agents. Retina. 2015;35(12):2489–97.
60. Pauleikhoff D. neovascular age-related macular degeneration: natural history and treatment outcomes. Retina. 2005;25(8):1065–84.
61. Ikuno Y. Overview of the complications of high myopia. Retina. 2017;37(12):2347–51.
62. Wang HY, Tao MZ, Wang XX, Li MH, Zhang ZF, Sun DJ, Zhu JT, Wang YS. Baseline characteristics of myopic choroidal neovascularization in patients above 50 years old and prognostic factors after intravitreal conbercept treatment. Sci Rep. 2021;11(1):7337.
63. Terry SF, Uitto J. Pseudoxanthoma elasticum. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2021.
64. Mimoun G, Ebran JM, Grenet T, Donati A, Cohen SY, Ponthieux A. Ranibizumab for choroidal neovascularization secondary to pseudoxanthoma elasticum: 4-year results from the PIXEL study in France. Graefes Arch Clin Exp Ophthalmol. 2017;255(8):1651–60.
65. Jain M, Gopal L, Padhi TR. Dome-shaped maculopathy: a review. Eye (Lond). 2021;35(9):2458–67. https://doi.org/10.1038/s41433-021-01518-w. Epub 2021 Apr 19.
66. Ravenstijn M, van Dijk EHC, Haarman AEG, Kaden TR, Vermeer KA, Boon CJF, Yannuzzi LA, Klaver CCW, Yzer S. Myopic presentation of central serous chorioretinopathy. Retina. 2021.
67. Besada E, Barr R, Schatz S, Brewer C. Vitreal pathogenic role in optic pit foveolar retinoschisis and central serous retinopathy. Clin Exp Optom. 2003;86(6):390–8.
68. Chen MS, Tsai WF. Congenital optic pits and central serous chorioretinopathy. Aust N Z J Ophthalmol. 1997;25(2):165–6.
69. Kim RS, Jain RR, Brown DM, Bretana ME, Kegley EN, Singer MA, Aragon AV, Schefler AC. Elevated choroidal thickness and central serous chorioretinopathy in the fellow eyes of patients with circumscribed choroidal hemangioma. Ocul Oncol Pathol. 2018;4(6):375–80.
70. Dave T, Dave VP, Shah G, Pappuru RR. Diffuse choroidal hemangioma masquerading as central serous chorioretinopathy treated with oral propranolol. Retin Cases Brief Rep. 2016;10(1):11–4.
71. Kwon HJ, Kim M, Lee CS, Lee SC. Treatment of serous macular detachment associated with circumscribed choroidal hemangioma. Am J Ophthalmol. 2012;154(1):137–145.e1.
72. Higgins TP, Khoo CT, Magrath G, Shields CL. Flat choroidal melanoma masquerading as central serous chorioretinopathy. Oman J Ophthalmol. 2016;9(3):174–6.
73. Shields CL, Honavar SG, Shields JA, Cater J, Demirci H. Circumscribed choroidal hemangioma: clinical manifestations and factors predictive of visual outcome in 200 consecutive cases. Ophthalmology. 2001;108(12):2237–48.
74. Muscat S, Srinivasan S, Sampat V, Kemp E, Parks S, Keating D. Optical coherence tomography in the diagnosis of subclinical serous detachment of the macula secondary to a choroidal nevus. Ophthalmic Surg Lasers. 2001;32(6):474–6.
75. Scott AW, Fekrat S, Mruthyunjaya P, Cummings TJ, Cooney MJ. Unusual case of diffuse choroidal melanoma masquerading as atypical central serous chorioretinopathy. Retin Cases Brief Rep. 2008;2(4):280–5.
76. Benson WE, Shields JA, Tasman W, Crandall AS. Posterior scleritis. A cause of diagnostic confusion. Arch Ophthalmol. 1979;97(8):1482–6.
77. Ando Y, Keino H, Nakayama M, Watanabe T, Okada AA. Clinical features, treatment, and visual outcomes of Japanese patients with posterior scleritis. Ocul Immunol Inflamm. 2020;28(2):209–16.
78. Aggarwal K, Agarwal A, Deokar A, Mahajan S, Singh R, Bansal R, Sharma A, Dogra MR, Gupta V; OCTA Study Group. Distinguishing features of acute Vogt-Koyanagi-Harada disease and acute central serous chorioretinopathy on optical coherence tomography angiography and en face optical coherence tomography imaging. J Ophthalmic Inflamm Infect. 2017;7(1):3.
79. Liu XY, Peng XY, Wang S, You QS, Li YB, Xiao YY, Jonas JB. Features of optical coherence tomography for the diagnosis of Vogt-Koyanagi-Harada disease. Retina. 2016;36(11):2116–23.

80. Lin D, Chen W, Zhang G, Huang H, Zhou Z, Cen L, Chen H. Comparison of the optical coherence tomographic characters between acute Vogt-Koyanagi-Harada disease and acute central serous chorioretinopathy. BMC Ophthalmol. 2014;28(14):87.
81. Panigrahi PK, Mahapatra MM, Minj A, Satapathy J, Samant S. Central serous chorioretinopathy mimicking as choroiditis. Clin Exp Optom. 2018;101(3):420–1.
82. Nagpal A, Biswas J. Pseudouveitis–analysis of cases misdiagnosed as posterior uveitis. Ocul Immunol Inflamm. 2006;14(1):13–20.
83. Agarwal A, Pichi F, Invernizzi A, Gupta V. Disease of the year: differential diagnosis of uveitic macular edema. Ocul Immunol Inflamm. 2019;27(1):72–88.
84. Zatreanu L, Freund KB, Leong BCS, Yu HG, Teke MY, Yzer S, Sadda SR, Sarraf D. Serous macular detachment in best disease: a masquerade syndrome. Retina. 2020;40(8):1456–70.
85. Giuffrè C, Miserocchi E, Modorati G, Carnevali A, Marchese A, Querques L, Querques G, Bandello F. Central serous chorioretinopathylike mimicking multifocal vitelliform macular dystrophy: an ocular side effect of mitogen/extracellular signal-regulated kinase inhibitors. Retin Cases Brief Rep. 2018;12(3):172–6.
86. Chowers I, Tiosano L, Audo I, Grunin M, Boon CJ. Adult-onset foveomacular vitelliform dystrophy: a fresh perspective. Prog Retin Eye Res. 2015;47:64–85.
87. Daruich A, Matet A, Moulin A, Kowalczuk L, Nicolas M, Sellam A, Rothschild PR, Omri S, Gélizé E, Jonet L, Delaunay K, De Kozak Y, Berdugo M, Zhao M, Crisanti P, Behar-Cohen F. Mechanisms of macular edema: beyond the surface. Prog Retin Eye Res. 2018;63:20–68.
88. Dhurandhar DS, Singh SR, Sahoo NK, Goud A, Lupidi M, Chhablani J. Identifying central serous chorioretinopathy biomarkers in coexisting diabetic retinopathy: a multimodal imaging study. Br J Ophthalmol. 2020;104(7):904–9.
89. Yamaguchi Y, Otani T, Kishi S. Serous macular detachment in branch retinal vein occlusion. Retina. 2006;26(9):1029–33.
90. Daruich A, Matet A, Marchionno L, De Azevedo JD, Ambresin A, Mantel I, Behar-Cohen F. Acute central serous chorioretinopathy: factors influencing episode duration. Retina. 2017;37(10):1905–15.
91. Breukink MB, Dingemans AJ, den Hollander AI, et al. Chronic central serous chorioretinopathy: long-term follow-up and vision-related quality of life. Clin Ophthalmol. 2016;11:39–46.
92. Mrejen S, Balaratnasingam C, Kaden TR, Bottini A, Dansingani K, Bhavsar KV, Yannuzzi NA, Patel S, Chen KC, Yu S, Stoffels G, Spaide RF, Freund KB, Yannuzzi LA. Long-term visual outcomes and causes of vision loss in chronic central serous chorioretinopathy. Ophthalmology. 2019;126(4):576–88.
93. Fok AC, Chan PP, Lam DS, Lai TY. Risk factors for recurrence of serous macular detachment in untreated patients with central serous chorioretinopathy. Ophthalmic Res. 2011;46(3):160–3.
94. Savastano MC, Rispoli M, Lumbroso B. The incidence of neovascularization in central serous chorioretinopathy by optical coherence tomography angiography. Retina. 2021;41(2):302–8.
95. Loo RH, Scott IU, Flynn HW Jr, Gass JD, Murray TG, Lewis ML, Rosenfeld PJ, Smiddy WE. Factors associated with reduced visual acuity during long-term follow-up of patients with idiopathic central serous chorioretinopathy. Retina. 2002;22(1):19–24.
96. Inomata H. Wound healing after xenon arc photocoagulation in the rabbit retina. Identification of the proliferating cells in the lesion by light and electron microscopic autoradiography using 3H-thymidine. Ophthalmologica. 1975;170:462–74.
97. Gass JDM. Discussion of central serous retinopathy. Mod Probl Ophthalmol. 1974;12:361. Karger: Basel.
98. Leaver P, Williams C. Argon laser photocoagulation in the treatment of central serous retinopathy. Br J Ophthalmol. 1979;63(10):674–7.
99. Manayath GJ, Ranjan R, Karandikar SS, Shah VS, Saravanan VR, Narendran V. Central serous chorioretinopathy: current update on management. Oman J Ophthalmol. 2018;11(3):200–6.
100. Frankhauser F, Kwasniewska S. Lasers in ophthalmology. Kugler Publications; 2003, pp. 269.
101. Robertson DM, Ilstrup D. Direct, indirect, and sham laser photocoagulation in the management of central serous chorioretinopathy. Am J Ophthalmol. 1983;95(4):457–66.

102. Goel N, Mehta A, Gupta AK. Multifocal electroretinography-assisted anatomical and functional evaluation of subthreshold green laser in acute central serous chorioretinopathy. Indian J Ophthalmol. 2021;69(9):2341–6.
103. Chang DB, Luttrull JK. Comparison of subthreshold 577 and 810 nm micropulse laser effects on heat-shock protein activation kinetics: implications for treatment efficacy and safety. Trans Vis Sci Tech. 2020;9(5):23.
104. Keunen JEE, Battaglia-Parodi M, Vujosevic S, Luttrull JK. International retinal laser society guidelines for subthreshold laser treatment. Trans Vis Sci Tech. 2020;9(9):15.
105. https://clinicaltrials.gov/ct2/show/NCT04410861?recrs=a&cond=Central+Serous+Chorioretinopathy&draw=2&rank=1
106. Ambiya V, Kumar A. Role of 532 nm transfoveal subthreshold micropulse laser in non-resolving central serous chorioretinopathy with subfoveal leaks. Ther Adv Ophthalmol. 2020;17(12):2515841420945107.
107. Scholz P, Ersoy L, Boon CJ, Fauser S. Subthreshold micropulse laser (577 nm) treatment in chronic central serous chorioretinopathy. Ophthalmologica. 2015;234(4):189–94.
108. Gawęcki M, Jaszczuk-Maciejewska A, Jurska-Jaśko A, Grzybowski A. Functional and morphological outcome in patients with chronic central serous chorioretinopathy treated by subthreshold micropulse laser. Graefes Arch Clin Exp Ophthalmol. 2017;255(12):2299–306.
109. Arsan A, Kanar HS, Sonmez A. Visual outcomes and anatomic changes after sub-threshold micropulse yellow laser (577-nm) treatment for chronic central serous chorioretinopathy: long-term follow-up. Eye (Lond). 2018;32(4):726–33.
110. Altınel MG, Acikalin B, Gunes H, Demir G. Optical coherence tomography parameters as predictors of treatment response to a 577-nm subthreshold micropulse laser in chronic central serous chorioretinopathy. Lasers Med Sci. 2021;36(7):1505–14.
111. Işık MU, Değirmenci MFK, Sağlık A. Efficacy of the subthreshold micropulse yellow wavelength laser photostimulation in the treatment of chronic central serous chorioretinopathy. Int J Ophthalmol. 2020;13(9):1404–10.
112. Luttrull JK. Low-intensity/high-density subthreshold diode micropulse laser for central serous chorioretinopathy. Retina. 2016;36:1658–63.
113. Scholz P, Ersoy L, Boon CJ, Fauser S. Subthreshold micropulse laser (577 nm) treatment in chronic central serous chorioretinopathy. Ophthalmologica. 2015;234:189–94.
114. Yadav NK, Jayadev C, Mohan A, Vijayan P, Battu R, Dabir S, Shetty B, Shetty R. Subthreshold micropulse yellow laser (577 nm) in chronic central serous chorioretinopathy: Safety profile and treatment outcome. Eye. 2015;29:258–64.
115. Kim JY, Park HS, Kim SY. Short-term efficacy of subthreshold micropulse yellow laser (577-nm) photocoagulation for chronic central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol. 2015;253:2129–35.
116. Sousa K, Calvão-Santos G, João M, Gomes N, Falcão M. 532-nm subthreshold micropulse laser for the treatment of chronic central serous retinopathy. Clin Ophthalmol. 2020;25(14):525–31.
117. Scholz P, Altay L, Fauser S. A review of subthreshold micropulse laser for treatment of macular. Disord Adv Ther. 2017;34:1528–55.
118. Gawęcki M, Jaszczuk-Maciejewska A, Jurska-Jaśko A, Kneba M, Grzybowski A. Transfoveal micropulse laser treatment of central serous chorioretinopathy within six months of disease onset. J Clin Med. 2019;8(9):1398.
119. Arora S, Sridharan P, Arora T, Chhabra M, Ghosh B. Subthreshold diode micropulse laser versus observation in acute central serous chorioretinopathy. Clin Exp Optom. 2019;102(1):79–85.
120. Zhou L, Lai K, Jin L, Huang C, Xu F, Gong Y, Li L, Zhu Z, Lu L, Jin C. Subthreshold micropulse laser vs. conventional laser for central serous chorioretinopathy: a randomized controlled clinical trial. Front Med (Lausanne). 2021;8:682264.
121. Zhou L, Chong V, Lai K, Huang C, Xu F, Gong Y, Youlidaxi M, Li T, Lu L, Jin C. A pilot prospective study of 577-nm yellow subthreshold micropulse laser treatment with two different power settings for acute central serous chorioretinopathy. Lasers Med Sci. 2019;34(7):1345–51.

122. Sun Z, Huang Y, Nie C, et al. Efficacy and safety of subthreshold micropulse laser compared with threshold conventional laser in central serous chorioretinopathy. Eye (Lond). 2020;34(9):1592–9.
123. Long H, Liu M, Hu Q, Li X. 577 nm subthreshold micropulse laser treatment for acute central serous chorioretinopathy: a comparative study. BMC Ophthalmol. 2022;22(1):105.
124. Gawęcki M. Increase in central retinal edema after subthreshold diode micropulse laser treatment of chronic central serous chorioretinopathy. Case Rep Ophthalmol Med. 2015;2015:813414.
125. Lavinsky D, Palanker D. Nondamaging photothermal therapy for the retina: initial clinical experience with chronic central serous retinopathy. Retina. 2015;35(2):213–22. https://doi.org/10.1097/IAE.0000000000000340. PMID: 25158944.
126. Schworm B, Siedlecki J, Keidel LF, Herold TR, Luft N, Priglinger SG. Subthreshold laser therapy with a standardized macular treatment pattern in chronic central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol. 2021;259(11):3271–81.
127. Seifert E, Tode J, Pielen A, Theisen-Kunde D, Framme C, Roider J, Miura Y, Reginald Birngruber MD, Brinkmann R. Selective retina therapy: toward an optically controlled automatic dosing. J Biomed Opt 2018;23(11):115002.
128. Brinkmann R, Roider J, Birngruber R. Selective retina therapy (SRT): a review on methods, techniques, preclinical and first clinical results. Bull Soc Belge Ophtalmol. 2006;302:51–69.
129. Elsner H, Pörksen E, Klatt C, Bunse A, Theisen-Kunde D, Brinkmann R, Birngruber R, Laqua H, Roider J. Selective retina therapy in patients with central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol. 2006;244(12):1638–45.
130. Park YG, Kang S, Kim M, Yoo N, Roh YJ. Selective retina therapy with automatic real-time feedback-controlled dosimetry for chronic central serous chorioretinopathy in Korean patients. Graefes Arch Clin Exp Ophthalmol. 2017;255(7):1375–83.
131. Kyo A, Yamamoto M, Hirayama K, Kohno T, Theisen-Kunde D, Brinkmann R, Miura Y, Honda S. Factors affecting resolution of subretinal fluid after selective retina therapy for central serous chorioretinopathy. Sci Rep. 2021;11(1):8973.
132. Lee JY, Kim MH, Jeon SH, Lee SH, Roh YJ. The effect of selective retina therapy with automatic real-time feedback-controlled dosimetry for chronic central serous chorioretinopathy: a randomized, open-label, controlled clinical trial. J Clin Med. 2021;10(19):4295.
133. Jeon SH, Kim M, Lee J, Roh YJ. The effect of selective retina therapy for bevacizumab-resistant chronic central serous chorioretinopathy. Ophthalmologica. 2022;245(1):91–100.
134. Kim M, Jeon SH, Lee JY, Lee SH, Roh YJ. Factors predicting response to selective retina therapy in patients with chronic central serous chorioretinopathy. J Clin Med. 2022;11(2):323.
135. Kaymak H, Funk S, Fricke A, Fulga R, Klabe K, Seitz B, Langenbucher A, Schwahn H. Efficacy of nanosecond laser treatment in central serous chorioretinopathy with and without atrophy of retinal pigment epithelium. Int J Retina Vitreous. 2020;4(6):11.
136. Funk S, Fulga R, Klabe K, Breyer D, Seitz B, Langenbucher A, Kaymak H. Nanosekunden-laserbehandlung bei Chorioretinopathia centralis serosa ohne RPE-Defekte: eine retrospektive Fallserie [Nanosecond laser treatment in chorioretinopathia centralis serosa without RPE defects: a retrospective case series]. Klin Monbl Augenheilkd. 2021;238(1):60–66. German.
137. Nassisi M, Lavia C, Alovisi C, Musso L, Eandi CM. Short-term choriocapillaris changes in patients with central serous chorioretinopathy after half-dose photodynamic therapy. Int J Mol Sci. 2017;18(11):2468.
138. Alovisi C, Piccolino FC, Nassisi M, Eandi CM. Choroidal structure after half-dose photodynamic therapy in chronic central serous chorioretinopathy. J Clin Med. 2020;9(9):2734.
139. Flores-Moreno I, Arcos-Villegas G, Sastre M, Ruiz-Medrano J, Arias-Barquet L, Duker JS, Ruiz-Moreno JM. Changes in choriocapillaris, sattler, and haller layer thicknesses in central serous chorioretinopathy after half-fluence photodynamic therapy. Retina. 2020;40(12):2373–8.
140. Inoue R, Sawa M, Tsujikawa M, Gomi F. Association between the efficacy of photodynamic therapy and indocyanine green angiography findings for central serous chorioretinopathy. Am J Ophthalmol. 2010;149:441–6.

141. Matušková V, Vysloužilová D, Uher M. Half-fluence photodynamic therapy for chronic central serous chorioretinopathy: predisposing factors for visual acuity outcomes. Semin Ophthalmol. 2017;33:690–9.
142. Rouvas AA, Stavrakas P, Theodossiadis PG, Stamatiou P, Milia M, Giannakaki E, Datseris I. Long-term results of half-fluence photodynamic therapy for chronic central serous chorioretinopathy. Eur J Ophthalmol. 2011;22:417–22.
143. Smretschnig E, Ansari-Shahrezaei S, Hagen S, Glittenberg C, Krebs I, Binder S. Half-fluence photodynamic therapy in chronic central serous chorioretinopathy. Retina. 2013;33:316–23.
144. Park DG, Jeong S, Noh D, Sagong M. Optimal fluence rate of photodynamic therapy for chronic central serous chorioretinopathy. Br J Ophthalmol. 2021;105(6):844–9.
145. Ruiz-Del-Tiempo MP, Calvo P, Ferreras A, Leciñena J, Pablo L, Ruiz-Moreno O. Anatomical retinal changes after photodynamic therapy in chronic central serous chorioretinopathy. J Ophthalmol. 2018;2018:1–4.
146. Noh SR, Kang MS, Kim K, Kim ES, Yu S-Y. Comparison of focal and conventional verteporfin photodynamic therapy for chronic central serous chorioretinopathy. Korean J Ophthalmol. 2019;33:506–13.
147. Ruiz-Moreno JM, Lugo FL, Armadá F, Silva R, Montero JA, Arevalo JF, Arias L, Gómez-Ulla F. Photodynamic therapy for chronic central serous chorioretinopathy. Acta Ophthalmol. 2010;88:371–6.
148. Fujita K, Imamura Y, Shinoda K, Matsumoto CS, Mizutani Y, Hashizume K, Mizota A, Yuzawa M. One-year outcomes with half-dose verteporfin photodynamic therapy for chronic central serous chorioretinopathy. Ophthalmology. 2015;122:555–61.
149. Haga F, Maruko R, Sato C, Kataoka K, Ito Y, Terasaki H. Long-term prognostic factors of chronic centralserous chorioretinopathy after half-dose photodynamic therapy: a 3-year follow-up study. PLoS ONE. 2017;12:e0181479.
150. Lai FH, Ng DS, Bakthavatsalam M, Chan VC, Young AL, Luk FO, Tsang CW, Brelén ME. A multicenter study on the long-term outcomes of half-dose photodynamic therapy in chronic central serous chorioretinopathy. Am J Ophthalmol. 2016;170:91–9.
151. Tseng C-C, Chen S-N. Long-term efficacy of half-dose photodynamic therapy on chronic central serous chorioretinopathy. Br J Ophthalmol. 2015;99:1070–7.
152. Missotten TO, Hoddenbach JG, Eenhorst CA, van den Born LI, Martinez Ciriano JP, Wubbels RJ. A randomized clinical trial comparing prompt photodynamic therapy with 3 months observation in patients with acute central serous chorioretinopathy with central macular leakage. Eur J Ophthalmol. 2021;31(3):1248–53.
153. Chan WM, Lai TY, Lai RY, Liu DT, Lam DS. Half-dose verteporfin photodynamic therapy for acute central serous chorioretinopathy: one-year results of a randomized controlled trial. Ophthalmology. 2008;115(10):1756–65.
154. Kim KS, Lee WK, Lee SB. Half-dose photodynamic therapy targeting the leakage point on the fluorescein angiography in acute central serous chorioretinopathy: a pilot study. Am J Ophthalmol. 2014;157(2):366–373.e1.
155. Wu ZH, Lai RY, Yip YW, Chan WM, Lam DS, Lai TY. Improvement in multifocal electroretinography after half-dose verteporfin photodynamic therapy for central serous chorioretinopathy: a randomized placebo-controlled trial. Retina. 2011;31(7):1378–86.
156. Lu HQ, Wang EQ, Zhang T, Chen YX. Photodynamic therapy and anti-vascular endothelial growth factor for acute central serous chorioretinopathy: a systematic review and meta-analysis. Eye (Lond). 2016;30(1):15–22.
157. Yannuzzi LA, Slakter JS, Gross NE, et al. Indocyanine green angiography-guided photodynamic therapy for treatment of chronic central serous chorioretinopathy: a pilot study. Retina. 2003;23(3):288–98.
158. Ladas ID, Andreanos K, Ladas DS, Moschos MM, Rotsos T, Kotsolis AI. Three-year results of fluorescein angiography-guided standard photodynamic therapy with multiple spots for central serous chorioretinopathy. Ophthalmol Retin. 2018;2:703–11.
159. Tarantola RM, Law JC, Recchia FM, Sternberg P Jr, Agarwal A. Photodynamic therapy as treatment of chronic idiopathic central serous chorioretinopathy. Lasers Surg Med. 2008;40:671–5.

160. Inoue R, Sawa M, Tsujikawa M, Gomi F. Association between the efficacy of photodynamic therapy and indocyanine green angiography findings for central serous chorioretinopathy. Am J Ophthalmol. 2010;149(3):441–6.e1–2.
161. Van Dijk EHC, Fauser S, Breukink MB, Blanco-Garavito R, Groenewoud JM, Keunen JEE, Peters PJ, Dijkman G, Souied EH, MacLaren RE, et al. Half-dose photodynamic therapy versus high-density subthreshold micropulse laser treatment in patients with chronic central serous chorioretinopathy: the place trial. Ophthalmology. 2018;125:1547–55.
162. Scholz P, Altay L, Fauser S. Comparison of subthreshold micropulse laser (577 nm) treatment and half-dose photodynamic therapy in patients with chronic central serous chorioretinopathy. Eye. 2016;30:1371–7.
163. Roca JA, Wu L, Fromow-Guerra J, Rodríguez FJ, Berrocal MH, Rojas S, Lima LH, Gallego-Pinazo R, Chhablani J, Arevalo JF, et al. Yellow (577 nm) micropulse laser versus half-dose verteporfin photodynamic therapy in eyes with chronic central serous chorioretinopathy: results of the Pan-American Collaborative Retina Study (PACORES) Group. Br J Ophthalmol. 2018;102:1696–700.
164. Nicolò M, Desideri LF, Vagge A, Traverso CE. Current pharmacological treatment options for central serous chorioretinopathy: a review. Pharmaceuticals (Basel). 2020;13(10):264.
165. Daruich A, Matet A, Dirani A, Gallice M, Nicholson L, Sivaprasad S, Behar-Cohen F. Oral mineralocorticoid-receptor antagonists: real-life experience in clinical subtypes of nonresolving central serous chorioretinopathy with chronic epitheliopathy. Transl Vis Sci Technol. 2016;5:2.
166. Zola M, Daruich A, Matet A, Mantel I, Behar-Cohen F. Two-year follow-up of mineralocorticoid receptor antagonists for chronic central serous chorioretinopathy. Br J Ophthalmol. 2019;103:1184–9.
167. Fraenkel D, Suffo S, Langenbucher A, Seitz B, Abdin AD. Eplerenone for treatment of chronic central serous chorioretinopathy. Eur J Ophthalmol. 2020;27:1120672120952648.
168. Venkatesh R, Pereira A, Jayadev C, Prabhu V, Aseem A, Jain K, Bavaharan B, Yadav NK, Chhablani J. Oral eplerenone versus observation in the management of acute central serous chorioretinopathy: a prospective, randomized comparative study. Pharmaceuticals (Basel). 2020;13(8):170.
169. Bousquet E, Dhundass M, Lejoyeux R, Shinojima A, Krivosic V, Mrejen S, Gaudric A, Tadayoni R. Predictive factors of response to mineralocorticoid receptor antagonists in nonresolving central serous chorioretinopathy. Am J Ophthalmol. 2019;198:80–7.
170. Karagiannis D, Parikakis E, Kontomichos L, Batsos G, Chatziralli I. The effect of eplerenone in chronic central serous chorioretinopathy refractory to photodynamic therapy. Semin Ophthalmol. 2019;34(6):436–41.
171. Petkovsek DS, Cherfan DG, Conti FF, Hom GL, Ehlers JP, Babiuch AS, Rachitskaya AV, Kaiser PK, Schachat AP, Srivastava SK, Sharma S, Singh RP. Eplerenone for the treatment of chronic central serous chorioretinopathy: 3-year clinical experience. Br J Ophthalmol. 2020;104(2):182–7.
172. van Rijssen TJ, van Dijk EHC, Tsonaka R, Feenstra HMA, Dijkman G, Peters PJH, Diederen RMH, Hoyng CB, Schlingemann RO, Boon CJF. Half-dose photodynamic therapy versus eplerenone in chronic central serous chorioretinopathy (SPECTRA): a randomized controlled trial. Am J Ophthalmol. 2021;29(233):101–10.
173. Schwartz R, Habot-Wilner Z, Martinez MR, Nutman A, Goldenberg D, Cohen S, Shulman S, Guzner-Gur H, Loewenstein A, Goldstein M. Eplerenone for chronic central serous chorioretinopathy-a randomized controlled prospective study. Acta Ophthalmol. 2017;95:e610–8.
174. Lotery A, Sivaprasad S, O'Connell A, Harris RA, Culliford L, Ellis L, Cree A, Madhusudhan S, Behar-Cohen F, Chakravarthy U, et al. Eplerenone for chronic central serous chorioretinopathy in patients with active, previously untreated disease for more than 4 months (VICI): a randomised, double-blind, placebo-controlled trial. Lancet. 2020;395:294–303.
175. Fasler K, Gunzinger JM, Barthelmes D, Zweifel SA. Routine clinical practice treatment outcomes of eplerenone in acute and chronic central serous chorioretinopathy. Front Pharmacol. 2021;10(12):675295.

176. van Rijssen TJ, van Dijk EHC, Yzer S, Ohno-Matsui K, Keunen JEE, Schlingemann RO, Sivaprasad S, Querques G, Downes SM, Fauser S, Hoyng CB, Piccolino FC, Chhablani JK, Lai TYY, Lotery AJ, Larsen M, Holz FG, Freund KB, Yannuzzi LA, Boon CJF. Central serous chorioretinopathy: towards an evidence-based treatment guideline. Prog Retin Eye Res. 2019;73:100770.
177. Gawęcki M, Jaszczuk A, Grzybowski A. Short term presence of subretinal fluid in central serous chorioretinopathy affects retinal thickness and function. J Clin Med. 2020;9(11):E3429.
178. Hata M, Oishi A, Shimozono M, Mandai M, Nishida A, Kurimoto Y. Early changes in foveal thickness in eyes with central serous chorioretinopathy. Retina. 2013;33:296–301.
179. Taban M, Boyer DS, Thomas EL, Taban M. Chronic central serous chorioretinopathy: photodynamic therapy. Am J Ophthalmol. 2004;137(6):1073–80.

Chapter 7
Laser for Retinal Vascular Occlusions

Sathy V. Bhavan and Jeffrey K. Luttrull

Retinal Vein Occlusions

Introduction

Retinal vein occlusion (RVO) is, after diabetic retinopathy, the most common cause retinal vascular cause of visual loss. The incidence of RVO increases with age, peaking in the 7th decade. Li et al., [20] Predispositions, in addition to age, include diabetes mellitus, hypertension, smoking, open angle glaucoma, hypercholesterolemia and cardiovascular disease. In younger patients, systemic inflammatory disease, hyperviscosity syndromes, and hyper coagulopathies should be investigated. Except in younger patients, medical and laboratory workups are seldom indicated or fruitful. Studies differ on whether or not male sex is an independent risk factor for RVO [34, 35].

For RVO, the predominant cause of VO is thought to be thrombus formation impeding venous outflow. Because retinal circulation has one entry (the central retinal artery) and one exit (the central retinal vein), impediment of venous outflow similarly reduces arterial inflow, and thus retinal vascular blood transit. By reducing retinal blood flow to the affected area, whether it be the entire retina (central RVO, or CRVO) or part of the retina (hemi-or branch RVO, HRVO or BRVO), retinal oxygenation is reduced causing partial to complete retinal ischemia and concomitant degrees of retinal dysfunction [1].

The cause of intravenous thrombus development in most cases of RVO is thought to be physical compression of the retinal vein by the adjacent retinal artery. Retinal veins can be thought of like fire hoses or "floppy" low pressure vessels that tend to collapse when nonperfused. In contrast, retinal arterioles carry blood under high

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_7

pressure. Thus, their structure is more robust, akin to typical garden hose or conduit, more firm and rigid.

With age, and further predisposed by systemic hypertension and cardiovascular disease, there is an increase in the retinal arterial wall-to-lumen ratio. This makes the retina arteries "harder" and more inflexible. Under the influence of systemic hypertension, myogenic hypertrophy may also occur, increasing the wall diameter [1].

The CRV and CRA lie side-by-side with the optic nerve, entering the eye through the highly inelastic lamina cribosa. Once entering the retina, the paths of the veins and arteries tend to diverge but remain roughly parallel, crossing paths at regular intervals. At these crossing points, the RVs and RAs are tightly bound together by a glial adventitial sheath which is also highly inelastic. Where the RV and RA are bound tightly together by inelastic sheaths, if there is thickening and increased density of the RA the only place the RA can expand is into the space occupied by the RV. This compression reduces the lumen of the retinal vein, leading to turbulent and variably reduced blood flow. If this reduction in flow is sufficient, patients may experience mild to moderate symptoms of visual disturbance, often intermittent and fluctuating, as well as clinical findings of retinal venous dilation and slowed retinal vascular transit by fundus fluorescein angiography in the affected area of the retina. More severe compression increases the chances of thrombus formation due to a combination of slowed and turbulent blood flow. Most often, thrombus formation results in incomplete obstruction of RV outflow. If the RV obstruction is complete, either due to severe arterial compression or complete thrombus formation, ischemia of the affected retina may be severe and permanent, and with it, the loss of visual function. Retinal, macular, and optic nerve edema, along with diffuse inner retinal hemorrhages, generally flame-shaped, are the typical clinical manifestations reflecting severe inner retinal ischemia due to RVO (the outer retina being served by the choroidal circulation). The superior hemi-retinal vein and superior branch retinal veins are most commonly affected, reflecting common anatomic variations in the posterior retinal distributions of retinal arteries and veins [27]. If it occurs or extends into the macula, retinal ischemia, indicated by capillary non-perfusion, will be visually significant. Elsewhere, areas of ischemia will result in scotomata of varying density that may or may not be symptomatic. However, the most important cause of visual loss in RVO is macular edema (ME) resulting from ischemic damage to perfused macular capillaries causing them to become incontinent and leak serum into the extracellular space of the macula, distorting anatomic relationships and reducing visual function. This tissue damage and dysfunction, along with the ischemia itself, lead to chronic inflammation which exacerbates and amplifies these changes, acting as an additional driving force maintaining the macular edema, and eventually leading to tissue degeneration [16] .

In mild and early non-ischemic, perfused cases of RVO (in which imaging of the retinal capillaries shows them to be present and intact), the macular capillaries are generally responsive to treatment. The response to treatment is to demonstrate reduced leakage and swelling of the macula and often improved visual acuity, which persists while effective treatment is present. Like any other disease process, milder

cases are generally more responsive to treatment, improving more, more quickly, and for longer periods than more severe cases. When the RVO is more severe and/or the ME more chronic, long-term ischemic damage to the macular capillaries, along with the effects of degenerative chronic inflammation, lead to permanent and irreversible damage to the microvasculature often rendering it unresponsive to any type of treatment, making visual loss permanent. Prior studies suggest the likelihood of developing degenerative, unresponsive ME is highest in cases 2 years or more in duration [11].

Severe ischemia resulting from total or near-total RVO results in loss of vascular perfusion and structure of both capillaries and larger vessels in the distribution of the watershed area served by the obstructed retinal vein. If this occurs in the macula irreversible visual loss occurs. Outside the macula, the main risk to visual function is the development of disc or retinal neovascularization (NV) and the resultant risks of vitreous hemorrhage, much less so, traction retinal detachment. The risk of NV is directly related to the degree and area of capillary non- perfusion, the more complete the capillary closure and larger the area involved, the greater the likelihood of developing disc or retinal NV. When such NV develops, it is typically at the junctions of perfused and non-perfused retina [16, 27].

As implied above, the clinical significance of RVO is largely due to a combination of severity and location. Unless completely non-perfused, and thus at risk for developing NV, extramacular RVO is generally inconsequential and requires no treatment. ME is the most common indication for treatment in RVO, thus RVO involving the macula is of primary importance. ME also may result from obstruction of the entire retinal outflow due to CRVO. In other cases, visually significant ME may result from obstruction of a small macular tributary retinal vein, sometimes described as a "twig" BRVO. Either may be difficult to treat, but generally the greater the area of impaired retinal circulation and greater the flow compromise, the more severe the ME and more difficult to treat [18].

Although the presumed thrombus at the heart of the VO primarily responsible for the impairment of blood flow will generally eventually resolve with re-cannalization of the vessel and restored or improved retinal vascular transit, damage to the retinal vasculature by this time in all but the very mildest cases is generally permanent. Thus, absent effective treatment, the ME associated with RVO will generally persist for many years, if not permanently. Because most effective treatments for RVO ME are short-lived, the clinical course of ME due to RVO is generally waxing and waning over many years [12].

Thus, the practical goal of treatment is to minimize both the severity of the ME, and the length of time the macula is swollen in order to prevent degenerative changes and preserve responsiveness to treatment with the hope that someday the ME will finally resolve and useful visual function will remain. Treatment of ME due to RVO is generally a long and difficult ordeal, with often modest rewards, for the patient and doctor alike [16, 20].

Subtypes of Retinal Vein Occlusion

Venous occlusive disease may affect either a branch retinal vein (BRVO), central retinal vein (CRVO), or in eyes in which the superior or inferior venous outflow of the retina has been occluded, the term hemiretinal vein occlusion (HRVO) is assigned.

Branch Retinal Vein Occlusion

BRVO occurs when a branch of the central vein is occluded. The site of obstruction usually occurs at a retinal venous artery intersection or crossover. BRVO usually occurs in the seventh decade of life [18]. An increased risk BRVO was seen in those with a history of cardiac disease, hypertension, an increased body mass index, history of elevated serum levels of alpha-2-globulin, and a history of glaucoma. Diabetes was not a strong independent risk factor for BRVO in one study. Elevated HDL cholesterol showed a decreased risk for BRVO [34]. Clinical findings for an acute BRVO, defined as one present for less than 6 months, consists of superficial and deep retinal hemorrhages, venous tortuosity and dilation, and retinal or macular edema [14].

Typically, the affected area is segmental in distribution corresponding to the region drained by the occluded branch retinal vein. Acutely, disc swelling and cotton wool spots may be present. The most affected branch is the superotemporal venous branch, seen 63% of the time. In almost all other cases, it is the inferotemporal branch [13]. Typically, visual acuity is worsened by ischemia of the macula, hemorrhage and or edema. Vision may not be affected if the blockage is outside the branches draining the macula or in the nasal retina. Generally, the peak of the distribution of the hemorrhages is the region where the obstruction occurred at an arteriovenous crossing. After 6 months, a BRVO may be defined as chronic. Collateral vessel formation may be seen along with a resolution of hemorrhage. A determination of perfusion status may be revealed with the use of fluorescein angiography. Existence of macular edema can be quantified with the use of OCT imaging. In about 40% of nonperfused or ischemic BRVO, retinal or disc neovascularization (NV) may develop. This may be further complicated by vitreous hemorrhage in about 60% of cases with NV. Neovascular tissue should not be confused with collateral vessel formation, which are venule to venule channels and can appear tortuous, dilated, intraretinal, and bypass the obstruction. Fluorescein angiography can be used to help differentiate. Neovascular glaucoma and neovascularization of the iris are not common in BRVO [14].

Central Retinal Vein Occlusion

CRVO is a common cause of visual loss in patients 50 years and older [14].

The Eye Disease Case−Control Study showed that systemic hypertension, diabetes mellitus, and open angle glaucoma are risk factors for the development of

CRVO [35]. In addition, hypercoaguable or hyperviscosity syndromes can increase risk. CRVO is distinguished by diffuse intraretinal hemorrhages are superficial and deep and spread from the optic nerve head out to the periphery in all four quadrants. Cotton wool spots may be seen, and optic nerve head and macular edema are usually present. During its clinical course, CRVO may resolve within a few months with minimal effect, or may persist for longer and sometimes worsen over this period of time. Neovascular glaucoma may develop in these cases. A CRVO may also be perfused or non-perfused. Angiography can help to differentiate. Perfused CRVO will generally have few hemorrhages and milder venous tortuosity and dilation. Minimal disc hyperemia may be seen with or without edema. Capillary nonperfusion tends to be minimal and cotton wool spots are generally rare. Perfused CRVO may become non-perfused [36]. Non-perfused or ischemic CRVO reveal significant retinal hemorrhages, cotton wool spots and disc, macular, and retinal edema. Macular edema is the primary cause of vision loss. There is notable venous dilation and tortuosity.

Hemiretinal Vein Occlusion

HRVO is seen in eyes with superior or inferior venous outflow of the retina has been blocked. Typically, one sees intraretinal hemorrhage and venous dilation and tortuosity involved either the superior or inferior half of the fundus. There is some debate whether HRVO represents a subtype of CRVO or BRVO. The course of HRVO is similar to that of BRVO. In some eyes, it is not possible to identify the occlusion site. Twenty percent of eyes show that the branch retinal veins draining the superior and inferior halves of the retina enter the lamina cribrosa separately before joining to form a single central retinal vein. The occlusion of one of these dual trunks of the central retinal vein within the nerve results in an HRVO. In some eyes, the nasal retina is not drained by a separate vein but by a branch of either the superior or inferior temporal vein. It is the obstruction of one of these veins draining both the nasal retina and the superior or inferior retina near the optic nerve that results in HRVO in the majority of eyes [30].

Conventional Photocoagulation

The Collaborative Branch Vein Occlusion Study (BVOS) was a multicenter, randomized clinical trial supported by the National Eye Institute designed to answer three questions regarding the management of BRVO related complications [4].

The questions the BVOS sought to answer were the following: Can grid argon laser photocoagulation improve visual acuity in eyes with visual acuity of 20/40 or worse caused by perfused macular edema? Can peripheral scatter argon laser

photocoagulation prevent the development of neovascularization? Can peripheral scatter argon laser photocoagulation prevent vitreous hemorrhage in eyes with neovascularization? [4].

In the BVOS, eyes that were randomized to treatment with grid laser photocoagulation who had a visual acuity of 20/40 or less were more likely to have visual acuity improvement and have a final vision of 20/40 or better than untreated eyes at 3 years. [5]. The treatment technique consisted of applying laser to the macula in a grid pattern, with the spots only in the area of vascular leakage evident on fluorescein angiogram. Spots were not to be placed closer to the fovea than the edge of the capillary free zone or farther into the periphery than the major vascular arcade. Thick intraretinal hemorrhage areas were to be avoided, as conventional laser uptake by blood within the retina can cause fibrosis. The recommend laser settings were typically 0.1 s duration, 50 to 100 micron spot size, and power sufficient to produce a light to medium white burn. Higher power was needed in thickened areas, and complications of overly heavy burns included subretinal hemorrhage and choroidal neovascularization, and areas of geographic atrophy that may eventually spread and risk involving the macula. The laser uptake occurs at the level of the retinal pigment epithelium (RPE) and slowly resulted in decreased retinal vascular leakage over a period of 2 to 3 months. The mechanism was unclear, although one theory was that the grid treatment resulted in retinal thinning which allowed the choroidal vasculature to support the inner retina and triggered autoregulatory constriction of the retinal vasculature and decreased leakage in the area [38].

Photocoagulation within the FAZ was always a concern. Staged approaches to treatment were typical, starting farther out and subsequently becoming closer toward the FAZ. Response to treatment was typically reassessed at 3 months. Retreatment was limited by photocoagulation scar development and decreasing space in which to add further laser spots.

In about 40% of untreated eyes with ischemic BRVO, NV develops [4]. The incidence of NV may be reduced to about 20% with the application of peripheral scatter laser photocoagulation. However, prophylactic laser was not recommended because if laser was added prior to NV as most eyes would have undergone laser treatment unnecessarily. Also, treatment of ischemic areas was effective for NV but not for macular edema. Vitreous hemorrhage developed in 60% of the 40% of untreated eyes with ischemic BRVO with NV. By adding peripheral scatter laser when NV first developed, one could decrease vitreous hemorrhage risk by 30%. The BVOS date showed that applying laser after the onset of NV was as effective in preventing vitreous hemorrhage as if it were applied before the development of NV. Sector PRP consisted of applying 200 to 500 micron spots of medium intensity laser spaced about one spot width apart to the entire area of ischemic retina and two disc diameters away from the fovea.

The Central Vein Occlusion Study (CVOS) was a multicenter, randomized, clinical trial designed to answer three questions about laser management of CRVO related complications including macular edema and anterior segment NV [36].

The questions the CVOS sought to answer were: Does macular grid pattern laser improve visual acuity in CRVO eyes with perfused macular edema? Does early PRP prevent iris NV in eyes with nonperfused CRVO? Is early PRP more effective than PRP at the first identification of iris NV in preventing neovascular glaucoma in eyes with perfused CRVO?

The CVOS found that eyes that were 20/50 or worse that received macular grid laser for macular edema did not have statistically significant improvement in visual acuity, although edema was decreased angiographically. Despite angiographic improvement, the visual outcome was comparable in eyes that were treated and that were not treated with laser. Therefore, the CVOS did not recommend the use of grid photocoagulation for CRVO macular edema.

The CVOS also did not support routinely performing prophylactic panretinal photocoagulation (PRP) for all ischemic CRVOs because in many of these eyes rubeosis never developed, and the treatment does not always prevent it from occurring [36]. Instead, it was recommended that the eyes be monitored closely and treated with PRP after iris or angle NV is first noted. This generally induced regression evident in 2 to 4 weeks post treatment. If any sign of NV progression was noted, supplemental PRP was recommended. Prophylactic treatment before NV of the iris developed could be considered in very ischemic CRVO. Rubeosis could still develop with prophylactic PRP, so close monthly examinations were still warranted. PRP could also be applied if disc or retinal NV was evident, as in diabetic retinopathy. With the advent of intravitreal injection of anti-VEGF agents, it became a superior option for early treatment of both and rapid reversal of edema and NV, superior to what conventional photocoagulation could offer. Certain sequelae of CRVO could also interfere with the delivery of PRP, in which case intravitreal injection was an alternative. If rubeosis and posterior synechiae prevented pupillary dilation, adequate PRP delivery may not be feasible. Also, corneal edema from elevated intraocular pressure may prevent PRP application. Vitreous hemorrhage could also limit laser application. Intravitreal anti-vascular endothelial growth factor (VEGF) drugs have become a mainstay in all these scenarios today. Also, since intravitreal anti-VEGF medications work rapidly and can be delivered at the onset of vascular occlusion, long term degenerative changes particularly to the macula secondary edema could be minimized when compared to laser photocoagulation protocols. In later studies, conventional PRP was studied to see if hoped for reduction in peripheral retinal ischemia by treating areas of peripheral capillary non-perfusion in CRVO might help reduce ME, but found not to be effective [9].

Intravitreal steroids such as dexamethasone and triamcinolone are also alternatives to anti-VEGF medications in retinal vein occlusion, especially in resistant cases. However, as monotherapy, steroids alone have not shown superiority to anti-VEGF medication.

Steroids also have more side effects after repeated dosing, including cataract formation and elevated intraocular pressure. Also, combination therapy of steroid and anti-VEGF has not shown superiority over anti-VEGF monotherapy [2]. However, intravitreal steroid implants such as Ozurdex has the advantage of controlling

edema in retinal vein occlusion for longer term, thus reducing the need for frequent injections.

Chorioretinal Anastomosis for Central Retinal Vein Occlusion

One procedure, designed to address the core cause of CRVO, is Laser Chorioretinal Anastomosis. This involves the creation of a laser-induced chorioretinal anastomosis (LCRA) between the blocked high pressure retinal venous circulation and the unobstructed low pressure choroidal venous circulation. This would, in theory, lower central venous pressure and help relieve macular edema [9]. The technique involves choosing a site, nasal to the optic disc preferably, to minimize risk of submacular hemorrhage or choroidal neovascularization. The laser application is at the margin of the retinal vein and designed to rupture Bruch's membrane and the wall of the vein simultaneously. Typical settings with the Ellex laser are power of 2.5 to 3.5 W, 50 micron spot size, and 0.1 duration. Argon green laser has been used with a spot size of 50 micron, 100 ms duration, and power from 3.5 to 6.0 W. Argon blue-green laser combined with Nd-YAG laser and krypton red laser has also been used [21]. High power is generally needed, and indocyanine green sensitization may help increase absorption. Anastomosis may take anywhere from 2 to 6 weeks to form. Complications of the procedure include choroidal neovascularization, vitreous and subretinal hemorrhage, epiretinal membrane formation and traction retinal detachment [22]. It is important to confirm presence of posterior vitreous detachment prior to the procedure to help reduce risk of vitreoretinal complications.

Combination therapy of LCRA and intravitreal anti-VEGF has been shown to reduce injection frequency and duration along with improved vision and anatomical outcomes. The procedure has had limited adoption thus far, likely due to its inherent risks and the effectiveness intravitreal anti-VEGF medications.

Short Pulse CW Laser (SRT, 2RT, PASCAL)

Short pulse continuous wave lasers include Selective Retina Therapy (SRT), Nanosecond laser (2RT) and PASCAL or Pattern Scanning Laser. All are designed with the intention of reducing but still producing laser-induced retinal damage (LIRD), as well as reducing treatment related discomfort. The following is a review of these technologies and their application in the treatment of retinal vein occlusion. There are notably few published studies to date.

PASCAL

The PASCAL, or pattern scanning laser, was the first partially automated laser that allows the physician to choose various laser pattern presets to apply to the retina with one pedal depression. Destruction of retinal photoreceptors to reduce their oxygen consumption to decrease retinal oxidative stress was the goal of the PASCAL design. With regard to retinal vein occlusions, this suggests that it's most suitable application would be treatment of retinal neovascularization (NV). The laser was a short pulse (~10us) duration 532 continuous wave laser [8].

PASCAL PRP has been found to be less painful than conventional PRP because of less heat spread and the short duration of the laser spot. However, it has been reported to have less therapeutic benefit than conventional PRP [7]. In an attempt to improve the performance of the PASCAL for proliferative diabetic retinopathy (PDR), an analogue of NV complicating RVO, treatment density was increased. Despite this, PASCAL was still found to be less effective than conventional PRP or ranibizumab for PDR [3]. An algorithm was devised for PASCAL to be used as sublethal treatment and avoid LIRD, called end point management (EPM). This involved titrating the power using a test burn, and then reducing the power a proscribed amount. One report on PASCAL EPM treatment of CSR reported no LIRD [19]. Despite titration, the short pulse CW laser's narrow therapeutic range (0.010 W) makes it highly susceptible to surgeon misjudgment and eye-specific variations such as pigmentation, retinal thickness, and media opacity, making avoidance of LIRD, while theoretically possible, clinically unreliable [8]. At the same time, the short CW pulse limits heat spread from the spot of retinal ablation, resulting in little affected but surviving retina to produce a therapeutic effect, limiting its effectiveness [26]. It has not been shown to date that PASCAL effectively for treatment of branch or central RVO [8] .

Selective Retina Therapy (SRT)

SRT was designed using microsecond pulses to selectively target the RPE for damage while reducing injury to the photoreceptors and choroid. One theory of its mechanism of action is the development of a new RPE cell barrier, strengthening the RPE pump and barrier function. Another theory is that activation HSP 70, and tissue matrix metalloproteinases might play a role in healing of the RPE damage resulting from SRT [32]. SRT has not been reported for treatment of RVO or its complications.

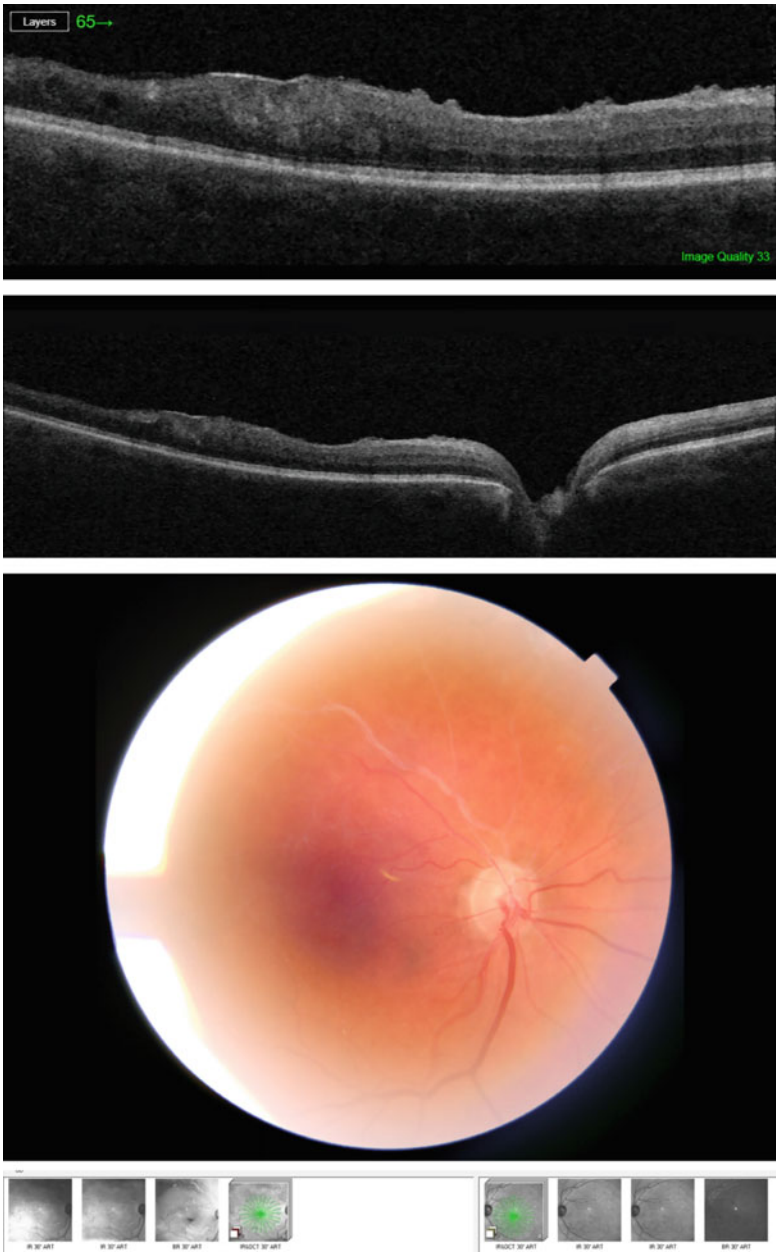
Nanosecond Laser (2RT)

Another laser with a goal of even more precisely selectively targeting the RPE are pulsed lasers in the nanosecond range (2RT). The 2RT laser (Ellex Pty Ltd, Adelaide Australia), is a 532 nm Q switched Yag laser. 2RT is designed to photodisrupt the RPE, hoping to avoid damage to Bruch's membrane and the neurosensory retina on either side [15] Nanosecond 2RT laser has been studied for the treatment of AMD and DME, but not thus far in RVO [15, 39] (Fig. 7.1).

Microsecond Pulsed Laser (MPL)

Before the arrival of intravitreal drugs, conventional laser photocoagulation was the only therapy for RVO. Although better than no treatment at all, photocoagulation had limited effectiveness, many adverse treatment effects, and little ability to retreat due to the threat to visual function with accumulating LIRD. With the advent of intravitreal injection, use of intravitreal medications rapidly replaced photocoagulation as it spared the retina while reducing macular edema. However, the results of drug therapy for RVO are still not always satisfactory, generally required frequently repeated treatment over many years [31]. Of all applications for MPL, MPL, like all other laser modes including photocoagulation, laser tends to have the least robust therapeutic effect in the treatment of retinal vein occlusions [8]. This is most likely due to the difference in disease process which is caused by dysfunction in inner retinal circulation and oxygenation rather than chronic progressive dysfunction of the RPE. MPL targets the retinal pigment epithelium which appears to have a limited role in retinal vein occlusion, which represents a catastrophic failure of retinal vascular perfusion, whether ischemic or non-ischemic. Either may cause permanent damage to the retinal vasculature and compromise perfusion, resulting in macular edema [12, 14]. In extreme injury or degeneration due to persistent chronic swelling, the edema may not respond to any therapy and atrophic and pigmentary damage may develop, worsening vision and limited any possibility of visual recovery [16].

Current treatment for retinal vein occlusion relies predominantly on monthly injection of intravitreal medications. However, tissue sparing laser like MPL can still play a part in a treatment regimen for RVO. Combination therapy has been shown to be beneficial by reducing injection burden [11, 26, 33, 37]. Less severe RVO may respond MPL alone, precluding the need for injection. A study comparing the efficacy of threshold grid laser treatment to subthreshold grid laser treatment with an infrared MPL for macular edema from BRVO showed similar vision improvements and edema resolution when compared to conventional threshold photocoagulation, but without LIRD in the MPL eyes [29]. In another study, Parodi et al. showed


Layers
65
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◀**Fig. 7.1** OCT macula fluorescein angiogram fundus photos 73 year old female with history of branch retinal vein occlusion and neovascularization who presented in 2015 with Hand Motion vision OD due to secondary vitreous hemorrhage. She required only Avastin × 3 and then was treated with SDM q 3 months. Her vision improved to 20/30 + 2 as of 2021 and has not required further Avastin injections

that vision results were superior with MPL combined with intravitreal triamcinolone compared to photocoagulation for RVO [28]. Luttrull et al. has also reported effective reversal of macular edema with subthreshold diode micropulse laser treatment absent LIRD by high-resolution macular imaging including spectral-domain OCT and autofluorescence fundus photography [26]. These studies suggest that MPL may help macular edema by stimulation of the RPE to normalize cytokines expression and response, increase the transretinal RPE fluid pump effectiveness, and reduce inflammation due to its anti-inflammatory effects [12]. It is useful to remember that anti-VEGF drugs are not anti-inflammatory and cannot address this critical part of the disease process. Laser-induced improvement in macular function and reduction of chronic inflammation may help preserve macular and visual function in the face of chronic recurrent swelling, the typical course of even effectively treated RVOs [14, 14] Even though MPL is generally insufficient as monotherapy for RVO macular edema, maximum MPL-induced preservation of macular function may afford the eye with RVO improved long-term prospects for retaining vision over the course of the disease.

NV development in ischemic retinal vein occlusion can be treated effectively with MPL, analogous to conventional laser photocoagulation in proliferative diabetic retinopathy. [24] MPL can be applied to the ischemic retina while sparing the retina and minimizing the need for intravitreal injections. Analogous to age-related geographic atrophy, MPL also can be used in hopes of reducing atrophic pigmentary damage that may develop due to chronic and recurrent macular edema in RVO, to limit scar expansion from previous photocoagulation, and augment drug treatment in eyes with scarring from prior conventional photocoagulation that cannot tolerate additional retinal damage [24, 25].

Gawecki [12] has shown that in terms of visual function, MPL may be more effective that conventional photocoagulation, likely due to avoidance of LIRD, with similar visual results to retina-sparing drug therapy in RVO [12]. MPL monotherapy has not been found to be as effective as intravitreal drug therapy, be it anti-VEGF medication or steroids [28]. Several studies of MPL with and without ranibizumab found that addition of MPL to ranibizumab for macular edema due to RVO did not improve macular thickening or VA, but did result in a reduced frequency of intravitreal injections [6, 11, 33]. Inagaki et al. showed that micropulse in patients with chronic edema in RVO and visual acuity better than 20/40 may benefit from MPL alone for long-term management [17] (Fig. 7.2).

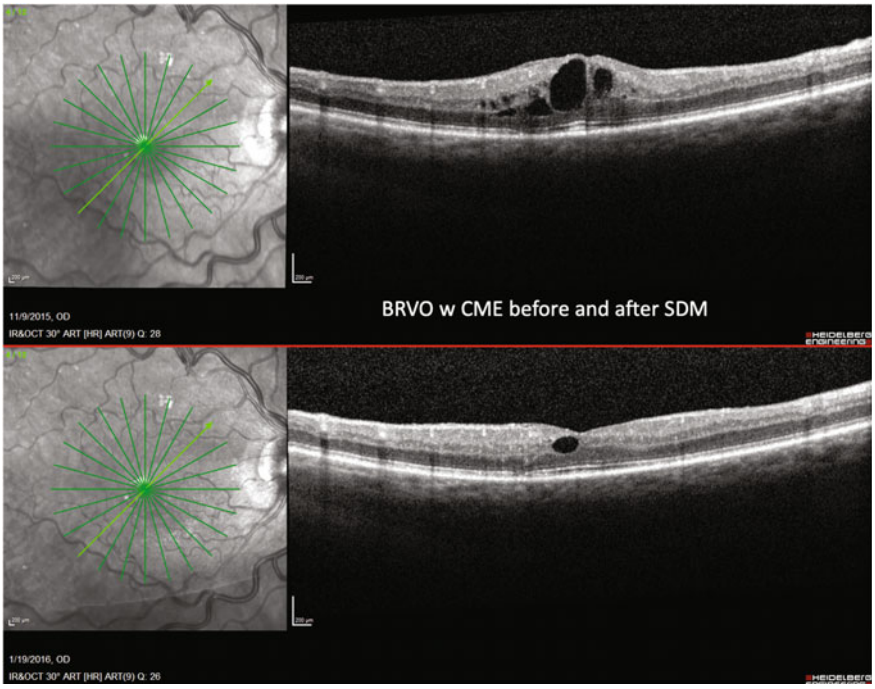

Fig. 7.2 OCTs of and eye with a branch retinal vein occlusion before and after MPL panmcular SDM monotherapy for CME. Not marked resolution of macular edema. While SDM is seldom effective monotherapy for RVO with ME, it may reduce the number of intravitreal injections required over time, and in some cases, such as mild ME or where injections are not possible or refused, SDM may be effective, as in the eye shown here

Retinal Artery Occlusion

Retinal arterial occlusion presents other potential roles for MPL. Fundus examination of CRAO reveals superficial whitening of the retina usually mostly in the macular region. A "cherry red spot" can sometimes be seen, because thinning of the opaque ischemic retina in the fovea allows visualization of the subretinal pigmentation. Segmentation of the blood column, or box-carring, may be seen in severe CRAO. In 20−40% of cases, emboli can be found. These are typically calcific or cholesterol, originating in the heart or internal carotid arteries. Ocular complications of CRAO, in addition to vision loss, include rubeosis and disc neovascularization. Rubeosis may occur in 18% of eyes at a mean time of 4−5 weeks after occlusion, with a range of 1−15 weeks [10].

Early in the course of the disease, conventional PRP in severe/complete CRAOs was to ablate the ischemic retina outside the major vascular arcades to decrease the ischemic drive and amount of VEGF released that might lead to new vessel formation, particularly in the anterior segment [10]. The typical visual adverse effects

of conventional PRP, such as permanent decrease in peripheral, color, and night vision, are less a concern in CRAO due to the already generally profound visual loss. Conventional panretinal photocoagulation can induce regression of iris vessels in about 65% of eyes. Disc neovascularization of the optic disc occurs in 2−3% of eyes [10]. There are no literature reports of the PASCAL, SRT, 2RT or MPL for the treatment of RAOs. However, experience with other causes of ischemic ocular neovascularization such as proliferative diabetic retinopathy suggest that MPL or PASCAL treatment may be helpful in CRAO should NV develop [7, 25].

Summary

Macular photocoagulation for macular edema from RVOs should be avoided, as it is ineffective in CRVO, and does not improve outcomes compared to retina sparing drug and/or MPL laser and may lead to late geographic atrophy in the macula due to laser scar expansion and coalescence. PRP for NV, particularly anterior segment NV from ischemic retinal vein occlusion or central retinal artery occlusion is effective, slightly slower acting than anti-VEGF therapy, but longer acting. The clinical setting should indicate if one, or both, is most appropriate to address anterior segment NV at any point in time. Retina-sparing sparing SDM MPL peripheral retinal treatment of ischemic eyes may also be effective, limiting peripheral vision loss and treatment associated inflammation that may aggravate macular edema.

Because the course of ME in BRVO waxes and wanes over many years, maximizing preservation of visual function while minimizing intravitreal injections is desirable. MPL maybe effective as monotherapy for eyes with better VA and lesser degrees of macular thickening. In eyes with worse VA and greater degrees of macular thickening, the addition of MPL has been shown to reduce the frequency of intravitreal injections. Finally, the development of anti-VEGF drug tolerance may occur over the long course of RVO treatment, rendering medication ineffective. MPL has been shown to reverse anti-VEGF drug tolerance in wet AMD [23]. MPL may thus also reduce the risk of drug tolerance in RVO, possibly accounting in part for reduced in anti-VEGF injection frequency in RVO management when combined with MPL. Because MPL is retina-sparing, MPL can be repeated as often as needed without adverse treatment effects, and important consideration as treatment of macular edema due to RVO may go on for years [31].

References

1. Arichika S, Uji A, Ooto S, Muraoka Y, Yoshimura N. Effects of age and blood pressure on the retinal arterial wall, analyzed using adaptive optics scanning laser ophthalmoscopy. Sci Rep. 2015;20(5):12283. https://doi.org/10.1038/srep12283.PMID:26192115; PMCID:PMC4507481.

2. Ashraf M, Ahmed A, Souka R. Steroids in central retinal vein occlusion: is there a role in current treatment practice?. J Ophthalmol. 2015.
3. Beaulieu WT, Bressler NM, Melia M, et al. Diabetic retinopathy clinical research network. Panretinal photocoagulation versus ranibizumab for proliferative diabetic retinopathy: patient-centered outcomes froma randomized clinical trial. Am J Ophthalmol. 2016;170:206–13.
4. Branch Vein Occlusion Study Group. Argon laser scatter photocoagulation for prevention of neovascularization and vitreous hemorrhage in branch vein occlusion a randomized clinical trial. Arch Ophthalmol. 1986;104:34−41.
5. Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. Am J Ophthalmol. 1984;98:271−82.
6. Buyru OY, Akkaya S, Aksoy S, Simsek MH. Comparison of ranibizumab and subthreshold micropulse laser in treatment of macular edema secondary to branch retinal vein occlusion. Eur J Ophthalmol. 2018;28:690–6.
7. Chappelow AV, Tan K, Waheed NK, Kaiser PK. Panretinal photocoagulation for proliferative diabetic retinopathy: pattern scan laser versus argon laser. Am J Ophthalmol. 2012;153:137–42.
8. Chhablani J, Roh YJ, Jobling AI, Fletcher EL, Lek JJ, Bansal P, Guymer R, Luttrull JK. Restorative retinal laser therapy: present state and future directions. Surv Ophthalmol. 2018;63(3):307−28.
9. Chorioretinal Anastomosis for Central Retinal Vein Occlusion. A review of its development, technique, complications, and role in management. Asia Pac J Ophthalmol. 2020;9(3):239−49.
10. Duker JS, Brown GC, Sivalingam A. A prospective study of acute central retinal artery obstruction. The incidence of secondary ocular neovascularization. Arch Opthalmol. 1991;109:339–42.
11. Garweg JG, Zandi S. Retinal vein occlusion and the use of a dexamethasone intravitreal implant (Ozurdex®) in its treatment. Graefes Arch Clin Exp Ophthalmol. 2016;254(7):1257–65. https://doi.org/10.1007/s00417-016-3350-x. Epub 2016 May 13. PMID: 27178087; PMCID: PMC4917582.
12. Gawecki M. Micropulse laser treatment of retinal diseases. J Clin Med. 2019;8(2):242.
13. Gutman FA, Zegarra H. The natural course of temporal retinal branch vein occlusion. Trans Am Acad Ophthalmol Otolaryngol. 1974;78:178–92.
14. Gutman FA. Evaluation of a patient with central retinal vein occlusion. Ophthalmology. 1990;90:481–3.
15. Guymer RH, Brassington KH, Dimitrov P, et al. Nanosecond- laser application in intermediate AMD: 12 month results of fundus appearance and macular function. Clin Exp Ophthalmol. 2014;42:466–79.
16. Hayreh SS. Photocoagulation for retinal vein occlusion. Prog Retin Eye Res. 2021;85: 100964. https://doi.org/10.1016/j.preteyeres.2021.100964.Epub. PMID:33713810.
17. Inagaki K, Ohkoshi K, Ohde S, Deshpande GA, Ebihara N, Murakami A. Subthreshold micropulse photocoagulation for persistent macular edema secondary to branch retinal vein occlusion including best-corrected visual acuity greater than 20/40. J Ophthalmol. 2014;2014:251−7. https://doi.org/10.1155/2014/251257. Epub 2014 Sep 4. PMID: 25276413; PMCID: PMC4167817.
18. Johnston RL, Brucker AJ, Steinmann W, et al. Risk factors of branch retinal vein occlusion. Arch J Ophthalmol. 1993;116:286–96.
19. Lavinsky D, palanker D. Nondamaging photothermal therapy for the retina: initial clinical experience with chronic central serous retinopathy. Retina 2015;35:213–22.
20. Li Y, Hall NE, Pershing S, Hyman L, Haller JA, Lee AY, Lee CS, Chiang M, Lum F, Miller JW, Lorch A, Elze T. Age, gender, and laterality of retinal vascular occlusion: a retrospective study from the IRIS® registry. Ophthalmol Retina. 2022;6(2):161–71. https://doi.org/10.1016/j.oret.2021.05.004. Epub 2021 May 12 PMID: 33991710.
21. Lu N, Wang NL, Li ZH, Wang GL, Zhang F, Peng XY. Laser-induced chorioretinal venous anastomosis using combined lasers with different wavelengths. Eye (Lond). 2007;21(7):962–7. https://doi.org/10.1038/sj.eye.6702362. Epub 2006 May 19 PMID: 16710438.

22. Luttrull JK. Epiretinal membrane and traction retinal detachment complicating laser-induced chorioretinal venous anastomosis. Am J Ophthalmol. 1997;123:698–9.
23. Luttrull JK, Chang DB, Margolis BW, Dorin G, Luttrull DK. LASER RESENSITIZATION OF MEDICALLY UNRESPONSIVE NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: efficacy and implications. Retina. 2015;35(6):1184–94. https://doi.org/10.1097/IAE.0000000000000458. PMID: 25650711.
24. Luttrull JK, Musch DC, Spink CA. Subthreshold diode micropulse panretinal photocoagulation for proliferative diabetic retinopathy. Eye (Lond). 2008;22(5):607–12. https://doi.org/10.1038/sj.eye.6702725. Epub 2007 Feb 9 PMID: 17293791.
25. Luttrull JK, Sinclair SH, Elmann S, Chang DB, Kent D. Slowed progression of age-related geographic atrophy following subthreshold laser. Clin Ophthalmology. 2020;14:2983–2993. https://doi.org/10.2147/OPTH.S268322.eCollection.
26. Luttrull JK, Sramek C, Palanker D, Spink CJ, Musch DC. Long term safety, high resolution imagin, and tissue temperature modeling of subvisible diode micropulse photocoagulation for retinovascular macular edema. Retina. 2012;32:375–86.
27. Oztas Z, Akkin C, Nalcaci S, Ilim O, Afrashi F. Branch retinal vein occlusion: the importance of the topographical distribution of retinal vessels among risk factors. Eye (Lond). 2017;31(5):726–31. https://doi.org/10.1038/eye.2016.318. Epub 2017 Jan 13. PMID: 28085135; PMCID: PMC5437329.
28. Parodi MB, Iacono P, Ravalico G. Intravitreal triamcinolone acetonide combined with subthreshold grid laser treatment for macular edema in branch retinal vein occlusion: a pilot study. Br J Ophthalmol. 2008;92:1046–50.
29. Parodi MB, Spasse S, Iacono P, Di Stefano G, Canziani T, Ravalico G. Subthreshold grid laser treatment of macular edema secondary to branch retinal vein occlusion with micropulse infrared 810nm diode laser. Ophthalmology. 2006;113(12):2237–42. In milder cases, MRT alone may be sufficient. Ischemic RVOs with retinal or disc neovascularization.
30. Sanborn FE, Magargal LE. Characteristics of the hemispheric retinal vein occlusion. Ophthalmology. 1984;91:1616–26.
31. Schmidt-Erfurth U, Garcia-Arumi J, Gerendas BS, Midena E, Sivaprasad S, Tadayoni R, Wolf S, Loewenstein A. Guidelines for the management of retinal vein occlusion by the european society of retina specialists (EURETINA). Ophthalmol. 2019;242(3):123–62. https://doi.org/10.1159/000502041. Epub 2019 Aug 14. PMID: 31412332.
32. Sramek C, Mackanos M, Spitler R, et al. Non-damaging retinal phototherapy: dynamic range of heat shock protein expression. Invest Ophthalmol Vis Sci. 2011;52:1780–7.
33. Terashima H, Hasebe H, Okamoto F, Matsuoka N, Sato Y, Fukuchi T. Combination therapy of intravitreal ranibizumab and subthreshold micropulse photocoagulation for macular edema secondary to branch retinal vein occlusion: 6 month result. Retina. 2019;39:1377–84.
34. The Eye Disease Case-Control Study Group. Risk factors for branch retinal vein occlusion. Am J Ophthalmol. 1993;116:286.
35. The Eye Disease Case-Control Study Group 1996 Risk factors for central retinal vein occlusion. Arch Ophthalmol. 1996;114:545−54.
36. The Central Vein Occlusion Study Group. Natural history and clinical management of central retinal vein occlusion. Arch Ophthalmol. 1997;115:486−91.
37. Eng VA, Leng T. Subthreshold laser therapy for macular edema from branch retinal vein occlusion: focused review. Brit J Ophthalmol. 2020;104(9):1184–9.
38. Wilson DJ, Finkelstein D, Quigley HA, et al. Macular grid photocoagulation. An experimental study on the primate retina. Arch Ophthalmol. 1988;106:100–5.
39. Wood JP, Plunkett M, Previn V, Chidlow G, Casson RJ. Nanosecond pulse lasers for retinal applications. Lasers Surg Med. 2011;43(6):499–510. https://doi.org/10.1002/lsm.21087. PMID: 21761420.

Chapter 8
Laser Treatment in Intraocular Tumors

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There are following intra ocular tumors:

Malignant tumors: choroidal melanoma, iris/irido-ciliary melanoma, retinoblastoma, metastatic tumor.

Benign tumors: iris nevus, choroidal hemangioma, retinal capillary hemangioma, vasoproliferative tumors, astrocytoma, iris melanocytoma (Table 8.1).

Some of the more important conditions that lend themselves to this modality of management are discussed below.

Uveal melanoma.

Laser photocoagulation. Death rate associated with uveal melanoma decreased in last decades from 60–80% to 25–30% [1, 2]. It's connected with improvement of early diagnostic and development of new possibilities of organ preservation treatment.

Currently there are two main directions in the therapy of patients with uveal melanomas–enucleation and organ preservation treatment. Enucleation was the main and alone treatment and the most reliable. However, analysis of long-term outcome showed that enucleation doesn't prevent development of metastatic lesions. Also it may leads to promotion of spreading of melanoma cells [3–8].

Photocoagulation as a means of treatment of of the choroidal melanoma was introduced by Meyer-Schwickerath in 1952 [9]. The technique aimed at surrounding the tumor with a scar which both limited its spread and deprived it of its blood supply. Subsequently the tumor itself was ablated by direct treatment.

Currently laser photocoagulation as monotherapy is used for limited indications. There are: small, pigmented and postequatorial uveal melanomas [2, 10–14]. Indicated for laser photocoagulation are: 3 mm or smaller in height and less 4 DD in diameter [13–15].

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_8

Table 8.1 Laser treatment options in intra ocular tumors

Type of tumor	Parameters of tumor for laser treatment	LPC	TTT	PDT	Combination with radiation
Choroidal melanoma		Up to 3.0 mm height, pigmented	Up to 4.0 mm height	Up to 4.0 mm height	Up to 6.0-12 mm height
Iris/irido-ciliary melanoma		+	+	No role	+
Metastatic tumors	Lesions up to 3 mm basal diameter and 2 mm height	+	+	No role	+
Retinoblastoma	Lesions up to 3 mm basal diameter and 2 mm height Cryo/TTT acceptable options Forms important part of consolidation after chemotherapy	+	+	No role	+
Choroidal hemangioma	Progressing	No role	+	+	No role
Retinal capillary hemangioma	Progressing	+, including feeder vessel closure	No role	+	
Vaso proliferative tumors		Thermal laser can be used. Combination with anti-VEGF	No role	No role	Brachytherapy needed on occasion
Astrocytoma		Rarely laser used	No role	No role	No role
Iris nevus		No role	No role	No role	No role
Iris melanocytoma		No role	No role	No role	No role

LPC: laser photocoagulation, TTT: transpupillar thermotherapy, PDT: photodynamic therapy. +: application is possible

Additional conditions are–maximal mydriasis and transparency of optic medias.

It may be used lasers with different wave lengths—532, 577, 810, 1064 nm (31, 105). Laser energy is absorbed by pigment epithelium cells of the retina and melanin in the choroid with following transformation into heat energy. This heat leads to denaturation of proteins of melanoma cell and their necrosis.

Operation has two stages. The first is formation of a restrictive barrier. Laser burns are applied 500−1500 mcm far from a visible border of a tumor. Diameter of a laser

burn is 50−500 mcm, exposition 0.5−1.0 s., power 100−700 mW. Laser lesion must be confluent, III stage by L'Esperance, but not damaging retinal vessels [16].

The second stage−coagulation of a tumor starts 3−4 weeks later when scar is formed. Parameters of laser are following: diameter of a laser burn is 200−1000 mcm, exposition 0.5−2.0 s., power 200−850 mW [17]. Laser lesion must be III−IV stage by L'Esperance. Laser power may widely vary because of an optic medias and pigmentation of melanoma. Laser burns are applied from a periphery of a tumor toward a central part as roof tiles. Starting power on the periphery of the tumor is much less then on central part.

Possible complications of laser photocoagulation are: retinal hemorrhages, occlusion of retinal vessels, optic disc swelling, exudative retinal detachment, vitritis and uveitis, choroidal neovascularisation, cystoids macular edema, IOP elevation, cataract.

A number of researchers [11, 18] showed promise of using laser with a wavelength 1.06 μm, capable of penetrating deep in tumor tissues and carrying sufficiently large thermal energy. Moreover, by changing the spatial and temporal characteristics of laser radiation and treatment tactics at the same time, it is possible to destroy a tumor with thickness of up to 4 mm [19].

Local radiotherapy had a significant impact on the enhancement of organ-preserving treatment for patients with uveal melanomae. Thus, according to a number of researchers [18, 20, 21], application of beta-therapy with the use of radioactive Sr-90 makes it possible to destroy the tumor with thickness of up to 5 mm while using Ru-106 allowed to achieve positive result with thickness tumors of up to 7 mm [18]. More impressive results have been obtained using gamma radiation for local treatment of uveal melanoma. Char D. H. and Grizzard W. S. [22, 23] succeeded to destroy a 12mm tumor by irradiating helium ions. The positive experience of using light energy and the application of beta-therapy in the treatment of patients with uveal melanoma, as well as the results of studying their biological effect on tumor cells, made it possible to substantiate the expediency of their combined use to obtain a potentiated positive therapeutic effect [24].

Conducted at the Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine analysis of the results of combined organ-preserving treatment (photocoagulation and application beta-therapy) in 560 patients with uveal melanomas with a tumor thickness of 2 to 12 mm showed in 27% of cases complete resorption of the tumor, in 35.9%—partial resorption, in 17.8 %—stabilization of malignant growth, and in 19.3% of cases—recurrence of tumor growth. In this group of patients, mortality from metastases after 5 years was 13.2% [12], while after enucleation it was 35.5% [8, 25].

Terentyeva et al. [12, 18] treated patients with uveal melanoma using combined photocoagulation and beta therapy (Ru−106). They have shown that this combined treatment allows the management of intraocular tumors with a thickness of more than 7 mm.

Transpupillar thermotherapy (TTT). Originally described by Oosterhuis, TTT was suggested for the treatment of small tumors near the optic disk or fovea [26]. TTT is performed by diode laser with wave length 810 nm. Infrared radiation penetrates

into melanoma tissue much deeper then visible laser with wave length—514, 532, 577 nm or even red radiation. So, it may heat melanomas with bigger height [27]. Histological examination of uveal melanomas after TTT shows necrosis 3.9 mm in depth [26].

TTT may be used as monotherapy or in combination with radiation therapy or/and surgery removal of a tumor [26, 28–30].

As monotherapy TTT is performed for melanomas with height 3.5−5.0 mm and diameter of basement less 12 mm (Figs. 8.1 and 8.2) [26, 31]. Parameters are following: diameter of laser beam 1−3 mm, exposition 60−90 s., power—200−900 mW, number of treatments 1−6 with interval 1−6 months [32–36]. Treatment includes exposition of tissues 200−1500 mcm from visible edge of melanoma [28, 37].

TTT starts from low power increasing it till mild graying of surface of tumor at the end of exposition. If surface starts graying at the beginning of exposition power must be decreased by 100 mW [28, 38]. In case of melanoma with height more than 4−5 mm may be used combination with brachytherapy [26, 30].

Effectiveness of TTT as monotherapy of melanomas with height less 3.5 is more than 90% [34, 36, 37]. However, Stoffelns B.M. used TTT of uveal melanomas with height up to 4.5 mm and diameter up to 12 mm [39, 31].

Possible complications of TTT are: retinal hemorrhages, occlusion of retinal vessels, traction of the retina, optic disc swelling, exudative retinal detachment, vitritis, choroidal neovascularisation, cystoid macular edema [33, 37, 40, 41].

Photodynamic therapy (PDT) with verteporphin. Cellular injury from PDT is mediated by singlet oxygen. The main advantage of PDT is the selectivity of the treatment and minimal disruption of tissues. PDT is a two steps treatment. The first step is intravenous injection of photosensitiser verteporphin with dosage 6 mg for square meter of a body surface of a patient. During the second step the photosensitizer verteporfin is activated by non-thermal red laser to obtain closure of neovascular structures. Parameters of laser are following: wave length 689 nm, diameter of laser beam 1−7 mm, exposition 83 s., energy–standard dose of 50 J/cm^2, irradiance of 600 mW/cm^2, number of treatments 1−6 with interval 3 months [42].

Preclinical and clinical studies indicated that PDT is a safe, selective, and effective treatment for choroidal neovascularization in age-related macular degeneration. No significant damage to the neurosensory retina was found, which explains why PDT does not cause loss of visual acuity and may be used in a larger population than laser photocoagulation [43].

Although treatment of small pigmented or amelanotic posterior choroidal melanoma with PDT effectively preserves visual acuity (Figs. 8.3 and 8.4). Roelofs K.A. et al. showed 5-year treatment-success calculated by Kaplan-Meier analysis was only 38.4%. Recurrences after PDT tend to occur along the tumor edges, often with minimal increase in thickness. Given the substantial risk of treatment failure, primary PDT with vertepofrin is recommended in exceptional cases of choroidal melanoma, for which other treatments with greater tumor control are not a feasible option [44, 45]. Possible complications of PDT are: retinal and subretinal hemorrhages, exudative retinal detachment and occlusion of retinal and choroidal vessels.

The existing methods of organ-preserving treatment of uveal melanomas and the evaluation of the effectiveness of their use allow us to draw the following conclusions:

Traditional enucleation for uveal melanoma, especially for small and medium-sized tumors, is being replaced by organ-preserving treatment techniques, which, in addition to saving the eye, significantly improve the prognosis for the patient's life. An essential point of organ-preserving treatment is that in 41−52% of cases it is possible to preserve visual functions, which is very important in the presence of a tumor in a single eye.

The effectiveness of treatment of intraocular melanomas depends on a size, cellular structure, pigmentation and localization of the tumor.

Choroidal hemangioma.

Choroidal haemangiomas are a benign vascular tumour of the choroid, which can be either circumscribed or diffuse. Circumscribed choroidal haemangiomas have no systemic association while diffuse choroidal haemangiomas are often associated with Sturge-Weber syndrome. The presentation of a choroidal haemangioma is dependent on its location, with diffuse haemangiomas more likely to cause retinal detachment [46]. Many however are asymptomatic and found incidentally. Treatment is indicated if a patient's vision is affected or threatened due to exudative retinal detachment, macular oedema or the lesions proximity to the fovea. Haemangiomas that involve the macula often cause reduced vision, metamorphopsia and progressive hypermetropia [47].

Diffuse choroidal haemangiomas have been treated with many modalities including radiotherapy, anti-vascular endothelial growth factor (VEGF), TTT, PDT and laser photocoagulation. PDT is an ideal treatment option as it selectively destroys tumour vasculature while sparing the overlying retina. PDT [48–53].

Treatment of Circumscribed Choroidal Hemangioma

Laser photocoagulation has been an effective treatment modality for hemangioma for many years. Shields and coworkers [51] reported 62% resolution of subretinal fluid and 71% stability of vision with argon laser photocoagulation. The main complication of laser photocoagulation is the expansion of RPE atrophy and coexistent scotoma. Other reported complications include preretinal membrane, choroidal neovascular membrane, vascular occlusion and retinal bleeding. Diode laser photocoagulation has been shown to be equally efficacious with probably lower absorption by the retinal pigment epithelium [48]. Currently, laser photocoagulation is rarely used to treat hemangiomas as this has been largely replace by photodynamic therapy.

In various studies the visual acuity improvement or stabilization after PDT for choroidal hemangioma ranges from 73 to 100% [52]. Blasi and co-workers reported the five year outcome of 25 patients treated with PDT for circumscribed hemangioma and found that visual acuity improved by two lines in 76% of patients with complete resolution of macular exudation in all cases and no complications

were observed [53]. Shields CL and co-workers nearly 50 patients treated with PDT, 95% of patients required only one session with complete resolution of the tumor and fluid. A second session was needed in 5% to resolve persistent or recurrent subretinal fluid. Long-term recurrence of subretinal fluid is uncommon [54].

The use of TTT is limited to extrafoveal tumors. Treatment with TTT successfully causes tumor regression in many patients (42%, partial 50%) complete but carries a risk of cystoid macular edema, preretinal fibrosis, focal iris atrophy and retinal vascular occlusion [46].

Treatment of Diffuse Choroidal Hemangioma

The management of diffuse choroidal hemangioma can be challenging. In addition to choroidal hemangioma, patients with Sturge-Weber syndrome also have congenital glaucoma in 70% of patients. The mechanism of raised intraocular pressure is angle anomaly and raised episcleral pressure. Treatment options for diffuse choroidal

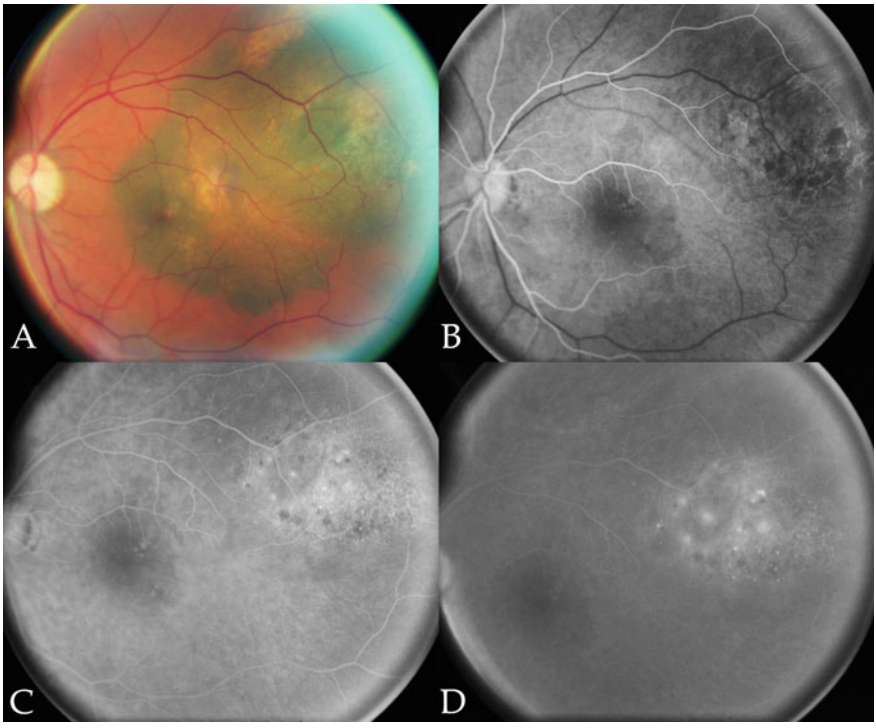

Fig. 8.1 Choroidal melanoma arose from benign nevus **A** Color fundus photograph shows dark nevus in the macula area and melanoma is located temporal to the nevus. **B–D** Fluorescein angiogram shows hyperfluorescence with diffuse leakage from melanoma

hemangioma include observation, amblyopic therapy, laser photocoagulation, irradiation, photodynamic therapy, retinal detachment surgery or even enucleation in advanced cases with neovascular glaucoma [55].

Multispot photodynamic therapy has been used successfully in patients with diffuse hemangioma. Reported cases in the literature document resolution of subretinal fluid, decrease in thickness of the tumor and improvement in visual acuity [56, 57].

Retinoblastoma (RB).

In the treatment of RB, laser (thermal/TTT) is used as primary modality of treatment only for very small tumors [58]. In most cases, however, it is used as an adjunct. Tumors are regressed with chemotherapy and then subjected to laser treatment to achieve total destruction. Tumors of up to 3 mm basal diameter and height of about 2 mm are amenable for laser treatment. The laser is applied around the tumor to cut off the blood supply. Direct treatment of the tumor can also be done although there are

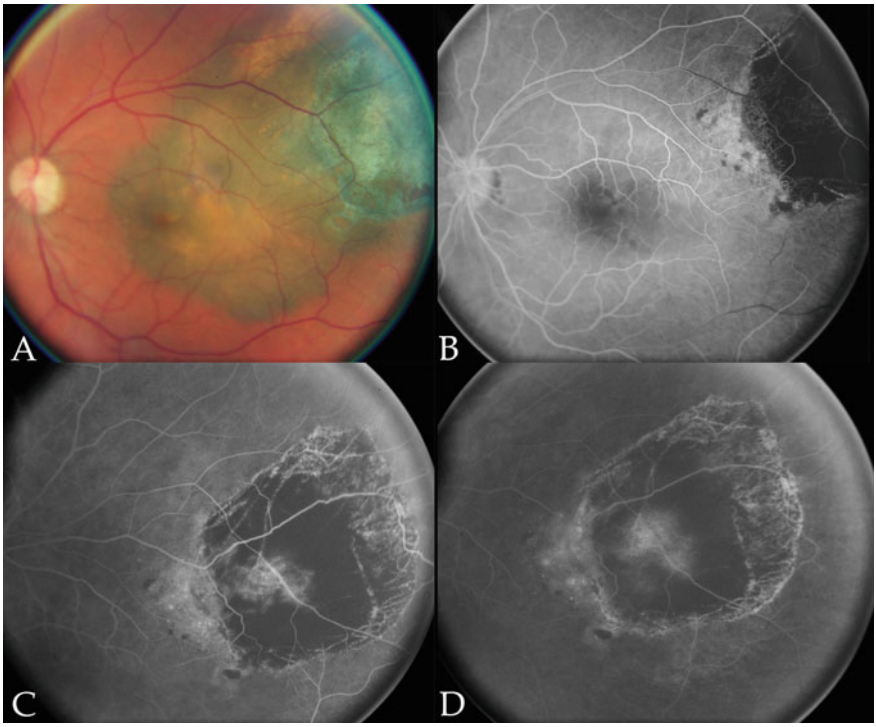

Fig. 8.2 Fundus images of a patient treated with TTT for choroidal melanoma arose from benign nevus **A** Color fundus photograph shows gray scar instead of the melanoma located temporal to the nevus. **B–D** Fluorescein angiogram shows hypofluorescence at the site of melanoma

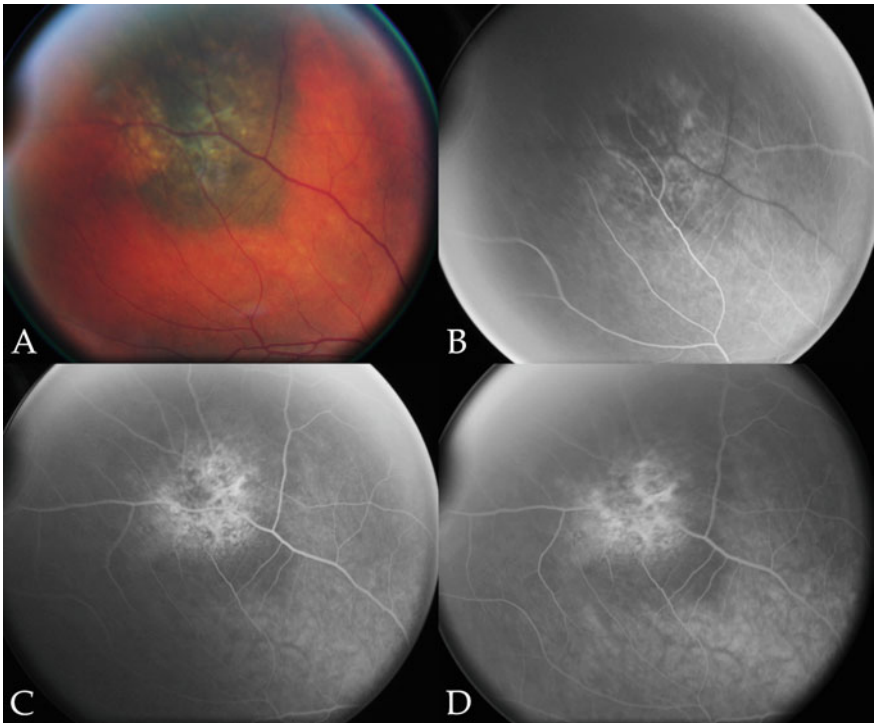

Fig. 8.3 Small pigmented choroidal melanoma **A** Color fundus photograph shows melanoma is located at the mid periphery. **B–D** Fluorescein angiogram shows hyperfluorescence with diffuse leakage from melanoma

concerns about the vitreous dissemination of tumor cells. Direct treatment of RB can be more safely done with TTT rather than by thermal photocoagulation. With TTT, the end point of each burn is the development of mild opalescence in the tumor. One can combine the treatment surrounding the tumor with thermal coagulation followed by TTT of the tumor itself.

Tumors bordering the macula are best allowed to shrink with chemotherapy till it is safe to destroy the residue without compromising the fovea. However, it may not always be possible to preserve the fovea-especially where the epicenter of the tumor lies in the foveal location, and it shrinks toward and not away from fovea [59].

Shields et al. have shown a success of 85.6% in achieving complete tumor regression. The risk factors for tumor recurrence were male sex, inability to produce a color change in the tumor with TTT and tumors being treated after chemo reduction [60].

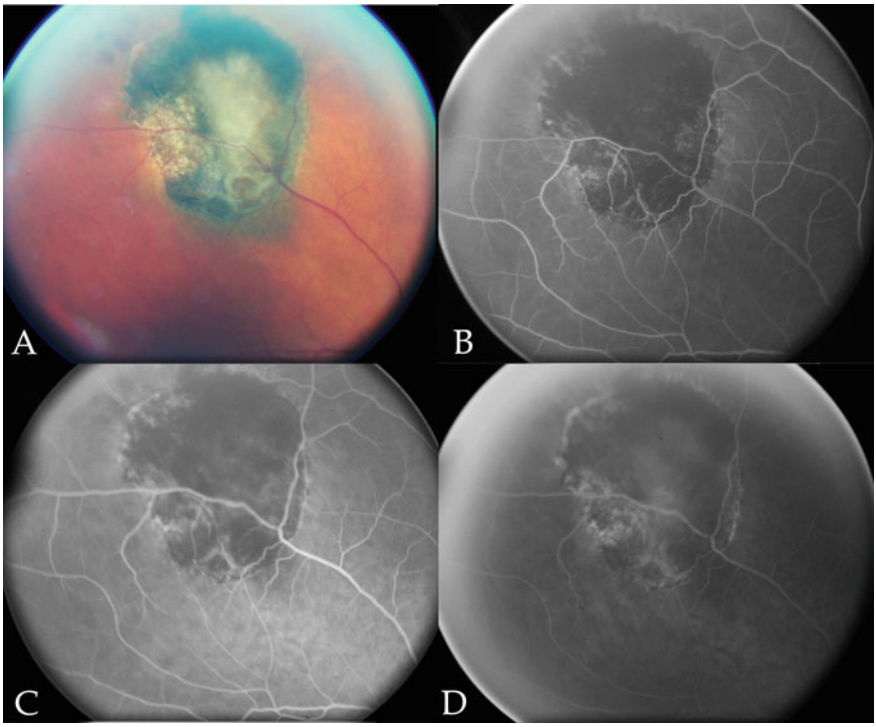

Fig. 8.4 Fundus images of a patient treated with PDT for choroidal melanoma **A** Color fundus photograph shows gray scar and hyperpigmentaton instead of the melanoma located at the mid periphery. **B–D** Fluorescein angiogram shows hypofluorescence at the site of melanoma

References

1. Kotelianskiĭ EO, Zaslavskaia AM. Outcomes and prognosis of uveal melanoblastomas following different variants of combined treatment. Oftalmol Zh. 1983; 38(1):9−12. Russian.
2. Terent'eva LS. Results of current methods of treatment of uveal melanoblastomas with preservation of the eye. Oftalmol Zh. 1977; 32(8):563−9. Russian.
3. Brovkina AF. Enucleation in the treatment of choroid melanoma. Vestn Oftalmol. 1984; (3):35−6. Russian.
4. Volkov VV. Indications for enucleation in the treatment of patients with intraocular melanoma. Vestn Oftalmol. 1983; (2):3−6. Russian.
5. Hykin PG, Mocartney ACE, Plowman PN, Hungerford JL. Postenu-cleaation orbital radiotherapy for the treatment of malignant melanoma of the choroid with extrascleral extension. Brit J Ophthalmol. 1990;74(1):36–9.
6. Milchelson SB, Felberg MT, Shields SA, et al. Evaluation of metastatic cornea to the eye. Carcinoembrionic antigen and gamma glutamyl transpeptidase. Arch. Ophthal. 1977; 96(4):692−4.
7. Packer S, Rotman M, Salanitro P. Iodine - 125 irradiation of choroidal melanoma. Clinical experience. Ophthalmol. 1984;71(12):1700–8.

8. Zimmerman LE, Melean TV, Foster WD. Does enucleation of the eye containing a malignant melanoma prevent or accelerate the dessemination of tumor cells. Brit J Opthalm. 1978; 62(6): 420−5.
9. Meyer-Schwickerath G. The preservation of vision by treatment of intraocular tumours with light coagulation. Arch Ophthalmol. 1961;66:458–66.
10. Volkov VV, Balashevich LI, Kaverina ZA. Effectiveness of existing methods of treatment of intraocular melanoblastomas. Oftalmol Zh. 1977; 32(8):569−72. Russian.
11. Volkov VV, Napol'skiĭ VP. The role of various current methods of treating patients with intraocular melanoma. Oftalmol Zh. 1986; (7):386−90. Russian.
12. Terent'eva LS, Vit VV. Current methods of treatment of intraocular malignant tumors and approaches to their improvement. Oftalmol Zh. 1983; 38(1):1−6. Russian.
13. Mangeney GHM. Traitement du melanome malin de la chorioide. Bull Mem Soc trranc Ophthalmol. 1985;96(5):217–22.
14. Shukla M, Gerke E, Bornfeld N, Meyer-Schivvickerath G. Tumor regression after photocoagulation of malignant melanomas of the choroid. An ultrasonographic study. Ophthalmologica. 1987;1994(2–3):119–25.
15. Cernak A. Treatment of choroidal melanoma using photocoagulation. Cesk Ophthalmol. 1991;47(5–6):363–6.
16. Brovkina AF. The current aspects of the treatment of uveal melanomas. Vestn Oftalmol. 1999; 115(3):3−6. Russian.
17. Erie JC, Robertson DM, Mieler WF. Presumed small choroidal melanomas with serous macular detachments with and without surface laser photocoagulation treatment. Am J Ophthalmol. 1990;109(3):259–64.
18. Terent'eva LS, Fokin VP. The potential for organ-preserving treatment in large uveal melanoma. Oftalmol Zh. 1989; (6):338-41. Russian.
19. Volkov VV, Balashevich LI, Gatsu AF, Berezin IuD, Kulakov IaL. Lasers with various radiation parameters in ophthalmic oncology. Vestn Oftalmol. 1987; 103(4):33−7. Russian.
20. Brovkina AF, Zarubeĭ GD. Treatment of ciliochoroidal melanomas with a medical narrow proton beam. Vestn Oftalmol. 1986; 102(3):30−3. Russian.
21. Loose LD, Mgirian R, Turisky G. Biochemical and functional alternations in macrophages after thermal injury. Inf anal immun. 1984; 44(3-h):554−8.
22. Char DH, Castro JR. Helium ion therapy for choroidal melanoma. Arch Ophthalmol. 1982;100(6):935-s8.
23. Grizzard WS, Torczynski E, Char DH. Helium ion charged-particle therapy for choroidal melanoma. Histopathologic findings in a successfully treated case. Arch Ophthalmol. 1984; 102(14):576−8.
24. Cruess AF, Augsburger JJ, Shields JA, Donoso LA, Amsel J. Visual results following cobalt plague radiotherapy for posterior uveal melanomas. Ophthalmol. 1984;91(2):131–6.
25. Zogrufos L. Les melanomes de l′uvee. Concours med. 1990; 112(6):545−7, 549-51.
26. Oosterhuis JA, Journee-de Korver HG, Kakebeeke-Kemme HM, Bleeker JC. Transpupillary thermotherapy in choroidal melanomas. Arch Ophthalmol. 1995;113(3):315–21.
27. Vogel A, Birngruber R. Temperature profiles in human retina and choroid during laser coagulation with different wavelengths ranging from 514 to 810 nm. Lasers Light Ophthalmol. 1992;5:9–16.
28. Bartlema YM, Oosterhuis JA, Journée-De Korver JG, Tjho-Heslinga RE, Keunen JE. Combined plaque radiotherapy and transpupillary thermotherapy in choroidal melanoma: 5 years' experience. Br J Ophthalmol. 2003;87(11):1370–3.
29. Journée-de Korver JG, Oosterhuis JA, Kakebeeke-Kemme HM, de Wolff-Rouendaal D. Transpupillary thermotherapy (TTT) by infrared irradiation of choroidal melanoma. Doc Ophthalmol. 1992;82(3):185–91.
30. Journée-de Korver JG, Keunen JE. Thermotherapy in the management of choroidal melanoma. Prog Retin Eye Res. 2002;21(3):303–17.

31. Stoffelns BM. Morphologische und funktionelle ergebnisse nach transpupillarer Thermotherapie (TTT) maligner aderhautmelanome [Tumor regression and visual outcome after transpupillary thermotherapy (TTT) for malignant choroidal melanoma]. Klin Monbl Augenheilkd. 2006;223(1):74−80. German.
32. De Potter P, Levecq L. Thermothérapie transpupillaire dans le traitement du mélanome de la choroïde [Transpupillary thermotherapy in the treatment of choroid melanoma]. J Fr Ophtalmol. 2001;24(9):937−43. French.
33. Godfrey DG, Waldron RG, Capone A Jr. Transpupillary thermotherapy for small choroidal melanoma. Am J Ophthalmol. 1999;128(1):88–93.
34. Robertson DM, Buettner H, Bennett SR. Transpupillary thermotherapy as primary treatment for small choroidal melanomas. Arch Ophthalmol. 1999;117(11):1512–9.
35. Schneider H, Fischer K, Fietkau R, Guthoff RF. Transpupilläre thermotherapie des malignen aderhautmelanoms [Transpupillary thermotherapy of choroidal melanoma]. Klin Monbl Augenheilkd. 1999; 214(2):90−5. German.
36. Shields CL, Shields JA, Perez N, Singh AD, Cater J. Primary transpupillary thermotherapy for small choroidal melanoma in 256 consecutive cases: outcomes and limitations. Ophthalmol. 2002;109(2):225–34.
37. Shields CL, Shields JA, Cater J, Lois N, Edelstein C, Gündüz K, Mercado G. Transpupillary thermotherapy for choroidal melanoma: tumor control and visual results in 100 consecutive cases. Ophthalmol. 1998;105(4):581–90.
38. Journée-de Korver JG, Oosterhuis JA, de Wolff-Rouendaal D, Kemme H. Histopathological findings in human choroidal melanomas after transpupillary thermotherapy. Br J Ophthalmol. 1997;81(3):234–9.
39. Stoffelns BM. Kinetik von Indozyaningrün (ICG) und adjuvanter einsatz zur transpupillaren thermotherapie (TTT) pigmentarmer kleiner aderhautmelanome [Kinetics of indocyanine green (ICG) and clinical use for enhancement of transpupillary thermotherapy (TTT) in hypopigmented small choroidal melanomas]. Klin Monbl Augenheilkd. 2004;221(5):374−8. German.
40. Rishi P, Agarwal V. Current role of photodynamic therapy in ophthalmic practice. Sci J Med & Vis Res Foun. 2015;XXXIII:97–9.
41. Michels S, Schmidt-Erfurth U. Photodynamic therapy with verteporfin: a new treatment in ophthalmology. Semin Ophthalmol. 2001;16(4):201–6.
42. Roelofs KA, et al. Long-term outcomes of small pigmented choroidal melanoma treated with primary photodynamic therapy. Ophthalmol Retina. 2021;5(5):468–78.
43. Turkoglu EB, et al. Photodynamic therapy as primary treatment for small choroidal melanoma. Retina. 2019;39(7):1319–25.
44. Witschel H, Font RL. Haemangioma of choroid. A clinicopathologic study of 71 cases and a review of the literature. Surv Ophthalmol. 1976;20(6):415–31.
45. Poh KW, Wai YZ, Rahmat J, Shunmugam M, Alagaratnam J, Ramasamy S. Treatment of diffuse choroidal haemangioma using photodynamic therapy. Int J Ophthalmol. 2017;10(3):488–90.
46. Gündüz K. Transpupillary thermotherapy in the management of circumscribed choroidal hemangioma. Surv Ophthalmol. 2004;49:316–27.
47. Tsipursky MS, Golchet PR, Jampol LM. Photodynamic therapy of choroidal hemangioma in sturge-weber syndrome, with a review of treatments for diffuse and circumscribed choroidalhemangiomas. Surv Ophthalmol. 2011;56(1):68–85.
48. Lanzetta P, Virgili G, Ferrari E, Menchini U. Diode laser photocoagulation of choroidal hemangioma. Int Ophthalmol. 1995-1996;19:239-47.
49. Schmidt-Erfurth UM, Michels S, Kusserow C, Jurklies B, Augustin AJ. Photodynamic therapy for symptomatic choroidal hemangioma: visual and anatomic results. Ophthalmology. 2002;109(12):2284–94.
50. Sagong M, Lee J, Chang W. Application of intravitreal bevacizumab for circumscribed choroidal hemangioma. Korean J Ophthalmol. 2009;23:127–31.
51. Shields CL, Honavar SG, Shields JA, Cater J, Demirci H. Circumscribed choroidal hemangioma: clinical manifestations and factors predictive of visual outcome in 200 consecutive cases. Ophthalmology. 2001;108:2237–48.

52. Jurklies B, Bornfeld N. The role of photodynamic therapy in the treatment of symptomatic choroidal hemangioma. Graefes Arch Clin Exp Ophthalmol. 2005;243:393–36.
53. Blasi MA, Tiberti AC, Scupola A, et al. Photodynamic therapy with verteporfin for symptomatic circumscribed choroidal hemangioma: five-year outcomes. Ophthalmol. 2010;117:1630–7.
54. Shields CL, Materin MA, Marr BP, Mashayekhi A, Shields JA. Resolution of advanced cystoid macular edema following photodynamic therapy of choroidal hemangioma. Ophthalmic Surg Lasers Imaging. 2005;36:237–9.
55. Shields JA, Shields CL. Vascular tumors and malformations of the uvea. Atlas of Intraocular Tumors. Philadelphia: Lippincott Williams & Wilkins;2008. p. 230–51.
56. Huiskamp EA, Müskens RP, Ballast A, Hooymans JM. Diffuse choroidal haemangioma in sturge-weber syndrome treated with photodynamic therapy under general anaesthesia. Graefes Arch Clin Exp Ophthalmol. 2005;243:727–30.
57. Anand R. Photodynamic therapy for diffuse choroidal hemangioma associated with sturge weber syndrome. Am J Ophthalmol. 2003;136:758–60.
58. Abramson DH, Schefler AC. Transpupillary thermotherapy as initial treatment for small intraocular retinoblastoma: technique and predictors of success. Ophthalmol. 2004;111:984–91.
59. Lingam G. Options for management of intra ocular tumors. Indian J Ophthalmol. 2015;63:204–10.
60. Shields CL, Santos MC, Diniz W, Gündüz K, Mercado G, Cater JR, et al. Thermotherapy for retinoblastoma. Arch Ophthalmol. 1999;117:885–93.
61. Currie ZI, Rennie IG, Talbot JF. Retinal vascular changes associated with transpupillary thermotherapy for choroidal melanomas. Retina. 2000;20(6):620–6.
62. Grüterich M, Mueller AJ, Ulbig M, Kampik A. Was kann die transpupilläre thermotherapie (TTT) in der behandlung von flachen posterioren aderhautmelanomen leisten? eine systematische Lliteraturübersicht [What is the value of transpupillary thermotherapy in treatment of flat posterior choroid melanomas? a systematic review of the literature]. Klin Monbl Augenheilkd. 1999;215(3):147−51. German.

Chapter 9
Laser Treatment in Rhegmatogenous Retinal Detachment

Jana Stefaničková and Igor Kozak

Retinal laser is an essential tool in the treatment and prevention of retinal detachment (RD). Laser retinopexy to fuse the retina to the underlying retinal pigment epithelium and choroid by photocoagulation (PC) can prevent progression of retinal breaks to prevent rhegmatogenous RD (RRD), contain and confine smaller and slowly progressive RDs by laser PC demarcation of the advancing edge of the RD to prevent spread and preclude the need for major surgery. It also, serves as an essential tool for sealing retinal breaks during scleral buckling (SB) and/or pars plana vitrectomy (PPV), and can be used to create thermal choroidal perforations to facilitate external drainage of subretinal fluid during RD repair. Laser retinopexy works only if the etiology of retinal detachment is rhegmatogenous. Alternative types of laser mechanisms have been used in exudative retinal detachments which are described in other chapters of this book. This chapter will describe processes and risk factors leading to rhegmatogenous retinal detachment formation and report published success rates in using laser retinopexy for rhegmatogenous RD.

The formation of retinal break leading to retinal detachment is usually preceded by the posterior vitreous detachment (PVD)—a separation of the posterior vitreous cortex from the internal limiting membrane of the retina which may be complete or partial [1]. The formation of vitreous traction at areas of significant vitreoretinal adhesion is responsible for most retinal breaks that lead to retinal detachment. Nearly 70% of the population develop a posterior vitreous detachment, but only about 4% of the population have retinal breaks [2]. Typical onset of PVD is between the ages of 45 and 65, however, the risk factors leading to earlier onset could be trauma and myopia. Other risk factors include aphakia, pseudophakia, cataract surgery, lattice retinal degeneration, uveitis, retinitis and hereditary vitreoretinopathies [3]. During

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_9

Fig. 9.1 Ultra wide-field color fundus image of barrier laser surrounding a large peripheral retinal tear (white arrow). The condition has been stable for several years. (*Source* Dr. Igor Kozak, Abu Dhabi, U.A.E.)

the acute onset of PVD patients typically report the light flashes mainly in the dark. As the vitreous separates from the retina, photopsias are the result of vitreoretinal tractions. The vitreous opacities or floaters may be due to condensations of vitreous collagen, release the epipapillary glial tissues (Weiss ring) from the optic nerve head or blood from a damaged retinal vessel. At the time of the first examination about 8–22% patients with acute PVD symptoms will have a retinal tear [4–6]. If no retinal tears appear upon presentation of acute, symptomatic PVD, there is a 2–5% chance of a retinal tear in the subsequent weeks [5].

Retinal tears are full-thickness discontinuities in the neurosensory retina. Asymptomatic operculated holes and atrophic round holes have a very low risk of retinal detachment [7]. In eyes with symptoms of acute PVD, atrophic retinal breaks with clinical features have been found suggesting that they are unrelated to this acute condition. The literature provides little evidence of necessity for further laser treatment [8].

In symptomatic PVD, retinal tears associated with symptoms of floaters and/or photopsias are more likely to cause rhegmatogenous retinal detachment. A symptomatic retinal break is caused by vitreoretinal traction in eyes with an acute onset of PVD [9]. Untreated, symptomatic horseshoe tears are reported to lead to retinal detachment in 30–50% of cases. Retinal break features that are particularly high risk for progression to RD include breaks of acute onset, superior location, large size and surrounding subretinal fluid [10] (Fig. 9.1). Some breaks are associated with subclinical RD, which is defined as an extension of subretinal fluid at least 1 disc diameter away from the break but not more than 2 disc diameters posterior to the equator. Operculated retinal breaks have a low risk of progression to RD because the operculum represents relief of the vitreoretinal traction.

Retinal laser photocoagulation to surround a retinal break reduces progression to RD (Figs. 9.2 and 9.3). Laser treatment creates adhesions between the retina and

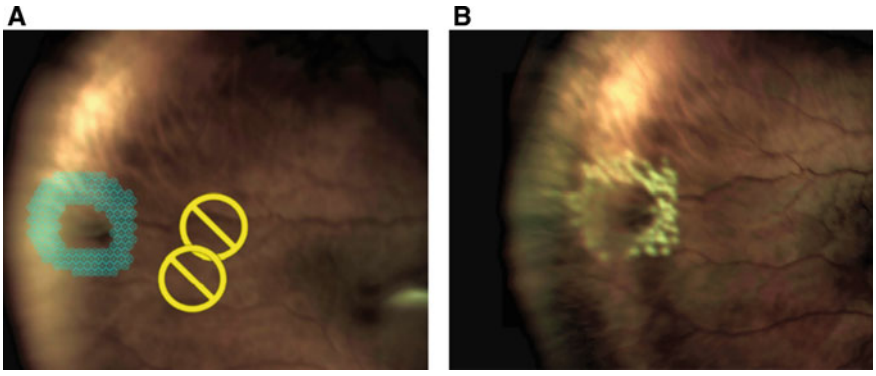

Fig. 9.2 Laser retinopexy using navigated retinal photocoagulation. 2A—Peripheral fundus view showing a horseshoe tear with laser application pre-planning (blue dots, yellow circles represent protective zones). 2B—The same horseshoe tear following laser photocoagulation. (*Source* Dr. Per Heuvels, Stade, Germany)

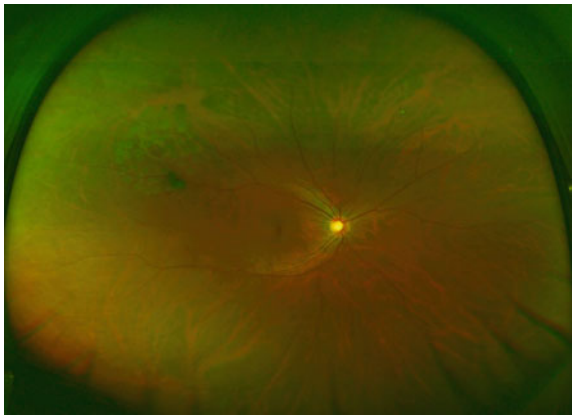

Fig. 9.3 Ultra wide-field color fundus image of barrier laser surrounding a symptomatic operculated retinal break. The condition has been stable for one year. (*Source* Dr. Igor Kozak, Abu Dhabi, U.A.E.)

retinal pigment epithelium and prevents migration of subretinal fluid [11, 12]. American Academy of Ophthalmology recommends prophylactic treatment of acute symptomatic horseshoe tears and dialyses, while leaving management options for acute symptomatic operculated holes, traumatic retinal breaks or asymptomatic retinal breaks to the treating physician's decisions [9].

Retinal detachment occurs in about 5% of eyes with symptomatic retinal breaks despite laser retinopexy. This can be caused by inadequate treatment to all margins of the break, subretinal fluid accumulation before chorioretinal adhesion from retinopexy is complete or because of missed or new breaks [2, 7, 8]. Subsequent retinal breaks occur after treatment of the first retinal break in 5–14% of eyes. Despite apparently adequate prophylactic treatment of retinal breaks, RD is diagnosed in 2–8.8% eyes [11, 12]. Nearly half of subsequent breaks occur within four to six weeks, but new breaks may occur months or even years later [13].

Lattice degeneration is a peripheral vitreoretinal degeneration characterized by retinal thinning, overlying vitreous liquefaction, and firm vitreoretinal adhesions at the margins of thinning. The incidence is about 6–8% of general populations and up to 30% of retinal detachments occur in these eyes; bilateral cases are seen in 45% [9]. Most lattice degenerations are ovoid, with the long axes of lattice running parallel to the ora serrata. Lattice lesions are usually localized between 11–1 o'clock and 5–7 o'clock meridians anterior to the equator [14]. Atrophic retinal holes can be localized in a lattice as a result of progressive retinal thinning [7]. Subsequently, retinal holes without posterior vitreous detachment, may develop in as many as 35% of these lesions and tends to occur in young myopic patients. Localized retinal detachments occur only in 2% of cases and, if they do become clinical, expand relatively slowly. The data from studies reported that the incidence of progression of lattice degenerations with or without round retinal holes to retinal detachment is very low in eyes without previous retinal detachment in fellow eye. Treatment is only recommended in cases of progressive retinal detachments [15].

Lattice can be associated with tractional retinal tears and treatment depends of the careful examination and patient history. In asymptomatic cases, prophylactic retinopexy is indicated in aphakic eyes, fellow eyes of patients with retinal detachment, eyes of patients with family history of retinal detachment. In symptomatic cases preventive treatment is indicated due to relatively high risk of progression to retinal detachment [16]. Bilateral incidence is reported in 45% of cases which open the debate whether to treat asymptomatic lattice prophylactically in the contralateral eye of a patient with history of lattice associated retinal detachment. The risk of retinal detachment in the contralateral eye is 5% (up to 25% in high myopic eyes with extensive lattice). To perform prophylactic retinopexy of lattice degeneration in fellow eyes may reduce the risk of RD two—to threefold, although this has been under discussion because new retinal breaks often develop in untreated areas or may occur at the edge of retinopexy scars if a posterior vitreous detachment occurs or extends [17, 18].

Degenerative (atrophic, senile) retinoschisis is generally benign and sometimes vision—threating. The schisis is characterized by smooth dome—shaped elevation of the retinal inner layers in the retinal periphery. The incidence is about 1% of the population and usually are bilateral located in inferotemporal quadrant. Outer wall breaks are usually large (greater than 3 disc diameters), round, located posteriorly, often with rolled edges [19]. If chronic, a ring of pigmentation can be found at the edge of subretinal fluid accumulation. In contrast, inner wall breaks are typically small and round [20]. Outer layer holes occur in approximately 17% and inner layer holes in less than 4% of cases. The large size and posterior location of outer wall breaks increase the amenability to laser prophylaxis, however, studies suggest that outer wall breaks usually remain stable [19, 20]. To develop progressive retinal detachment, (less than 2.5%), breaks should be found in both the inner and outer retinal layers. Prophylactic therapy (laser retinopexy) may not be beneficial, since the schisis may progress through the treated area or may develop in new areas. Treatment is indicated if patients have symptomatic, progressive RD [19–21].

Another risk factor leading to retinal detachment is a giant retinal tear, defined as a full-thickness neurosensory retinal break that extends 3 clock hours (90°) or more around the circumference of the globe and has rolled edges. Its incidence in large population—based studies has been estimated in 1.5% of rhegmatogenous retinal detachments, bilateral in 12.8% of cases. Most giant retinal tears are idiopathic—trauma, hereditary vitreoretinopathies and high myopia are less frequent causative factors. Non-traumatic giant retinal tears are often associated with a high rate of vitreoretinal pathology in the fellow eye. The incidence of retinal tears of fellow eyes is 59%, and the progression to retinal detachment is reported in nearly 18% [22]. Prophylactic treatment under these circumstances may be considered but there is no firm evidence of its efficacy at the present time. Similarly, a strong evidence is lacking whether prophylactic laser in infectious retinitis leads to prevention of retinal detachment and containment of retinitis spread.

Laser retinopexy is an outpatient procedure performed under local anesthesia with usually three rows of moderately visible laser spots surrounding the break (Figs. 9.1, 9.2 and 9.3). Follow-up examination takes place at an estimated formation of chorioretinal scarring (7–14 days) or earlier if visual symptoms worsen. Additional laser can be added with extension of the retinal tear or subretinal fluid increase. Laser retinopexy can be done using either slit-lamp delivery via contact lens or via indirect ophthalmoscope laser delivery. Intraoperative laser is performed at the time of pars plana vitrectomy surgery where both drainage retinotomy and peripheral retinal tears are surrounded by laser applications followed by intraocular endotamponade.

References

1. Johnson MW. Posterior vitreous detachment: evolution and role in macular disease. Retina. 2012;32(Suppl 2):S174–178.
2. Combs J, Welch R. Retinal breaks without detachment: natural history, management, and long-term follow-up. Trans Am Ophthalmol Soc. 1982;80:64–97.
3. Snead MP, Snead DR, James S, Richards AJ. Clinicopathological changes at the vitreoretinal junction: posterior vitreous detachment. Eye (Lond). 2008;22(10):1257–62.
4. Tani P, Robertson DM, Langworthy A. Rhegmatogenous retinal detachment without macular involvement treated with scleral buckling. Am J Ophthalmol. 1980;90(4):503–8.
5. Coffee RE, Westfall AC, Davis GH, Mieler WF, Holz ER. Symptomatic posterior vitreous detachment and the incidence of delayed retinal breaks: case series and meta-analysis. Am J Ophthalmol. 2007;144(3):409–13.
6. Benson WE, Grand MG, Okun E. Aphakic retinal detachment. Management of the fellow eye. Arch Ophthalmol. 1975;93(4):245–49.
7. Byer NE. Natural history of posterior vitreous detachment with early management as the premier line of defense against retinal detachment. Ophthalmology. 1994;101:1503–13.
8. Wilkinson CP. Interventions for asymptomatic retinal breaks and lattice degeneration for preventing retinal detachment. Cochrane Database Syst Rev. 2014(9):CD003170
9. Posterior vitreous detachment, retinal breaks, and lattice degeneration PPP—2019. American Academy of Ophthalmology. Updated October 2019. https://www.aao.org/preferred-practice-pattern/posterior-vitreous-detachment-retinal-breaks-latti Accessed 25 Feb 2022.
10. Mitry D, Singh J, Yorston D, et al. The fellow eye in retinal detachment: findings from the Scottish retinal detachment study. Br J Ophthalmol. 2012;96:110–3.

11. Smiddy WE, Flynn HW, Nicholson JR, et al. Results and complications in treated retinal breaks. Am J Ophthalmol. 1991;112:623–31.
12. Blindbaek S, Grausland J. Prophylactic treatment of retinal breaks - a systemic review. Acta Ophthalmol. 2015;93:3–8.
13. Goh YW, Ehrlich R, Stewart J, et al. The incidence of retinal breaks in the presenting and fellow eyes in patients with acute symptomatic posterior vitreous detachment and their associated risk factors. Asia Pac J Ophthalmol (Phila.) 2015;4:5–8.6.
14. Foos RY, Simons KB. Vitreous in lattice degeneration of retina. Ophthalmology. 1984;91:452–7.
15. Byer NE. Long-term natural history of lattice degenerations of the retina. Ophthalmology. 1989;96:1396–401.
16. Silva RE, Blumenkraz MS. Prophylaxis for retinal detachment. American Academy of Ophthalmology. https://www.aao.org/munnerlyn-laser-surgery-center/prophylaxis-retinal-detachments. Accessed March 2022.
17. Chauhan DS, Downie JA, Eckstein M, et al. Failure of prophylactic retinopexy in fellow eyes without a posterior vitreous detachment. Arch Ophthalmol. 2006;124:968–71.
18. Robertson DM, Norton EW. Long-term follow-up of treated retinal breaks. Am J Ophthalmol. 1973;75:395–404.
19. Byer NE. Long-term natural history study of senile retinoschisis with implications for management. Ophthalmology. 1986;93:1127–36.
20. Reed DC, Gupta OP, Garg SJ. Managing complications of retinoschisis. Retin Today. 2014;November/December:32–39.
21. Okun E, Cibis PA. The role of photocoagulation in the management of retinoschisis. Arch Ophthalmol. 1964;72:309–14.
22. Freeman HM. Fellow eyes of non-traumatic giant retinal breaks. In: Ryan SJ, editors. Retina, vol. 3. St. Louis: Mosby;2001. p. 2366–70.

Chapter 10
Laser Treatment of Vitreous Floaters

Maram E. A. Abdalla Elsayed and Igor Kozak

The vitreous is an extended, translucent, fibrillar meshwork of extracellular matrix situated between the lens and the retina, circa 4.0 mL in volume and encompassing approximately 80% of the overall volume of the globe. Immuno-cytochemistry and western blot analysis have revealed that the vitreous is composed of collagens II, V/XI, IX, and XVIII, and the non-collagenous components fibrillin, fibronectin, opticin, and tenascin. The collagens and fibrillin create the dominant extracellular structure whilst the long arrays of glycosaminoglycans (high-molecular-weight carbohydrate polymer) help bind water molecules. Type IX collagen in particular has chondroitin sulfate glycosaminoglycan chains attached to it which spread away from the fibril surfaces and separate the collagen fibrils, thus thwarting aggregation of fibrils. This delicate composition preserves the gelatinous nature of the vitreous: maintaining its optical transparency (interfibrillar spacing minimizes the scattering of light); providing the intraocular pressure that is necessary for maintaining the apposition of the retina to the retinal pigment epithelium; and acting as a "shock absorber," during rapid eye movements. Additionally, the vitreous happens to be a storage area for metabolites for the retina and lens and provides a conduit for the movement of these substances within the eye [1, 2].

Ordinarily, the vitreous body has adhesions to the vitreous base, optic disk, major vessels, and the macula. However, with age, cross-linkage between collagen fibers results in collagen aggregation which leads to formation of heterogeneous zones of density within the vitreous. This reorganization is named syneresis and eventually may lead to detachment of the posterior vitreous—a posterior vitreous detachment (PVD). This is due to the formation of liquid pockets that enter the potential space

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_10

between the vitreous and the retina forcing its parting. The vitreous collapses and relocates to behind the lens. Such a detachment of posterior hyaloid from the vitreo-retinal interface influences the fluid dynamics within the vitreous cavity, giving rise to a greater flux of molecules between the vitreous cavity and the retina. Based on their size these may be seen as "floaters". Local gradients are also dissipated consequent to the rise in molecular diffusion within the vitreous cavity. It is worth noting that symptomatic floaters in an eye with an attached vitreous hyaloid may be produced by the pathological infiltration of cellular or acellular material into the vitreous such as in uveitis or intraocular lymphomas [1, 2].

Floaters result from the scattering of incident photons by the collagen aggregates that consist of thick, irregular fibres, or from scattering by the glial tissues of epi-papillary origin. They result form entoptic phenomena as shadows are cast upon the retina. The vitreous opacities can be of different sizes and shapes and can also induce glare sensitivity and may even decrease objectively-measured contrast sensitivity. Symptomatic floaters are one of the most diagnosed conditions in adults. The perception of floaters can be especially troublesome for patients if they inconveniently reside close to the centre of the visual axis and are more obvious when seen against a light-coloured background such as a white wall or clear sky. A Weiss ring is a distinct type of floater associated with PVDs which consists of the glial remnants of a previous vitreo-papillary attachment. These rings may cast a particularly dense solitary shadow onto the retina, which patients usually describe as round or semicircular in shape. These floaters can have significant clinical and prognostic relevance if YAG laser vitreolysis is attempted [1, 2].

Schulz-Key et al. have estimated the incidence of symptomatic vitreous opacities as 3.1/100 000 per year based in their cohort [3]. Increasing age is a strong risk factor for the development of PVD and remarkably, it has been highlighted that 80% of elderly patient's eyes on the day of admission for cataract surgery have evidence of partial or complete posterior vitreous detachment on optical coherence tomography. In people who either experience both flashes and floaters or just floaters, PVD has occurred in 89% and 40%, respectively, demonstrating the robust association between posterior vitreous detachment and symptomatic floaters [4–6].

Recent evidence confirms that a sizeable cohort of patients experience remarkable infuriation as a result of these vitreous floaters with a significant impact on their quality of life. Wagle et al. demonstrate that patients experiencing symptomatic floaters in the absence of other co-morbidities were willing to decrease their remaining life by 11% to become asymptomatic; and were willing to undertake a procedure with an 11% mortality rate and 7% risk of blindness if the procedure guaranteed successful elimination of their symptoms. It was shown that patients were willing to make greater sacrifices to alleviate these symptoms than to cure age-related macular degeneration or glaucoma, and that their bothersome effect on quality of life has been found to be as profound as the effects of diabetic retinopathy, colon cancer, mild angina, mild stroke and asymptomatic human immunodeficiency virus infection [7].

The authors further report that patients were bothered by their floaters regardless of their chronicity putting to rest the notion that with significant lengths of time,

patients would adapt to their symptoms through central adaptation or through anterior migration of these structures which causes them to become less in focus and hence minimally debilitating. The utility values in their study did not demonstrate any significant relationship with duration of symptoms, presence of a posterior vitreous detachment, and presence or severity of myopia [7, 8]. It may therefore, be judicious to consider how this visually disabling condition can be effectively managed to alleviate its impact on the patient's quality of life, especially as they are particularly bothersome to individuals who have high levels of psychosocial stress and as they are becoming more widespread due to the increasing prevalence of myopia worldwide. In myopia in particular, patients may become symptomatic at a younger age due to the fact that the vitreous changes arise earlier in life in such eyes. Furthermore, myopes may experience more disturbing symptoms due the magnification of the retinal image.

For the mild, asymptomatic floaters found incidentally, the treatment remains observation and for the severe, diffuse, dense floaters, a vitrectomy may be indicated**.** However, it is in the middle of this spectrum where the bulk of patients lie. Various treatment options have been described for symptomatic vitreous opacities including neodymium-doped yttrium aluminium garnet (Nd:YAG) laser vitreolysis, cataract surgery combined with deep anterior vitrectomy and pars plana vitrectomy. New floaters are usually treated conservatively, and laser treatment is not usually indicated until the floaters stabilize in size and density [9–11].

Photo-disruptive lasers are a relatively non-invasive option for treatment as opposed to vitreoretinal surgery. With intense pulses of short duration laser focused on the opaque vitreous floaters, it is possible to raise the temperature of these confined spots to excessive degrees, producing plasma and hence disintegration of these lesions. This either results in less aberrant light transmission through the vitreous, or the displacement of this vitreous area to a zone outside of the patient's visual axis providing the patient with immediate symptomatic relief. Only sharply-defined and relatively small objects can be treated in this manner and typically, Nd:YAG laser directed through the mydriatic pupil is utilized for this purpose [9–11].

There is no consensus protocol for the YAG vitreolysis procedure. The energy of the application would naturally be dependent on both position and density of the floater. Published series have revealed a mean number of 218–564 laser shots (and a mean total power of 366.7–3,384 mJ) being required in single laser sessions. It would be beneficial for future randomized control trials to determine relevant laser pulse duration, laser power intensity, total number of laser shots, and the anatomical location of the laser shots in relation to the distance from the eye's visual axis, posterior lens capsule, and retina. Some clinicians may prefer multiple sittings rather than one session to avoid utilizing a large amount of energy all at once which may result in intraocular pressure spikes [12–14].

Even though the safety of the procedure has been established by several studies, possible side effects of YAG vitreolysis include increased symptomatic floaters, intraocular pressure elevation, lens opacities, posterior capsule damage in phakic patients and retinal tears or detachments [15–17]. Karickhoff's long-term studies have shown success rates of 92% and higher and complication rates as low as 0.1%

[18]. More recently, a randomized clinical trial by Shah and Heier evaluated 52 patients who had symptomatic PVD with complete Weiss ring, of which 36 patients were randomized to YAG vitreolysis and 16 were randomized to a sham YAG laser procedure. 53% of the YAG vitreolysis patients reported a significant or complete resolution of symptoms compared to none in the sham arm at 6 months follow-up ($P < 0.001$). An extended follow-up study beyond 6 months revealed that 8.6% of patients in the treatment arm went on to develop a retinal tear [19]. In contrast, Mason et al. [20] reported a high success rate, with 94% of patients reporting their experience as a complete success and 92% of patients reporting either no symptoms or very mild symptoms following pars plana vitrectomy (PPV) for symptomatic vitreous floaters. Sebag et al. [21] reported on 76 eyes with vitreous floaters undergoing PPV and prospectively evaluated contrast sensitivity in 16 of these patients. They report complete symptom resolution in 93.8% patients in the surgical arm of the study. The patients would, however, be exposed to the known possible complications associated with PPV which encompass secondary retinal complications, endophthalmitis and possible anesthesia complications.

Presently, there are ongoing and completed clinical trials that compare Nd:YAG laser vitreolysis to 'sham' Nd:YAG laser vitreolysis for symptomatic floaters (NCT01970267; NCT02812004; NCT02897583) however, these studies were not designed to analyse how Nd:YAG laser vitreolysis compares to pars plana vitrectomy for the treatment of symptomatic floaters. There are currently no randomized control trials that compare Nd:YAG laser vitreolysis with pars plana vitrectomy and these are desperately required to accurately evaluate the efficacy of this procedure and its safety profile. Numerous complications have been described following laser floaterectomy including retinal and lenticular damage [22–24]. While some can be attributed to physician's learning curve, the effects of high power YAG laser applied to moving structures inside the vitreous cavity cannot be underestimated. These can be safely avoided performing surgical vitreous removal. A recent Cochrane Review aiming to find out whether laser or vitrectomy is the most effective and safe treatment for vitreous floaters, however, concluded that ophthalmologists do not have strong evidence to recommend pars plana vitrectomy over Nd:YAG laser vitreolysis (or visa versa) for the treatment of symptomatic floaters [25].

References

1. Remington LA. Clinical anatomy and physiology of the visual system, 3rd ed. Butterworth-Heinemann;2012.
2. Halfter W, Balasubramani M, Ring C, Schurer B. Cellular origin, formation and turnover of the vitreous. Encyclopedia of the eye. Academic Press;2010.
3. Schulz-Key S, Carlsson JO, Crafoord S. Longterm follow-up of pars plana vitrectomy for vitreous floaters: complications, outcomes and patient satisfaction. Acta Ophthalmol. 2011;89(2):159–65.
4. Hilford D, Hilford M, Mathew A, et al. Posterior vitreous detachment following cataract surgery. Eye 2009;23:1388–1392.

5. Hikichi T, Trempe CL. Relationship between floaters, light flashes, or both, and complications of posterior vitreous detachment. Am J Ophthalmol. 1994;117(5):593–8. https://doi.org/10.1016/s0002-9394(14)70065-0.
6. Sebag J. Floaters and the quality of life. Am J Ophthalmol. 2011;152(1):3-4.e1.
7. Wagle AM, Lim W-Y, Yap T-P, et al. Utility values associated with vitreous floaters. Am J Ophthalmol. 2011;152(1):60-65.e1.
8. Kim YK, Moon SY, Yim KM, Seong SJ, Hwang JY, Park SP. Psychological distress in patients with symptomatic vitreous floaters. J Ophthalmol. 2017;3191576.
9. Roufail ED, Polkinghorne P. Vitreous floaters. Compr Ophthalmol Updat. 2006;7(4):171–177.
10. Vandorselaer T, Van De Velde F, Tassignon MJ. Eligibility criteria for Nd-YAG laser treatment of highly symptomatic vitreous floaters. Bull Soc Belge Ophtalmol. 2001;280:15–9.
11. Yuan Y, Shi P. Degradation of contrast sensitivity function following posterior vitreous detachment. Am J Ophthalmol. 2017;177:225.
12. Katsanos A, Tsaldari N, Gorgoli K, Lalos F, Stefaniotou M, Asproudis I. Safety and efficacy of YAG laser vitreolysis for the treatment of vitreous floaters: an overview. Adv Ther. 2020;37(4):1319–27.
13. Shah CP. The art and science of YAG vitreolysis. In: Paper presented at: the american academy of ophthalmology annual meeting. Chicago, IL;2018.
14. Singh IP. Modern vitreolysis - YAG laser treatment now a real solution for the treatment of symptomatic floaters. Surv Ophthalmol. 2020;65:581–8.
15. Delaney YM, Oyinloye A, Benjamin L. Nd:YAG vitreolysis and pars plana vitrectomy: surgical treatment for vitreous floaters. Eye (Lond). 2002;16(1):21–6.
16. Su D, Shah CP, Hsu J. Laser vitreolysis for symptomatic floaters is not yet ready for widespread adoption. Surv Ophthalmol. 2020;65:589–91.
17. Hahn P, Schneider EW, Tabandeh H, Wong RW, Emerson GC. American society of retina specialists research and safety in therapeutics (ASRS ReST) committee. Reported complications following laser vitreolysis. JAMA Ophthalmol. 2017;135:973–976.
18. Karickhoff JR. Laser treatment of eye floaters. Washington Medical Publishing, LLC;2017.
19. Shah CP, Heier JS. YAG laser vitreolysis vs sham YAG vitreolysis for symptomatic vitreous floaters: a randomized clinical trial. JAMA Ophthalmol. 2017;135(9):918–23.
20. Mason JO, Neimkin MG, Mason JO, et al. Safety, efficacy, and quality of life following sutureless vitrectomy for symptomatic vitreous floaters. Retina. 2014;34:1055–61.
21. Sebag J, Yee KMP, Wa CA, Huang LC, Sadun AA. Vitrectomy for floaters—prospective efficacy analysis and retrospective safety profile. Retina. 2014;34:1062–8.
22. O'Day R, Cugley D, Chen C, Fabinyi D. Bilateral posterior capsule injury after Nd:YAG laser vitreolysis: unintended consequence of floaters treatment. Clin Exp Ophthalmol. 2018;46:956–57.
23. Liu X, Wang Q, Zhao J. Acute retinal detachment after Nd:YAG treatment for vitreous floaters and posterior capsule opacification: a case report. BMC Ophthalmol. 2020;20:157.
24. Souza CE, Lima LH, Nascimento H, Zett C, Belfort R Jr. Objective assessment of YAG laser vitreolysis in patients with symptomatic vitreous floaters. Int J Retin Vit. 2020;6:1.
25. Kokavec J, Wu Z, Sherwin JC, Ang AJS, Ang GS. Nd:YAG laser vitreolysis versus pars plana vitrectomy for vitreous floaters. Cochrane Database Syst Rev. 2017;(6).

Chapter 11
Ischemic Peripheral Retinopathies

Maciej Gawęcki and Andrzej Grzybowski

Introduction

Laser photocoagulation of the retina is applied in a group of clinical entities, which vary in their etiology but share one most important characteristic: they present with areas of peripheral hypoperfusion. As the goals and the technique of treatment are alike in those cases, we decided to characterize them in one chapter.

Consequences of peripheral hypoperfusion

Occurrence of retinal hypoperfusion in different clinical entities has a consequence in the risk of development of complications, ratio of which depends mainly on the extent of ischemic areas. A good example of such relationship is classification of central retinal vein occlusion, which indicated ischemic type of CRVO with the 10 DA (disc areas) or more of hypo-perfused retina diagnosed on classic 7-field fluorescein angiography (FA) [1]. Vast retinal ischemia induces production of proangiogenic cytokines, and if untreated, may lead to retinal neovascularization (branch retinal vein occlusion) or anterior segment neovascularization (in case of central retinal vein occlusion). Untreated retinal neovascularization usually progresses to proliferation of fibrovascular membranes and vitreoretinal traction. Possible consequences of such scenario include retinal tears and retinal detachment as well as vitreal or subhyaloid haemorrhages.

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_11

Diagnostics

Detection of peripheral ischemia requires the use of proper diagnostic tools. First step should always include examination of the fundus in stereoscopic image, often with the help of contact panfundoscope lens, typically used for panretinal photocoagulation (PRP). The use of wide field lenses enables to detect changes at the retinal periphery that are not visible with standard Volk lenses, such as retinal neovascularization or vessels devoid of blood flow.

The second, most reliable diagnostic modality for detection of peripheral ischemia, is fluorescein angiography (FA) of the fundus, preferable ultra-wide field (UWF). Obtained images reveal dark peripheral areas devoid of capillaries and possibly areas of leakage in case of neovascularization. UWF-FA exams are more sensitive in detecting such changes as they cover the field of approximately 200° compared to 45–60° with standard 7-field FA. Thus, while using standard equipment it has to be remembered that some areas of hypoperfusion might be omitted due to optical limitations of the device.

Cases complicated by vitreous hemorrhage, epiretinal membranes or suspected of retinal traction and/or retinal detachment always require ultrasound examination of the eyeball, especially if located at the far periphery.

In case of concomitant occurrence of macular edema, spectral domain optical coherence tomography (SD-OCT) should be performed.

Treatment options

Treatment of peripheral ischemia in the course of different clinical entities involves some similar options that are presented below. It has to be remembered though, that besides these typical procedures described below, there are available therapeutic strategies specific for each retinal disorder.

Laser photocoagulation

Mechanism of action of laser photocoagulation (LPC) against retinal ischemia is usually explained by the oxygen theory [2]. Destruction of photoreceptors reduces retinal need for oxygen and in consequence a decrease in production of angiogenic factors is noted [3]. Traditionally, retinal laser scars serve as bridges for the oxygen to pass from the choroid to inner retinal layers, hence retinal oxygenation improves. Taken altogether, the LPC procedure reduces the risk of retinal neovascularization or induces regression of already existing neovascularization.

Technique

Typically, treatment involves areas of hypoperfusion detected in FA, not the whole peripheral retina. Nevertheless panretinal photocoagulation (PRP) remains an option in cases with extensive areas of non-perfusion or complicated by anterior segment neovascularization. Treatment protocols and laser parameters can be adopted from DRS recommendations for proliferative diabetic retinopathy or treatment of BRVO [4, 5].

An example of LPC protocol:
Spot size at the retina: 500 μm
Spacing: usually 1 spot diameter
Duration: 0.1 s
Power: adjusted to obtain retinal whitening (take caution—laser power at the periphery should be significantly reduced).

Anti—VEGF treatment

Anti-VEGF intravitreal treatment can be used as an adjunct to LPC in cases with aggressive neoavascularization (NV) or retinal edema that potentially decreases the quality of laser photocoagulation. Usually, anti-VEGF injection is applied prior to LPC in order to reduce the intensity and pace of progression of NV and/or retinal edema in the place of planned LPC. Anti-VEGF treatment can also be an option in cases with initial neovascularization, where they can lead to its regression without the need for LPC or pars plana vitrectomy (PPV). It has to be remembered though, that cases with extensive vitreoretinal neovascular membranes treated with anti-VEGF may contract after regression of their vessels and cause tractional retinal detachment. Nevertheless, anti-VEGF is also used before planned surgical treatment to reduce possible intraoperative bleeding and improve the quality of PPV.

Pars plana vitrectomy

Extensive retinal ischemia elicits proliferation of fibrovascular membranes that may cause significant vitreoretinal traction and lead to retinal tears, hemorrhages and retinal detachment. Therefore, cases burdened with significant retinal traction, retinal detachment or non-resorbing vitreous or subhyaloidal heamorrhage, which obscure the visualization of the peripheral retina, require surgical treatment, usually PPV. PPV is also required in cases with macular involvement: epiretinal membranes or macular edema with vitreoretinal traction.

LPC in Specific Ischemic Retinopathies

Sickle cell retinopathy (SCR)

SCR is a consequence of sickle cell disease (SCD), which is a group of inherited hemoglobinopathies that affect multiple organs, eyeballs included. SCD is the most prevalent in African descent patients, less in Hispanic—descent and the least frequent in white population [6]. The pathophysiology of the disease relies on anomalous composition of hemoglobin, that causes abnormal shape of red blood cells. Due to conversion of soluble hemoglobin into crystalline hemoglobin they become sickle-shape, and rigid, thus prone to occlude small vessels. This factor, together with adhesive properties of endothelial cells due to hypoxia, leads to hypoperfusion of peripheral retina [7]. Depending on the extend of hypoxia, changes occurring in the

retina can have non-proliferative or proliferative character (NPSR—non proliferative sickle cell retinopathy or PSR—proliferative sickle cell retinopathy).

Grading of SCR into 5 stages was developed by MF Goldberg in 1971 [8]. First two refer to non-proliferative changes such as peripheral arterial occlusion (stage I) and peripheral arteriovenous anastomoses (stage II). The latter three classify more advanced lesions: neovascular and fibrous proliferations with characteristic fan-shape present at the posterior border of nonperfusion (stage III), vitreous hemorrhage (stage IV) and tractional retinal detachment (stage V).

Treatment

The goal of treatment in SCR is to avoid to progression to stages IV and V. Screening for SCR in SCD patients begins at age 10 and includes referral to an ophthalmologist for a dilated eye examination. Rescreening is scheduled at one- to two-year intervals for persons without retinopathy [9, 10]. Nowadays, UWF-FA is recommended for screening and monitoring of SCR patients [11].

Scatter LPC is recommended for patients with large, vascularized sea fan areas of neovascularization, enlarging sea-fans, monocular patients and/or patients with advanced retinopathy in the collateral eye and in patients with predicted poor compliance. Small sea-fan lesions can be closely monitored without LPC, as they might spontaneously infarct and regress in 30% [12]. It has to be remembered, that LPC in SCR reduces the risk of vitreous hemorrhage, however it does not prevent formation of new sea-fan lesions [13, 14].

Typically, LPC is applied to areas of non-perfused retina, transitional zone between perfused and non-perfused retina and posterior to that zone [15]. LPC of nonperfused areas without neovascularization is not recommended. So far there are no strong recommendations for anti-VEGF treatment in SCR, however it is used to speed-up resolution of vitreous hemorrhage (VH) and enable to perform LPC [16]. Otherwise, it can be applied to control cases with extensive neovascularization or before vitrectomy, to reduce intraoperative bleeding.

Surgical treatment in SCR is burdened with potential iatrogenic complications due to altered consistency of the retina, susceptible to breaks. Thus, it is reserved for cases with vision-threatening retinopathy, in whom other treatment modalities were not effective. Indications for posterior vitrectomy in SCR include non-clearing vitreous hemorrhage, retinal detachment, symptomatic epiretinal membrane, macular hole and vitreomacular traction [17].

Position of laser in the treatment of SCR

Scatter LPC is the first line of treatment in SCR with anti-VEGF therapy serving as an auxiliary procedure.

Idiopathic retinal vasculitis (IRV)

Retinal vasculitis is often thought to be associated mainly with systemic disease or specific ocular disease, however, epidemiological studies prove that most of retinal vasculitis cases are idiopathic [18, 19]. IRV was characterized in a large retrospective study by Graham et al. in 1989 [20]. Most of patients in that study were diagnosed with fundus examinations and FA and presented with peripheral vascular sheathing (64%) and macular edema (60%). Anterior uveitis and pigmentary changes at the fundus were observed in 33%. Capillary closure on FA was noted in 23% of cases and retinal neovascularization in 16%. Later study from 2017 by Sharief et al. analyzed retrospectively 236 cases of uveitis with retinal vasculitis [21]. Among that cohort idiopathic cases sustained 43.6% and ischemic vasculitis type accounted for 18.6% of the whole group.

Treatment

Treatment of idiopathic uveitis with peripheral vasculitis is symptomatic and involves topical, periocular and systemic anti-inflammatory and immunosuppressive drugs.

LPC is the primary form of treatment of ischemic type of idiopathic vasculitis in patients with retinal neovascularization.

Position of LPC in the treatment of IRV

LPC is the primary form of treatment in cases with retinal neovascularization.

Inflammatory diseases with peripheral retinal vasculitis

Retinal ischemia can occur in the course of inflammatory disease with peripheral retinal vasculitis. That includes a large range of different disorders of variable etiopathogenesis, both local ocular and systemic. These entities bare some similarities according to their course and staging. Hereunder we will present the general overview of these disorders followed by specific remarks towards more common entities from that group.

The frequency of occurrence of ischemic type vasculitis in different clinical entities is not easy to be evaluated. Most of the disorders associated with this symptom are quite rare, so statistical analysis is not always possible. In mentioned earlier large material by Sharief et al. among 1169 patients with uveitis, 236 eyes had vasculitis, including 121 of ischemic type [21]. In that group 38% of cases were idiopathic, 19% were associated with tuberculosis hypersensitivity (Eales's disease, tuberculosis), 13% with Adamantiades-Behcet's disease, 9% with systemic lupus erythematosus

(SLE) and 7% with sarcoidosis. Each of the remaining clinical entities occurred in this cohort with frequency under 3%. Below we present the list of most important entities occurring with peripheral vasculitis and associated relative incidences of retinal ischemia.

List of diseases with peripheral vasculitis is presented in Table 11.1 [22].

All of the above disorders typically have a common course that involves the following stages (signs) [74]:

1. Inflammation. This stage is recognized by the presence of sheathing around vessel wall, perivascular infiltrates (in some cases severe—frosted branch angiitis), retinal edema, hemorrhages, cotton-wool spots, cystoid macular edema and inflammatory infiltrates in the vitreous (concomitant symptoms vary depending on the clinical entity). Certain clinical entities, such as toxoplasmosis and most of viral vasculitis, may present with retinal necrosis.
2. Retinal ischemia. This stage is noted in case of presence of peripheral sclerotic vessels and tortuous collaterals. Fluorescein angiography (preferable UWF) shows areas devoid of capillary perfusion, however without neovascularization.
3. Neovascularization. Pathological vessels are seen at the periphery, usually accompanied by vitreous or preretinal hemorrhage. FA shows intensive leakage from neovascular vessels.
4. Complications. They develop usually in untreated and/or long-standing cases and include non-resorbing vitreous hemorrhage, vitreoretinal traction, retinal detachment (tractional, rhematogenous or combined, epiretinal membranes, neovascular glaucoma, neovascularization of iris etc.).

Every case of retinal vasculitis require treatment specific for the etiopathogenesis. Infectious types of vasculitis need anti-bacterial, anti-viral or anti-parasitic treatment in active phase of the disease. Topical, periocular or systemic steroids are applied in systemic variants of that disease or in combination with specific drugs in infectious diseases to taper the inflammatory reaction and in cases with macular involvement. Sometimes immunosuppressants are prescribed in non-infectious types of vasculitis.

Laser scatter photocoagulation is typically applied at the proliferative stage; however, it is sometimes permissable in cases with large areas of hypoperfusion without neovascularization. Cases with extensive NV and vitreoretinal complications usually require pars plana vitrectomy.

Intraocular tuberculosis (IOTB)

Retinal vasculitis may occur due to active tuberculous infection or hyperreactivity to tuberculoprotein (Eales' disease) [75]. Definite diagnosis would require vitreous sample, so usually it is presumptive. IOTB is prevalent in Asia and in that region, it typically affects Asian Indian young males. Patients with IOTB develop granulomatous anterior uveitis and intermediate and posterior uveitis. Typical retinal

Table 11.1 List of most important retinal diseases with peripheral vasculitis together with the frequency of occurrence of retinal hypoperfusion nad neovascularization

Disease		Predominant vessel type involvement	Relative incidence of retinal hypoperfusion/neovascularization in cases with vasculitis
Infectious			
Bacterial	Tuberculosis [23]	Veins	High
	Syphilis [24]	Arteries and veins	High
	Lyme disease [25, 26]	Arteries and veins	Low
	Whipple's disease [27]	Arteries	Low
	Brucellosis [28]	Arteries and veins	Low
	Cat-scratch disease [29]	Arteries	Low
Viral	Herpes simplex	Arteries	Low
	Varicella zoster [30, 31]	Arteries	Low
	Human T-cell lymphoma [32]	Veins	Low
	Rift Valley fever virus [33]	Veins	Low
	HIV (acquired immunodeficiency syndrome) [34]	Arteries and veins	Low
	West Nile [35]	Arteries	High
	Acute retinal necrosis [36]	Arteries	
	PORN (progressive outer retinal necrosis) [37]	Arteries	low
	Cytomegalovirus [38]	Arteries	Low
	Infectious mononucleosis [39]	Arteries and veins	Low
Fungal	Coccidiomycosis [40]	Arteries and veins	Low
	Candidiasis [41]	Arteries and veins	Low
Parasitic	Toxoplasmosis [42]	Arteries and veins	Low
	Toxocariasis [43]	Veins	Low

(continued)

Table 11.1 (continued)

Disease		Predominant vessel type involvement	Relative incidence of retinal hypoperfusion/neovascularization in cases with vasculitis
	Amoebiasis [44]	Arteries and veins	Low
Rickettsia	Mediterranean spotted fever [45]	Arteries	Low
Local-ocular			
Eales' disease [46]		Veins	High
Pars planitis (idiopathic) [47]		Veins	High
Birdshot chorioretinopathy [48]		Veins	Low
Vogt-Koyanagi-Harada syndrome [49]		Arteries and veins	low
IRVAN retinal vasculitis, aneurysm and neuroretinitis [50]		Arteries	High
Idiopathic recurrent arterial branch retinal occlusion [51]		Arteries	Low
Acute multifocal hemorrhagic retinal vasculitis [52]		Arteries and veins	Low
Systemic disease			
Adamantiades-Behcet's disease [53]		Veins	High
Sarcoidosis [54]		Veins	High
Wegener's granulomatosis [55]		Arteries and veins	Low
Systemic lupus erythomatosus [56]		Arteries	High
Relapsing polychondritis [57]		Arteries and veins	Low
Takayasu disease [58]		Arteries	High
Polyarteritis nodosa [59]		Arteries	High
Crohn's disease [60]		Arteries and veins	High
Sjogren syndrome [61]		Arteries	Low
Rheumatoid arthritis [62]		Arteries and veins	High
Dermatomyositis [63]		Arteries	High
Multiple sclerosis [64]		Veins	High if uveitis present
Buerger's disease [65]		Arteries and veins	Low
Seronegative arthritis [66]		Arteries and veins	Low
Churg-Strauss syndrome [67]		Arteries	High

(continued)

Table 11.1 (continued)

Disease	Predominant vessel type involvement	Relative incidence of retinal hypoperfusion/neovascularization in cases with vasculitis
HLA-27 associated uveitis [68]	Veins	Low
APS—antiphospholipid syndrome [69]	Arteries and veins	High
Malignancy		
Ocular lymphoma [70]	Arteries and veins	Low
Paraneoplastic syndromes	Veins	Low
Acute leukemia [71]	Arteries and veins	Low
Cancer-associated retinopathy [72, 73]	Arteries and veins	Low

complication is periphlebitis, which results in vein occlusion and can be complicated by retinal neovascularization even in 29% of cases, as reported in one study [76]. The mechanism behind the vein occlusion is edema of the optic disc or inflammatory hyperreaction to tuberculoprotein. Patients present with thick exudates and hemorrhages, observed in a few quadrants (central retinal vein occlusion (CRVO is possible)) [77].

Treatment

Active infection in IOTB always require systemic anti-tuberculosis treatment. Diagnosis is confirmed by skin test and culture of Mycobacterium tuberculosis from body fluids. Cases complicated by NV require PRP with possible auxiliary anti-VEGF injections. It has to be remembered, that peripheral capillary non-perfusion may cause development of NV with recurrent intravitreal hemorrhages despite lack of signs of inflammation, that receded after treatment [78]. Non-resorbing vitreal hemorrhages and its vitreoretinal complications usually need surgical treatment with PPV.

Position of LPC in the treatment of IOTB

PRP is a choice of treatment in cases complicated by retinal neovascularization.

Eales' disease (ED)

Among peripheral vasculopathies Eales disease is more common and as such requires larger description. It is defined as idiopathic inflammatory retinal venous occlusion characterized by a triad of findings: venous inflammation (periphlebitis), vascular occlusion and retinal neovascularization. Characteristic feature of ED are recurrent vitreous hemorrhages, which are responsible for visual loss in that entity. ED typically affects young males in the second or third decade of life [79]. Majority of cases are noted in India and Middle-East countries, however ED occurs worldwide. The location of vascular changes is mid-periphery and far-periphery. Typically, as much as 50–90% of patients develop bilateral form of the disease, however unilateral cases are also noted [80].

The pathophysiological sequelae in ED involves inflammation and occlusion of peripheral veins, retinal ischemia, subsequent development of retinal neovascularization and recurrent vitreous hemorrhages. The etiology of described processes is unclear, however at present the concept of immunological reaction to exogenous factor (ex. tuberculoprotein after exposure to Mycobacterium tuberculosis) has gained wide support [81, 82]. Patients usually present with decrease of vision and floaters, due to vitreous hemorrhages. Macular involvement (macular edema, epiretinal membranes) is not common; however, it may occur in some cases [83]. Patients' examination usually reveals overlap of different phases of the disease, especially as regression of new vessels and recanalization of previously occluded ones is also possible. Therefore, a clear staging system is difficult to be outlined, nevertheless it has been proposed [84]. First stage covers peripheral phlebitis with retinal hemorrhage, second capillary nonperfusion with or without revascularization, third—fibrovascular proliferation with possible vitreous hemorrhage, fourth—tractional or combined tractional/rhematogenous retinal detachment followed by rubeosis iridis, neovascular glaucoma and complicated cataract.

Diagnostic methods in ED include fluorescein angiography, preferably UWF for detection of peripheral vascular abnormalities, ultrasound examination to evaluate vitreous hemorrhage and peripheral retinal traction and SD-OCT to assess macular involvement.

Differential diagnosis aims to exclude other entities with autoimmune peripheral vasculitis (such as sarcoidosis, multiple sclerosis, Adamantiades-Behcet disease, pars planitis, HIV related retinal inflammation, systemic lupus erythematosus, aneurysms and neuroretinitis (IRVAN), polyarteritis nodosa, Wegener's granulomatosis, Crohn's disease), infectious diseases (syphilis, tuberculosis, Lyme disease), leukemia and congenital (such as familial exudative vitreoretinopathy).

Treatment

Treatment of Eales disease is symptomatic and depends on the stage of the disease [85]. The goal of treatment is to reduce vascular inflammation and vitritis, prevent occurrence of vitreous hemorrhage in proliferative stage and clear persistent vitreous hemorrhage or remove vitreoretinal traction. Thus, treatment modalities involve anti-inflammatory agents, laser ablation of hyperperfused retina, anti-VEGF intravitreal injections and vitreoretinal surgery. Systemic and/or periocular or intravitreal steroids are used in active forms of vasculitis, especially if widespread or macula threatening [86]. The doses are tapered as periphlebitis regresses. Intravitreal anti-VEGF are helpful in cases with initial neovascularization and may prevent pars plana vitrectomy [87, 88].

Laser PRP proved effective in preventing visual loss from ED [89, 90]. Scatter LPC is applied to the areas of retinal hypoperfusion, focal LPC is used to treat flat retinal neovascularization and it is permittable to treat directly neovascular fronds into vitreal cavity [91]. Regression of neovascularization was noted in more than 80% of cases. The question whether to perform a full PRP or treat non-perfused retina only is still debatable. Das et al. advocate the use of moderate laser power and limited extend of scatter photocoagulation. It is not determined, either, whether LPC is efficient in pre-proliferative stage of the disease [92]. Stages with vitreoretinal traction, extensive epiretinal membranes, non-clearing vitreous hemorrhage or retinal detachment require pars plana vitrectomy. Application of endolaser photocoagulation is mandatory in all such cases. The prognosis after PPV in Eales disease is good, with improvement of visual acuity in majority of cases [93].

Position of laser in the treatment of Eales disease

LPC is the mainstay of treatment in proliferative stage of the disease.

Sarcoidosis

Sarcoidosis is a systemic inflammatory disease characterized by formation of noncaseating granulomas. It can affect any organ, however usually it is recognized in lungs, skin and lymphatic nodes. Diagnosis is made on the basis of histological confirmation of affected tissue, examination of the lungs, level of angiotensin converting enzyme (ACE) and exclusion of other granulomatous diseases, such as tuberculosis and syphilis. Ocular involvement in sarcoidosis is relatively high, as it is reported at 12–76% in different studies [94–96]. The most common manifestation of sarcoidosis is uveitis, reported in 30–70% of cases [97]. It may locate in anterior, intermediate or posterior segment, with bilateral anterior involvement occurring most frequently. It usually presents with pain, conjunctival redness, iris nodules, keratic precipitates and anterior and posterior synechiae. Intermediate uveitis typically causes floaters, infiltrates, snowballs and snowbanks in the vitreous. Posterior uveitis, usually bilateral,

bares very characteristic features, such as periphlebitis and perivascular exudates described as “candle wax drippings”.

Treatment

The mainstay of treatment of sarcoid uveitis involves application of systemic, periocular or topical steroids. Long-term cases may require immunosuppressive agents. LPC is applied in cases complicated by retinal neovascularization which are not extremely rare [98]. Cases complicated by macular edema usually are treated with steroid intravitreal implants, anti-VEGF injections or PPV.

Position of LPC

LPC is the treatment of choice in cases complicated with retinal NV.

Systemic lupus erythematosus (SLE)

SLE is a systemic disease characterized by formation of immune-complexes that deposit in vessel walls, subsequent activation of complement and fibrinoid cascade that add to vessel occlusion. Consequence of that processes is vessel damage visible as vasculitis and occlusion of different caliber of vessels, mainly arteries [99]. Symptoms occur in different organs and include arthritis, myocarditis, nephritis, Raynaud’s phenomenon and retinopathy.

Retinopathy is the major sight threatening ocular finding in SLE, occurring in 2–30% of SLE patients, depending on the study [100, 101]. Incidence of retinopathy increases with the presence of risk factors, such as anticardiolipin antibodies, involvement of central nervous system, serum carnitine level and activity of SLE. Occurrence of NV is reported at 40% of cases with occlusive retinopathy [102]. Severe visual loss (BCVA < 6/60) is noted in 55% of such cases.

Treatment

SLE treatment usually requires systemic treatment with steroids and immunosuppressants. Patient who developed ischemic retinopathy with NV are treated with LCP, however this procedure proves to be less effective in SLE than in other ischemic retinopathies. Stabilization of vision after PRP was reported only in 54% of treated patients [103]. Adjunct of intravitreal anti-VEGF was reported effective in treatment of neovascularization in the course of SLE in a few case reports and is recommended in eyes with extensive NV [103, 104]. Nevertheless anti-VEGF drugs should be used in caution in patients with concomitant ischemic maculopathy [105].

Position of LPC

LPC is a treatment of choice in proliferative retinopathy secondary to SLE, usually combined with systemic medication and possible adjunct of anti-VEGF.

Antiphospholipid syndrome (APS)

APS is an autoimmune disease characterized by the presence of antiphospholipid antibodies (lupus anticoagulant–LA, anti-cardiolipin antibodies-aCL and anti-β 2 glycoprotein-I) which is associated with vascular thrombosis of both veins and arteries, miscarriage and thrombocytopenia [106]. Vascular thrombosis most frequently affects lower limbs (deep venous thrombosis), less often lungs and brain. APS typically affects young and middle-aged adults, more commonly women. It can occur in its primary form, when no other systemic diseases are recognized, or secondary, when it is accompanied by comorbid disorders, most commonly SLE. Interestingly, as high as 22.5% of cases with vascular occlusive events with retinal thrombosis without other risk factors were reported to have anticardiolipin antibodies [107]. Occurrence of ocular symptoms in APS is high, so ophthalmic assessment is crucial for proper patient's management [108]. Neuro-ophthalmologic manifestations are not uncommon in APS and include arteritic and non-arteritic ischemic optic neuropathy, ocular motility disorders and central nervous system infarctions. Anterior segment manifestations may include conjunctivitis sicca, conjunctival telangiectasis and punctate epithelial keratopathy. Anterior uveitis is usually associated with posterior segment involvement, which is relatively common in APS. Retinal findings include venous tortuosity, retinal hemorrhages, microaneurysms and cotton wool-spots. Retinal ischemia as usual should be evaluated with FA. SD-OCT reveals paracentral acute middle maculopathy in spot corresponding to occlusion of microcirculation. More advanced vascular pathologies include central and branch retinal vein occlusion as well as central or branch artery occlusion [109]. Characteristically, in APS retinal vein occlusion do not occur with arterial/venous crossing sign, but may present in multiple locations at the fundus [110]. Similarly, arterial occlusion in APS is not associated with vessel bifurcations. Risk of RVO in APS is significantly increased with higher levels of antiphospholipid antibodies [111]. Other ophthalmic symptoms noted less frequently in the presence of antiphospholipid antibodies are retinal vasculitis, vitritis and posterior scleritis [112].

Treatment

Primary treatment of APS aims at prevention of thrombotic events associated with antiphospholipid antibodies, thus is conducted with application of anticoagulants.

Special care is needed for patients with the history of vascular thrombosis, in whom anticoagulation therapy is carried out for life [113].

Complications of vascular occlusive disease with significant ischemia, such as neovascular glaucoma or retinal neovascularization, require LPC as primary form of treatment, with possible adjunct of anti-VEGF therapies. There is no accepted preventive ocular treatment for APS.

Position of LPC in the treatment of APS

LPC is the treatment of choice in retinal neovascularization or neovascular glaucoma in the course of APS. Anti-VEGF injections may serve as an adjunct.

Adamantiades-Behcet disease (ABD)

ABD belongs to spectrum of HLA-B51 associated systemic inflammatory disorders. Major international criteria for recognition of ABD are the following: recurrent oral ulceration (major symptom), genital ulcerations, eye lesions, skin lesions and positive pathergy tests (concomitant syndromes out of which two are necessary for the diagnosis) [114]. Ocular symptoms occur usually later than ulcerations and include anterior uveitis, vitreous infiltrates, retinal hemorrhages and infiltrates, nongranulomatous necrotizing retinal vasculitis with possible vessel occlusion. Risk of incidence of macular edema in ocular ABD is high. BRVO has been reported as first manifestation of ocular ABD in relatively high percentage of patients (28%) as well as occlusive vasculitis (21%) while CRVO or CRAO are less frequent [115]. Development of neovascularization in ABD depends on two factors, intensity of inflammation and retinal ischemia. In a study by Tugan-Tutkul on neovascularization at the disc occurring in the course of ABD, 87% of NVD cases were inflammation-induced and only 13% ischemia induced [116]. In a large retrospective study by the same author (880 patients and 1567 eyes) incidence of NV in patients with uveitis was 4% [117].

Treatment

Primary treatment of ABD are corticosteroids and immunosuppressive drugs. Usually, acute onset is targeted with systemic corticosteroids and chronic phase with combination of steroids and immunomodulatory medications. Laser photocoagulation can be effective in ischemia induced neovascularization. Regression of NV was noted in majority of LPC treated eyes [118].

Position of LPC in the treatment of ABD

Auxiliary therapy in cases with retinal ischemia.

Ocular ischemic syndrome (OIS)

OIS is a rare entity occurring twice more frequently in males than females, usually in sixth decade of life and rarely before 50 [119]. The pathogenesis of OIS includes carotid artery occlusion or stenosis leading to impaired perfusion of the eyeball. The disease always involves systemic aspects, such as atherosclerosis and possibility of cerebral infarction [120]. The severity of OIS corresponds to the degree of stenosis, laterality (bilateral cases are more severe), disease chronicity and presence or absence of collateral vessels at the fundus [121].

Diagnosis is made on the basis of ocular symptoms, fundus appearance and ancillary tests, such as fluorescein angiography, electroretinography and imaging of carotid arteries and retrobulbar vessels.

Patients usually present with visual loss, transient visual loss and ischemic pain. Decreased visual acuity is noted in majority of patients, while transient visual loss concerns about 10–15% of patients. Pain is reported by 40% of patients affected by OIS. Usually, origin of pain in OIS is ocular ischemia and as such pain is described as dull, constant, overtaking the orbit, face and temple. Secondary origin of pain in OIS can be increased intraocular pressure due to neovascular glaucoma.

Fundus appearance varies depending on the severity of ischemia, starting from widening of veins and narrowing of arteries, midperipheral hemorrhages, telangiectasias and arteriovenous anastomoses, cotton wool spots to more serious signs, like neovascularization on the disc, neovascularization elsewhere and vitreous hemorrhages.

Appearance of anterior segment depends on the duration of ischemia and development of its complications. Sole rubeosis iridis and signs of neovascular glaucoma are noted in short-standing cases, however long-standing ischemia can lead to iridocyclitis, complicated cataracts, corneal edema and melting and anterior and posterior synechiae.

OIS should be differentiated from other vascular retinal disorders, such as diabetic retinopathy, hypertensive retinopathy, central retinal vein occlusion and hyperviscosity syndromes.

Treatment

Treatment in OIS aims to minimize ocular complications, prevent systemic complications and improve flow through carotid arteries.

Ocular treatment should control inflammation with anti- inflammatory topical and systemic drugs and cycloplegics, that stabilize blood-aqueous barrier. Increase in IOP should be treated with topical medications, preferable beta-blockers and alfa-agonists, avoiding prostaglandins, anticholinergic medications and pilocarpine that exacerbate inflammatory reaction. Surgical procedures are recommended in unresponsive cases, especially in neovascular glaucoma.

The other important target of ocular management is retinal ischemia, that can be treated with panretinal photocoagulation. PRP might prevent development of neovascular glaucoma in certain cases. In eyes with poor visualization of the fundus retinal cryopexy or transscleral diode retinopexy should be considered.

Anti-VEGF therapy is used as an adjunct to PRP in cases with rubeosis iridis and in cases complicated by cystoid macular edema.

Systemic treatment in OIS should be conducted by general practitioners and neurologist. Despite targeting systemic disorders, it involves changing of the lifestyle, cessation of smoking and weight reduction.

Surgical treatment of carotid arteries (endarterectomy or stenting) is conducted by specialists in the field.

Position of LPC in the treatment of OIS

PRP is used for treatment of retinal ischemia in cases with good visualization of the fundus.

Carotid cavernous fistula (CCF)

CCF is a result of an abnormal connection between internal (ICA) or external carotid artery (ECA) and the cavernous sinus. CCFs are classified according to their anatomy, hemodynamics and etiology [122]. Direct CCFs are characterized by a straight connection between ICA and cavernous sinus. On the other hand, indirect or dural CCFs, present with a connection between meningeal branches of ICA, ECA or both and cavernous sinus. Taking into account fistulas' hemodynamics, CCFs can be classified as high flow or low flow. Etiological division distinguishes traumatic and spontaneous types of CCF. Spontaneous type is significantly less frequent than posttraumatic (about 30%) and occurs predominantly in postmenopausal women burdened with atherosclerosis, hypertension or collagen related disorders [123]. These cases are more often dural and low-flow. Traumatic CCFs are usually direct, high flow and occur in younger patients.

Ocular symptoms are a result of obstruction of venous drainage from the orbit and impaired arterial perfusion. Patients may present with symptoms of diplopia, headache and vision loss. Possible ophthalmic findings include proptosis, pulsatile exophthalmos, eyelid swelling, conjunctival chemosis and arterialization of conjunctival vessels, ophthalmoplegia, especially paresis of abducens nerve, pupillary abnormalities and elevated intraocular pressure. Fundus examination may reveal papilledema, dilated retinal veins, ischemic optic neuropathy, central retinal vein occlusion, or choroidal detachment.

Diagnostics in CCF is based on cerebral imaging, especially cerebral angiography, however CT and magnetic resonance imaging (MRI) might also be helpful.

Treatment

Direct CCFs require surgical treatment aiming to close the abnormal communication, preferably with endovascular approach. Dural CCFs can be observed for spontaneous closure, however due to significant improvement in neurointerventional techniques, surgical treatment is often preferred as initial treatment as well.

Ophthalmic treatment

Elevated intraocular pressure (IOP) is usually successfully controlled with topical medication and only in rare cases surgical filtering procedures are required. Sometimes peripheral iridotomy is performed in cases of pupillary block. CCF can be complicated by venous stasis retinopathy, central retinal vein occlusion and subsequent neovascular glaucoma [124, 125]. Such cases are usually initially treated with PRP [126]. Same treatment is applied in rare cases of proliferative retinopathy in patients with CCF [127, 128].

Position of LPC in the treatment of CCF

PRP is required in cases with neovascular glaucoma and proliferative retinopathy.

Proliferative hypertension retinopathy (PHR)

The term "proliferative hypertensive retinopathy" is relatively young, as it was first proposed in 2016 with the presentation of case report by Stryjewski et al. [129]. It refers to cases of hypertensive retinopathy complicated by retinal neovascularization in the absence of vein occlusions or other vascular complications that would explain the occurrence of NV in a patient with systemic arterial hypertension (SAH). So far only a few case reports of such phenomenon were published [130–132]. The cause of retinal NV in SAH is thought to be up-regulation of growth factors in the course of retinal ischemia occurring as a result of vasculopathy. Disease affects young patients with poorly controlled blood pressure in the course of SAH. Ophthalmic examination reveals multiple fundus changes typical of hypertensive retinopathy, including hemorrhages, cotton-wool spots, hard exudates, vein widening and arterioles narrowing, together with areas of neovascularization at the disc or located at the periphery and possible vitreous hemorrhage. Fluorescein angiography enables to precisely visualize areas of non-perfusion and neovascularization.

Treatment

As only a few cases were reported, there are no strong preferences towards management of PHR. Both PRP and anti-VEGF treatment were reported effective in

achieving regression of NV, either in monotherapy or combined treatment [133]. Nevertheless, PRP seems to be the first choice treatment modality for some authors [130].

Position of LPC in the treatment of PHR

LPC is a mainstay of treatment in PHR with possible auxiliary anti-VEGF treatment.

Peripheral exudative hemorrhagic chorioretinopathy (PEHC)

PEHC is a group of chorioretinal disorders similar to exudative form of age-related macular degeneration but occurring at the retinal periphery. It was first described in 1980 by Annesley [134]. In the contrary to peripheral retinal vasculopathies associated with purely retinal neovascular proliferations, in PEHC abnormal choroidal circulation contributes significantly to the development of neovascularization. Etiology of that clinical entity is unknow, however main risk factors include advanced age and systemic arterial hypertension.

PEHC presents with variety of symptoms at the fundus, among which peripheral hemorrhagic retinal pigment detachment is the most common [135]. Other findings include retinal tears, subretinal fibrosis, subretinal hemorrhage, subretinal fluid, lipid exudations and vitreal hemorrhage. Sometimes subretinal hemorrhage or fluid extends towards macular region [136]. Most of the patients have choroidal polyps detected on ICGA, which resembles the course of polypoidal choroidal vasculopathy (PCV).

Diagnosis of PEHC should be based on multimodal imaging and include FA, ICGA (preferably UWF) and ultrasound examination. SD-OCT is required in cases with macular involvement. PEHC is often misdiagnosed with ocular tumors, especially choroidal melanoma.

Treatment

Some of PEHC cases have self-limiting course that ends-up with disciform scar formation. Such patients require close observation only [137]. Treatment is indicated in cases with non-resorbing vitreous hemorrhage and/or retinal traction and macular involvement and include the following procedures: anti-VEGF injections (most often), LPC, cryotherapy, photodynamic therapy (PDT) and PPV [138, 139]. Visual improvements are noted in cases treated with PPV.

Position of LPC in the treatment of PEHC

LPC has an auxiliary role in the treatment of PEHC in cases with detectable peripheral neovessel network [140].

Hiperviscosity syndromes (HVS)

HVS constitutes a clinical scenario characteristic for a group of systemic disorders with increased blood viscosity, such as Waldenström macroglobulinemia, multiple myeloma, leukemias, polycythemia and myeloproliferative disorders. Typically, presentation of HVS include mucosal bleeding, decline of vision and neurological symptoms, sometimes also cardiorespiratory symptoms.

Ocular changes observed in HVS are a consequence of occlusion of retinal vessels due to increased blood viscosity and increased risk of formation of arterial clots and vein thrombosis. These include retinal vein occlusions, peripheral retinal ischemia with periphlebitis, venous dilation and hemorrhages and macular edema [141–144]. The abnormal retinal circulation can be observed even in absence of subjective ocular symptoms [145]. Among additional symptoms conjunctival infiltration is worth mentioning.

HVS are recognized primarily by the blood test that reveal increased blood viscosity and abnormal blood cell count and results of bone marrow biopsy.

Treatment

Primary treatment for HVS depends on the etiology of a specific disorder and include intravascular procedures such as plasmapheresis. Systemic corticosteroids and cytostatics are also used. LPC is applied for the complications of HVS occurring with retinal ischemia, that is retinal neovascularization [146, 147].

Position of LPC in the treatment of HVS

LPC has plays a role in rare cases of HVS complicated by retinal neovascularization.

Familial exudative vitreoretinopathy (FEVR)

FEVR is a group of hereditary diseases characterized by abnormal vascularization of peripheral retina with subsequent ischemia and development of vasoproliferative lesions. FEVR bares resemblance to retinopathy of prematurity, however it occurs in children born full-term and with normal birthweight [148]. Typically, it is bilateral but asymmetric disease were also reported. Mean age of onset is 6 years; however, it can present in adultery as well. Pathogenesis of FEVR relies on development of peripheral retinal ischemia that triggers vasoproliferative reaction with consecutive possible vitreoretrinal traction, dragging of the vessels, retinal folds, hemorrhages, retinal tears and retinal detachment. Moreover, FEVR is associated with increased permeability of retinal vessel, what can lead to subretinal exudation and exudative retinal detachment. Staging of FEVR was proposed by Pendergast et al. [149] who

specified the following phases: (1) avascular retinal periphery, (2) panretinal neovascularization with or without exudate, (3) macular sparing retinal detachment with or without exudate, (4) macula-involving retinal detachment with or without exudate and (5) total retinal detachment. FEVR severity depends on the age of presentation and its course is characterized by active phases and relapses. Younger patients develop more serious changes, nevertheless retinal detachment may occur many years after initial presentation. Thus, FEVR patients require regular follow-up visits, in fact throughout life. Fluorescein angiography, preferably UWF is a basic diagnostic tool, that enables to recognize and follow FEVR. FA shows the areas of non-perfusion, in particular the border between perfused and avascular retina, anastomoses, abnormalities of the course of the vessels and retinal neovascularization. Potential peripheral vitreoretinal traction can be assessed with the ultrasound exam. SD-OCT is used in cases complicated by macular edema, epiretinal membranes and/or traction in the macular area.

Treatment

Treatment should be guided by the staging of the disease. Stage 1 usually can be observed, however cases, in which the other eye has lost sight may be treated with PRP. Stage 2 requires PRP in both exudative and non-exudative form. Stages 3–5 usually require surgical treatment with PPV [150, 151].

Anti-VEGF injections were reported as alternative to retinal ablation, nevertheless such reports are scarce [152, 153]. Besides, it has to be borne in mind, that anti-VEGF treatment can provoke intensive fibrous traction after regression of neo-vessels and patient will still require surgical treatment.

Position of LPC in the treatment of FEVR

PRP is the mainstay of treatment of FEVR in stage 2 and sometimes in stage 1.

Incontinentia pigmenti (IP)

IP or Bloch-Sulzberger syndrome is an X-linked dominant disease. Most of patients (97%) are female, as male affected fetuses do not survive [154]. The disorder is described as ectodermal dysplasia and affects skin, teeth, nails, hair, eyes and neurological system. It presents at birth or in early childhood with characteristic vesiculobullous skin lesions that gradually progress to verrucous stage, followed by hyperpigmented stage and finally hypopigmented stage. Patients require neurological assessment, as neurological abnormalities, such as convulsive disorders, spastic paralysis, motor retardation, and mental retardation occur in up to 30% of cases [155]. Dental examination is also required in patients with IP, as teeth abnormalities are found in 70% of patients. Ocular involvement is noted in 35–40% of patients with IP [156].

Retinal lesions are a result of occlusion of small arteries with subsequent ischemia and possible retinal neovascularization [157]. Changes can progress to development of vitreoretinal traction and retinal detachment, which is typically noted in the first six years of child's life and very rarely occurs in older age. Retinal ischemia may extend to the macular area with characteristic cherry red spot sign. Optic nerve atrophy and foveal hypoplasia were also reported in IP. Cortical blindness is rare, but possible early in the course of IP. Other ocular findings in IP include cataracts, uveitis, strabismus and nystagmus. IP bares similarities to FEVRROP, Eales disease and SCR and should be differentiated from these diseases, however usually characteristic skin lesions determine the diagnosis. Ophthalmic assessment typically requires general anesthesia and include fundus evaluation, FA and SD-OCT.

Treatment

Treatment of IP requires multidisciplinary approach and involves dermatologic, neurologic, ophthalmic, genetic and dental diagnostics and treatment. Management of IP is usually symptomatic and supportive. Ophthalmic treatment involves LPC or cryotherapy of the avascular retina performed in similar fashion as in ROP [158, 159]. Treatment with anti-VEGF injections has been also reported effective in a few cases, but needs evaluation in larger studies [160]. Surgical treatment is reserved for retinal detachment cases.

Position of LPC in the treatment of IP

PRP is crucial for treatment of avascular zones of the retina.

Norrie disease (ND)

Norrie disease is a rare, genetic, X-linked recessive disorder that exclusively affects males, with female carriers. ND results from the mutation of Norrie Disease Neuroglioma (NDP) gene involved in development of vascularization of inner ear and retina [161]. Retinal anomalies are primary symptoms in ND usually leading to blindness at birth or soon after. Pathological vascularization of the retina leads to development of fibrovascular tissue, intravitreal hemorrhages and tractional retinal detachment. Loss of retinal ganglion cells is also noted in ND cases [162]. Most of the patients present with total or partial retinal detachment. Retina appears as dense, globular and dysplastic tissue, avascular at the periphery. Characteristically, the changes are bilateral and symmetric, often present at birth. Usually, diagnosis is made soon after birth, as retinal lesions occur in utero. If retinal detachment develops, leukocoria is the major sign provoking further diagnostics. Other ocular abnormalities that may be present, include cataract, atrophy of the iris, anterior and posterior synechiae and shallow anterior chamber. In the course of ND secondary glaucoma,

band-keratopathy and finally phthisis bulbi may also occur [163]. Diagnosis is made on the basis of physical examination, fundus evaluation, ultrasound exam and results of antenatal testing. Symptoms from other systems in ND include progressive hearing loss with the onset in the second decade of life, abnormal sleep–wake cycles and behavioral disturbances. Significant variance in concomitant symptoms is noted and rarely all of them are present in one child.

Treatment

ND requires multidisciplinary approach including ophthalmologists, audiologists, pediatricians and genetic counselling. Antenatal testing is necessary to plan treatment soon after child's birth or plan preterm delivery [164]. Most of the patients require early surgery for total or partial retinal detachment [165, 166]. Sometimes preterm delivery is planned in ND to deliver early laser photocoagulation of neovascular retina before the retinal detachment develops [164, 167, 168].

Position of LPC in the treatment of ND

LPC is reported to preserve some vision in patients with planned preterm delivery in ND.

Talc retinopathy

Talc retinopathy is a rare finding noted in long term intravenous drug users. Talc is used as a filler in oral medications and narcotics (ex. heroin). It is described as embolic condition of small arteries and capillaries in the inner retina. Fundus examination reveals characteristic crystal deposits in the posterior pole. These debris are also visible as hyperreflective foci on SD-OCT exam [169]. Fundus examination findings may persist for years, without progression or retinal complications [170–172]. Nevertheless, in few cases emboli cause significant retinal ischemia followed by retinal neovascularization [173, 174]. Singular reports on rapid neovascularization of optic nerve disc and peripheral retina after intravenous injection of drug are also available [175].

Diagnosis is made on the basis of medical history of drug abuse, fluorescein angiography that reveals areas of retinal non-perfusion and neovascularization and SD-OCT findings [176].

Treatment

Tale retinopathy is rare condition, so recommendations for its treatment have to base on case reports and commonly accepted rules for ophthalmic surgery. Therefore,

treatment of this retinopathy should be related to the extent of retinal neovascularization and vitreous hemorrhage. Cases without vitreoretinal traction with good visualization of the fundus are treated with PRP, while more advanced cases complicated by vitreoretinal abnormalities require PPV.

Position of LPC in the treatment of talc retinopathy

LPC is a primary form of treatment for cases complicated by retinal neovascularization without significant vitreoretinal traction.

Radiation retinopathy (RR)

Radiation retinopathy may develop after exposure to any type of radiation, including external source (treatment of orbital, paranasal or nasopharyngeal tumors) or internal—after brachytherapy. Occurrence of RR is dose-dependent. Although there are no precise thresholds, increase in RR is noted with radiation doses between 15 and 60 GY, while clear increase is noted above 45 GY dose. Fractioning of radiation dose significantly diminishes the incidence of RR [177]. Typically RR appears 6 months to 3 years after exposure to radiation [178].

Typical fundus signs for RR are microaneurysms, telangiectasias, hard exudates, cotton-wool spots, macular edema, optic disc edema, neovascularization and vitreous hemorrhage, sometimes even retinal detachment. Other possible ocular features include cataract, neovascularization of iris and angle. Patients may present asymptomatic in cases of mild RR or report decline of vision and floaters in well-developed RR.

Diagnosis is made on the basis of medical history, fundus appearance and auxiliary exams, such as fluorescein angiography for detection of leakage sites, capillary non-perfusion and neovascularization as well as SD-OCT for evaluation of macular changes (Fig. 11.1).

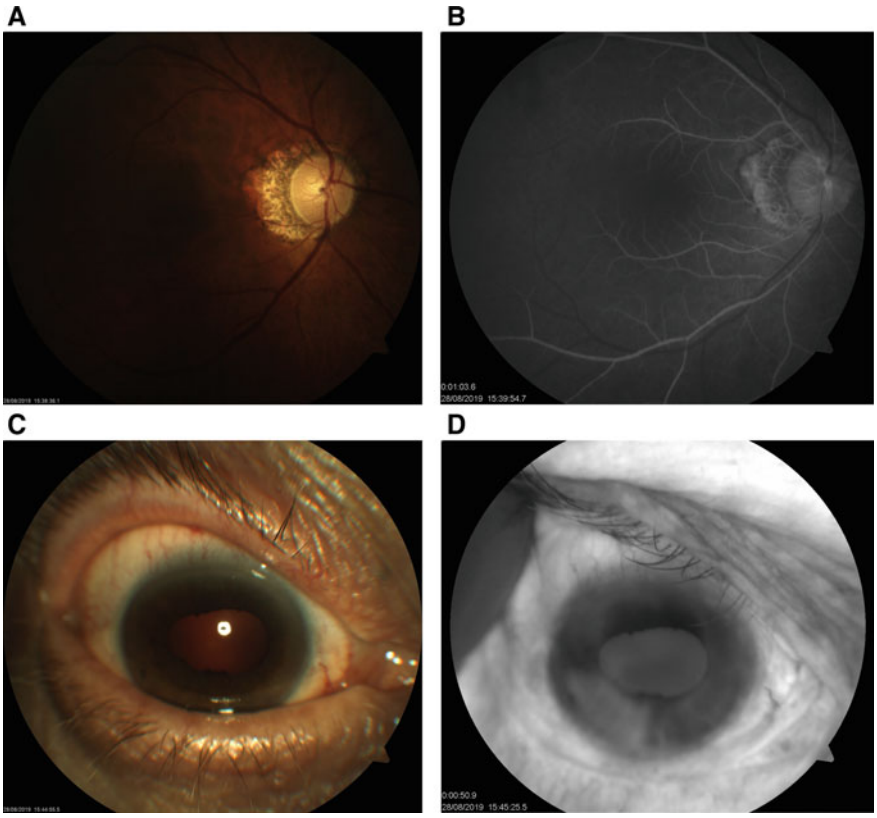

Fig. 11.1 Ocular ischemic syndrome. **A** Color photograph of the fundus shows pale optic disc. **B** FA reveals delayed filling of retinal vessels. **C** Photograph of anterior segment presents rubeosis iridis and nuclear cataract. **D** FA of the anterior segment reveals leakage from irideal neovascularization

Treatment

Primary treatment for macular changes of vascular origin in RR are intravitreal therapies with anti-VEGF agents or corticosteroids [179–181]. Nevertheless, to maintain vision (improvements are rarely reported) patients require repeated injections.

PRP or scatter laser photocoagulation is used for proliferative and non-proliferative RR [182, 183]. Regression of retinopathy was noted in more than 60% of patients in both cited studies. Successful combined treatments of anti-VEGF plus LPC are also reported [184]. Recent randomized controlled trial analyzing regression of RR after intravitreal ranibizumab versus PRP proved similar effects for both modalities at one year [185]. Cases with non-resorbing vitreous hemorrhage or retinal detachment require PPV.

Position of LPC in the treatment of RR

Nowadays LPC serves as primary procedure for the treatment of neovascular RR at the retinal periphery.

References

1. The Central Vein Occlusion Study Group A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion: the Central Retinal Vein Occlusion Study Group N Report. Ophthalmology. 1995;102:1434–44.
2. Stefansson E. The mechanism of retinal photocogulation—how does the laser work? Eur Ophthalmic Rev. 2008;2:?
3. Pournaras CJ. Retinal oxygen distribution Its role in the physiopathology of vasoproliferative microangiopathies. Retina. 1995;15:332–47.
4. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. The diabetic retinopathy study research group. Ophthalmology. 1981;88(7):583–600
5. Branch Vein Occlusion Study Group. Argon laser scatter photocoagulation for prevention of neovascularization and vitreous hemorrhage in branch vein occlusion A randomized clinical trial. Arch Ophthalmol. 1986;104:34–41.
6. Schnog JB, Duits AJ, Muskiet FA, ten Cate H, Rojer RA, Brandjes DP. Sickle cell disease; a general overview. Neth J Med. 2004;62(10):364–74.
7. Jackson H, Bentley CR, Hingorani M, Atkinson P, Aclimandos WA, Thompson GM. Sickle retinopathy in patients with sickle trait. Eye (Lond). 1995;9(Pt 5):589–93.
8. Goldberg MF. Classification and pathogenesis of proliferative sickle retinopathy. Am J Ophthalmol. 1971;71(3):649–65.
9. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312:1033–48.
10. Li J, Bender L, Shaffer J, et al. Prevalence and onset of pediatric sickle cell retinopathy. Ophthalmology. 2019;126:1000–6.
11. Ahmed I, Pradeep T, Goldberg MF, Liu TYA, Aradhya A, Montana MP, Photiadis N, Williams E, Smith B, Tian J, Lanzkron SM, Scott AW. Nonmydriatic ultra-widefield fundus photography in a hematology clinic shows utility for screening of sickle cell retinopathy. Am J Ophthalmol. 2022;236:241–8.
12. Downes SM, Hambleton IR, Chuang EL, et al. Incidence and natural history of proliferative sickle cell retinopathy: observations from a cohort study. Ophthalmology. 2005;112:1869–75.
13. Farber MD, Jampol LM, Fox P, et al. A randomized clinical trial of scatter photocoagulation of proliferative sickle cell retinopathy. Arch Ophthalmol. 1991;109:363–7.
14. Myint KT, Sahoo S, Thein AW, Moe S, Ni H. Laser therapy for retinopathy in sickle cell disease. Cochrane Database Syst Rev. 20159;2015(10):CD010790.
15. Rodrigues M, Kashiwabuchi F, Deshpande M, Jee K, Goldberg MF, Lutty G, Semenza GL, Montaner S, Sodhi A. Expression pattern of HIF-1α and VEGF supports circumferential application of scatter laser for proliferative sickle retinopathy. Invest Ophthalmol Vis Sci. 2016;57(15):6739–46.
16. Cai CX, Linz MO, Scott AW. Intravitreal bevacizumab for proliferative sickle retinopathy: a case series. J of VitRet Dis. 2018;2:32–8.
17. Chen RWS, Flynn HW, Lee WH, et al. Vitreoretinal management and surgical outcomes in proliferative sickle retinopathy: a case series. Am J Ophthalmol. 2014;157:870-875.e1.
18. Rosenbaum JT, Ku J, Ali A, Choi D, Suhler EB. Patients with retinal vasculitis rarely suffer from systemic vasculitis. Semin Arthritis Rheum. 2012;41(6):859–65.

19. Hughes EH, Dick AD. The pathology and pathogenesis of retinal vasculitis. Neuropathol Appl Neurobiol. 2003;29(4):325–40. https://doi.org/10.1046/j.1365-2990.2003.00499.x. PMID: 12887593.
20. Graham EM, Stanford MR, Sanders MD, Kasp E, Dumonde DC. A point prevalence study of 150 patients with idiopathic retinal vasculitis: 1. Diagnostic value of ophthalmological features. Br J Ophthalmol. 1989;73(9):714–21.
21. Sharief L, Lightman S, Blum-Hareuveni T, Bar A, Tomkins-Netzer O. Clinical outcome of retinal vasculitis and predictors for prognosis of ischemic retinal vasculitis. Am J Ophthalmol. 2017;177:206–12.
22. Agarwal A, Rübsam A, Zur Bonsen L, Pichi F, Neri P, Pleyer U. A comprehensive update on retinal vasculitis: etiologies, manifestations and treatments. J Clin Med. 2022;11(9):2525.
23. Shukla D, Kalliath J, Dhawan A. Tubercular retinal vasculitis: diagnostic dilemma and management strategies. Clin Ophthalmol. 2021;15:4681–8.
24. Pan SW, Yusof NS, Hitam WH, Noor RA, Embong Z. Syphilitic uveitis: report of 3 cases. Int J Ophthalmol. 2010;3(4):361–4.
25. Smith JL, Winward KE, Nicholson DF, Albert DW. Retinalvasculitis in Lyme borreliosis. J Clin Neuro-Ophthalmol. 1991;11:7–15.
26. Mora P, Carta A. Ocular manifestations of Lyme borreliosis in Europe. Int J Med Sci. 2009;6(3):124–5.
27. Avila MP, Jalkh AE, Feldman E, Trempe CL, Schepens CL. Manifestations of Whipple's disease in the posterior segment of the eye. Arch Ophthalmol. 1984;102(3):384–90.
28. Bazzazi N, Yavarikia A, Keramat F. Ocular involvement of brucellosis. Middle East Afr J Ophthalmol. 2013;20(1):95–7.
29. Tolou C, Mahieu L, Martin-Blondel G, Ollé P, Matonti F, Hamid S, Benouaich X, Debard A, Cassagne M, Soler V. Posterior segment involvement in cat-scratch disease: a case series. J Fr Ophtalmol. 2015;38(10):974–82.
30. Albert K, Masset M, Bonnet S, Willermain F, Caspers L. Long-term follow-up of herpetic non-necrotizing retinopathy with occlusive retinal vasculitis and neovascularization. J Ophthalmic Inflamm Infect. 2015;28(5):6.
31. Narayanan S, Gopalakrishnan M, Giridhar A, Anthony E. Varicella Zoster-related Occlusive Retinal Vasculopathy–A Rare Presentation. Ocul Immunol Inflamm. 2016;24(2):227–30.
32. Merle H, Hage R, Meniane JC, Deligny C, Plumelle Y, Donnio A, Jean-Charles A. Retinal manifestations in adult t-cell leukemia/lymphoma related to infection by the human t-cell lymphotropic virus type-1. Retina. 2016;36(7):1364–71.
33. Siam AL, Meegan JM, Gharbawi KF. Rift valley fever ocular manifestations: observations during the 1977 epidemic in Egypt. Br J Ophthalmol. 1980;64(5):366–74.
34. Roth DB, McCabe CM, Davis JL. HIV-related occlusive vasculitis. Arch Ophthalmol. 1999;117(5):696–8.
35. Garg S, Jampol LM, Wilson JF, Batlle IR, Buettner H. Ischemic and hemorrhagic retinal vasculitis associated with West Nile virus infection. Retina. 2006;26(3):365–7.
36. Mayer CS, Blobner K, Storr J, Baur ID, Khoramnia R. Acute retinal necrosis: signs, treatment, complications and outcome. Diagnostics (Basel). 2022;12(2):386.
37. Tseng CC, Chen SN, Hwang JF, Lin CJ, Chen HS. Progressive outer retinal necrosis associated with occlusive vasculitis in acquired immunodeficiency syndrome. J Formos Med Assoc. 2015;114(5):469–72.
38. Downes KM, Tarasewicz D, Weisberg LJ, Cunningham ET Jr. Good syndrome and other causes of cytomegalovirus retinitis in HIV-negative patients-case report and comprehensive review of the literature. J Ophthalmic Inflamm Infect. 2016;6(1):3.
39. Suzuki K, Namba K, Hase K, Mizuuchi K, Iwata D, Ito T, Kitaichi N, Takase H, Ishida S. A case of Epstein-Barr virus acute retinal necrosis successfully treated with foscarnet. Am J Ophthalmol Case Rep. 2022;29(25): 101363.
40. Nordstrom B, Sherpa N, Marshall M, Chawla A, Heidari A, Johnson R. Coccidioidomycosis Chorioretinitis. J Investig Med High Impact Case Rep. 2019;7:2324709619881561.

41. Vinekar A, Avadhani K, Maralusiddappa P, Prabhu VM, Mahendradas P, Indumathi VA. Retinal vasculitis as an early indicator of systemic candidal abscesses in a premature infant. J AAPOS. 2011;15(1):96–7.
42. Butler NJ, Furtado JM, Winthrop KL, Smith JR. Ocular toxoplasmosis II: clinical features, pathology and management. Clin Exp Ophthalmol. 2013;41(1):95–108.
43. Despreaux R, Fardeau C, Touhami S, Brasnu E, Champion E, Paris L, Touitou V, Bodaghi B, Lehoang P. Ocular toxocariasis: clinical features and long-term visual outcomes in adult patients. Am J Ophthalmol. 2016;166:162–8.
44. Shi L, Hager T, Fries FN, Daas L, Holbach L, Hofmann-Rummelt C, Zemova E, Seitz B, Szentmáry N. Reactive uveitis, retinal vasculitis and scleritis as ocular end-stage of *Acanthamoeba* keratitis: a histological study. Int J Ophthalmol. 2019;12(12):1966–71.
45. Beselga D, Campos A, Castro M, Mendes S, Campos J, Neves A, Violante L, Castro Sousa JP. A rare case of retinal artery occlusion in the context of mediterranean spotted fever. Case Rep Ophthalmol. 2014;5(1):22–7.
46. Atmaca LS, Idil A, Gündüz K. Visualization of retinal vasculitis in Eales' disease. Ocul Immunol Inflamm. 1993;1(1–2):41–8.
47. Ozdal PC, Berker N, Tugal-Tutkun I. Pars Planitis: epidemiology, clinical characteristics, management and visual prognosis. J Ophthalmic Vis Res. 2015;10(4):469–80.
48. Knickelbein JE, Tucker W, Kodati S, Akanda M, Sen HN. Non-invasive method of monitoring retinal vasculitis in patients with birdshot chorioretinopathy using optical coherence tomography. Br J Ophthalmol. 2018;102(6):815–20.
49. Arellanes-García L, Hernández-Barrios M, Fromow-Guerra J, Cervantes-Fanning P. Fluorescein fundus angiographic findings in Vogt-Koyanagi-Harada syndrome. Int Ophthalmol. 2007;27(2–3):155–61.
50. Bajgai P, Katoch D, Dogra MR, Singh R. Idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) syndrome: clinical perspectives. Clin Ophthalmol. 2017;6(11):1805–17.
51. Johnson MW, Thomley ML, Huang SS, Gass JD. Idiopathic recurrent branch retinal arterial occlusion Natural history and laboratory evaluation. Ophthalmology. 1994;101(3):480–9.
52. Blumenkranz MS, Kaplan HJ, Clarkson JG, Culbertson WW, Williams GA, Kleiner RC, Meissner RH. Acute multifocal hemorrhagic retinal vasculitis. Ophthalmology. 1988;95(12):1663–72.
53. Davatchi F, Chams-Davatchi C, Shams H, Shahram F, Nadji A, Akhlaghi M, Faezi T, Ghodsi Z, Sadeghi Abdollahi B, Ashofteh F, Mohtasham N, Kavosi H, Masoumi M. Behcet's disease: epidemiology, clinical manifestations, and diagnosis. Expert Rev Clin Immunol. 2017;13(1):57–65.
54. Bypareddy R, Takkar B, Azad SV, Chawla R, Venkatesh P. Optic nerve head granuloma, retinal vasculitis and elevated levels of angiotensin-converting enzyme: dilemma of forme fruste ocular sarcoidosis. J Ophthalmic Vis Res. 2019;14(1):105–108.
55. Matlach J, Freiberg FJ, Gadeholt O, Göbel W. Vasculitis-like hemorrhagic retinal angiopathy in Wegener's granulomatosis. BMC Res Notes. 2013;10(6):364.
56. Chen XH, Shi JC, Wei JC, Chen HH, Mo HY. Increased risk of retinal vasculitis in patients with systemic lupus erythematosus: a nationwide population-based cohort study. Front Med (Lausanne). 2021;28(8): 739883.
57. Paroli MP, Priori R, Spinucci G, Abicca I, Valesini G. Uveitis with retinal occlusive vasculitis and sensorineural hypoacusia as first symptoms of relapsing polychondritis. Clin Exp Rheumatol. 2012;30(1 Suppl 70):S101–3.
58. Bajgai P, Singh R. Retinal vasculitis in Takayasu's arteritis. N Engl J Med. 2018;378(21): e28.
59. Morgan CM, Foster CS, D'Amico DJ, Gragoudas ES. Retinal vasculitis in polyarteritis nodosa. Retina. 1986 Winter;6(4):205–9.
60. Garcia-Diaz M, Mira M, Nevado L, Galván A, Berenguer A, Bureo JC. Retinal vasculitis associated with Crohn's disease. Postgrad Med J. 1995;71(833):170–2.
61. Watanabe T, Marumo Y, Ishizu A. Retinal vasculitis in primary Sjögren's syndrome. Rheumatology (Oxford). 2019;58(7):1244.

62. Turk MA, Hayworth JL, Nevskaya T, Pope JE. Ocular manifestations in rheumatoid arthritis, connective tissue disease, and vasculitis: a systematic review and metaanalysis. J Rheumatol. 2021;48(1):25–34.
63. Backhouse O, Griffiths B, Henderson T, Emery P. Ophthalmic manifestations of dermatomyositis. Ann Rheum Dis. 1998;57(8):447–9.
64. AlBloushi AF, Dheyab AM, Al-Swaina NF, Al-Obailan M, Daif AK, Abu El-Asrar AM. Clinical findings and outcomes of uveitis associated with multiple sclerosis. Eur J Ophthalmol. 2021;31(2):482–90.
65. Szydełko-Paśko U, Przeździecka-Dołyk J, Małecki R, Szuba A, Misiuk-Hojło M. Ocular manifestations of Buerger's disease—a review of current knowledge. Clin Ophthalmol. 2022;18(16):851–60.
66. Trese MGJ, Yonekawa Y, Thomas BJ, Randhawa S. Vasculitic central retinal vein occlusion: the presenting sign of seronegative rheumatoid arthritis. Am J Ophthalmol Case Rep. 2016;18(2):26–9.
67. Akella SS, Schlachter DM, Black EH, Barmettler A. Ophthalmic eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome): a systematic review of the literature. Ophthalmic Plast Reconstr Surg. 2019;35(1):7–16.
68. Braakenburg AM, Rothova A. The clinical characteristics of retinal vasculitis in HLA-B27-positive patients. Ocul Immunol Inflamm. 2014;22(3):197–202.
69. Lally L, Sammaritano LR. Vasculitis in antiphospholipid syndrome. Rheum Dis Clin North Am. 2015;41(1):109–23.
70. Sonne SJ, Shieh WS, Srivastava SK, Smith BT. Lymphoma masquerading as occlusive retinal vasculitis: a case study. Am J Ophthalmol Case Rep. 2020;10(19): 100777.
71. Ksiaa I, Kechida M, Zina S, Lahdhiri M, Abroug N, Khairallah M. Acute lymphoblastic leukemia relapse presenting as retinal vasculitis. Clin Case Rep. 2020;8(8):1467–71.
72. Anastasakis A, Dick AD, Damato EM, Spry PG, Majid MA. Cancer-associated retinopathy presenting as retinal vasculitis with a negative ERG suggestive of on-bipolar cell pathway dysfunction. Doc Ophthalmol. 2011;123(1):59–63.
73. Suzuki T, Obara Y, Sato Y, Saito G, Ichiwata T, Uchiyama T. Cancer-associated retinopathy with presumed vasculitis. Am J Ophthalmol. 1996;122(1):125–7.
74. Agarwal A. Retinal vasculitis. https://eyewiki.aao.org/Retinal_Vasculitis.
75. Manousaridis K, Ong E, Stenton C, Gupta R, Browning AC, Pandit R. Clinical presentation, treatment, and outcomes in presumed intraocular tuberculosis: experience from Newcastle upon Tyne, UK. Eye. 2013;27(4):480–6.
76. Al-Mezaine HS, Al-Muammar A, Kangave D, Abu El-Asrar AM. Clinical and optical coherence tomographic findings and outcome of treatment in patients with presumed tuberculous uveitis. Int Ophthalmol. 2008;28(6):413–423.
77. Yuksel E, Ozdek S. Unusual presentation of ocular tuberculosis: multiple chorioretinitis, retinal vasculitis and ischaemic central retinal vein occlusion. Clin Exp Optom. 2013;96(4):428–9.
78. Gupta V, Gupta A, Rao NA. Intraocular tuberculosisan update. Surv Ophthalmol. 2007;52(6):561–87.
79. Das T, Pathengay A, Hussain N, Biswas J. Eales' disease: diagnosis and management. Eye (Lond). 2010;24(3):472–82.
80. Murthy KR, Abraham C, Baig SM, Badrinath SS. Eales' disease. Proc All lnd Ophthalmol Soc. 1977;33:323.
81. Renie WA, Murphy RP, Anderson KC, et al. The evaluation of patients with Eales' disease. Retina. 1983;3:243–8.
82. Verma A, Biswas J, Dhanurekha L, Gayathri R, Lily TK. Detection of Mycobacterium tuberculosis with nested polymerase chain reaction analysis in enucleated eye ball in Eales' disease. Int Ophthalmol. 2016;36(3):413–7.
83. Goel N, Kumar V, Arora S, Jain P, Ghosh B. Spectral domain optical coherence tomography evaluation of macular changes in Eales disease. Indian J Ophthalmol. 2018;66(3):433–8.

84. Saxena S, Kumar D. A new staging system for idiopathic retinal periphlebitis. Eur J Ophthalmol. 2004;14(3):236–9.
85. Biswas J, Ravi RK, Naryanasamy A, Kulandai LT, Madhavan HN. Eales' disease—current concepts in diagnosis and management. J Ophthalmic Inflamm Infect. 2013;3(1):11.
86. Ishaq M, Feroze AH, Shahid M, Baig MA, Ameen SS, Feroze SH, et al. Intravitreal steroids may facilitate treatment of Eales' disease (idiopathic retinal vasculitis): an interventional case series. Eye. 2007;21:1403–5.
87. Patwardhan SD, Azad R, Shah BM, Sharma Y. Role of intravitreal bevacizumab in Eales disease with dense vitreous hemorrhage: a prospective randomized control study. Retina. 2011;31:866–70.
88. Chanana B, Azad RV, Patwardhan S. Role of intravitreal bevacizumab in the management of Eales' disease. Int Ophthalmol. 2010;30:57–61.
89. El-Asrar AM, Al-Kharashi SA. Full panretinal photocoagulation and early vitrectomy improve prognosis of retinal vasculitis associated with tuberculoprotein hypersensitivity (Eales' disease). Br J Ophthalmol. 2002;86(11):1248–51.
90. Ishaq M, Niazi MK. Usefulness of laser photocoagulation in managing asymptomatic eyes of Eales disease. J Ayub Med Coll Abbottabad. 2002;14(4):22–32.
91. Gopal L, Abraham C. Efficacy of photocoagulation in Eales' disease. Trans Asia-Pacific Acad. 1985;10:689.
92. Das TP, Namperumalsamy P. Photocoagulation in Eales' disease. Results of prospective randomised clinical study. Presented in XXVI International Congress of Ophthalmology. Singapore; 1990. (gdzie to bylo opublikowane?).
93. Shukla D, Kanungo S, Prasad NM, Kim R. Surgical outcomes for vitrectomy in Eales' disease. Eye. 2008;22:900–4.
94. Jabs DA, Johns CJ. Ocular involvement in chronic sarcoidosis. Am J Ophthalmol. 1986;102:297–301.
95. Obenauf CD, Shaw HE, Sydnor CF, Klintworth GK. Sarcoidosis and its ophthalmic manifestations. Am J Ophthalmol. 1978;86:648–55.
96. Ungprasert P, Tooley AA, Crowson CS, Matteson EL, Smith WM. Clinical characteristics of ocular sarcoidosis: a population-based study 1976–2013. Ocul Immunol Inflamm. 2017;27(3):389–95.
97. Matsou A, Tsaousis KT. Management of chronic ocular sarcoidosis: challenges and solutions. Clin Ophthalmol. 2018;12:519–32.
98. Lobo A, Barton K, Minassian D, Du Bois RM, Lightman S. Visual loss in sarcoid-related uveitis. Clin Exp Ophthalmol. 2003;31(4):310–6.
99. Jabs DA, Fine SL, Hochberg MC, Newman SA, Heiner GG, Stevens MB. Severe retinal vaso-occlusive disease in systemic lupus erythematosus. Arch Ophthalmol. 1986;104:558–63.
100. Asherson RA, Merry P, Acheson JF, Harris EN, Hughes GR. Antiphospholipid antibodies: a risk factor for occlusive ocular vascular disease in systemic lupus erythematosus and the 'primary' antiphospholipid syndrome. Ann Rheum Dis. 1989;48(5):358–61.
101. Klinkhoff AV, Beattie CW, Chalmers A. Retinopathy in systemic lupus erythematosus: relationship to disease activity. Arthritis Rheum. 1986;29(9):1152–1156.
102. Au A, O'Day J. Review of severe vaso-occlusive retinopathy in systemic lupus erythematosus and the antiphospholipid syndrome: associations, visual outcomes, complications and treatment. Clin Exp Ophthalmol. 2004;32(1):87–100.
103. Lee WJ, Cho HY, Lee YJ, Lee BR, Shin JP. Intravitreal bevacizumab for severe vaso-occlusive retinopathy in systemic lupus erythematosus. Rheumatol Int. 2013;33(1):247–51.
104. Dammacco R. Systemic lupus erythematosus and ocular involvement: an overview. Clin Exp Med. 2018;18(2):135–49.
105. Jeon S, Lee WK. Aggravated capillary non-perfusion after intravitreal bevacizumab for macular edema secondary to systemic lupus erythematosus and anti-phospholipid syndrome. Lupus. 2012;21(3):335–7.
106. Uludag G, Onghanseng N, Tran ANT, et al. Current concepts in the diagnosis and management of antiphospholipid syndrome and ocular manifestations. J Ophthal Inflamm Infect. 2021;11:11.

107. Cobo-Soriano R, S´anchez-Ram´on S, Aparicio MJ et al. Antiphospholipid antibodies and retinal thrombosis in patients without risk factors: a prospective case-control study. Am J Ophthalmol 1999;128(6):725–732.
108. Durrani OM, Gordon C, Murray PI. Primary anti-phospholipid antibody syndrome (APS): current concepts. Surv Ophthalmol. 2002;47(3):215–38.
109. Utz VM, Tang J. Ocular manifestations of the antiphospholipid syndrome. Br J Ophthalmol. 2011;95(4):454–9.
110. Lima Cabrita FV, Foster CS. Anticardiolipin antibodies and ocular disease. Ocul Immunol Inflamm. 2005;13(4):265–70.
111. Zhu W, Wu Y, Xu M, Wang JY, Meng YF, Gu Z, Lu J. Antiphospholipid antibody and risk of retinal vein occlusion: a systematic review and meta-analysis. PLoS ONE. 2014;10(4): e0122814.
112. Miserocchi E, Baltatzis S, Foster CS. Ocular features associated with anticardiolipin antibodies: a descriptive study. Am J Ophthalmol. 2001;131(4):451–6.
113. Chighizola CB, Ubiali T, Meroni PL. Treatment of thrombotic Antiphospholipid syndrome: the rationale of current management-an insight into future approaches. J Immunol Res. 2015:951424.
114. International Study Group for Behcet's Disease. Criteria for diagnosis of Behcet's disease. Lancet. 1990;335:1078–80.
115. Ho T-Y, Chung Y-M, Lee A-F, Tsai C-Y. Severe vasoocclusive retinopathy as the primary manifestation in a patient with systemic lupus erythematosus. J Chin Med Assoc. 2008;71(7):377–80.
116. Tugal-Tutkun I, Onal S, Altan-Yaycioglu R, Kir N, Urgancioglu M. Neovascularization of the optic disc in Behcet's disease. Jpn J Ophthalmol. 2006;50(3):256–65.
117. Tugal-Tutkun I, Onal S, Altan-Yaycioglu R, Huseyin Altunbas H, Urgancioglu M. Uveitis in Behcet disease: an analysis of 880 patients. Am J Ophthalmol 2004;138(3):373–380.
118. Atmaca LS, Batioğlu F, Idil A. Retinal and disc neovascularization in Behçet's disease and efficacy of laser photocoagulation. Graefes Arch Clin Exp Ophthalmol. 1996;234(2):94–9.
119. Brown GC, Magargal LE. The ocular ischemic syndrome. Clinical, fluorescein angiographic and carotid angiographic features. Int Ophthalmol. 1988;11(4):239–251.
120. Biousse V. Carotid disease and the eye. Curr Opin Ophthalmol. 1997;8(6):16–26.
121. Mizener JB, Podhajsky P, Hayreh SS. Ocular ischemic syndrome. Ophthalmology. 1997;104(5):859–64.
122. Fattahi TT, Brandt MT, Jenkins WS, Steinberg B. Traumatic Carotid-Cavernous Fistula: Pathophysiology and Treatment. J Craniofac Surg. 2003;14(2):240.
123. Ellis JA, Goldstein H, Connolly ES, Meyers PM. Carotid-cavernous fistulas. Neurosurg Focus 2012;32(5).
124. Komiyama M, Yamanaka K, Nagata Y, Ishikawa H. Dural carotid-cavernous sinus fistula and central retinal vein occlusion: a case report and a review of the literature. Surg Neurol. 1990;34(4):255–9.
125. Suzuki Y, Kase M, Yokoi M, Arikado T, Miyasaka K. Development of central retinal vein occlusion in dural carotid-cavernous fistula. Ophthalmologica. 1989;199(1):28–33.
126. Barke RM, Yoshizumi MO, Hepler RS, Krauss HR, Jabour BA. Spontaneous dural carotid-cavernous fistula with central retinal vein occlusion and iris neovascularization. Ann Ophthalmol. 1991;23(1):11–7.
127. Harris MJ, Fine SL, Miller NR. Photocoagulation treatment of proliferative retinopathy secondary to a carotid-cavernous fistula. Am J Ophthalmol. 1980;90(4):515–8.
128. Kalina RE, Kelly WA. Proliferative retinopathy after treatment of carotid-cavernous fistulas. Arch Ophthalmol. 1978;96(11):2058–60.
129. Stryjewski TP, Papakostas TD, Vavvas D. Proliferative hypertensive retinopathy. JAMA Ophthalmol. 2016;134(3):345–6.
130. Abu Sbeit RHS, Mohammed OA, Alamlih LI. Hypertension as an unusual cause of proliferative retinopathy: case report and literature review. Case Rep Ophthalmol. 2021;12(2):594–602.

131. Konstantinidis L, Guex-Crosier Y. Hypertension and the eye. Curr Opin Ophthalmol. 2016;27(6):514–21.
132. Avila SA, Golshani C, Friedman AH. Hypertensive crisis with massive retinal and choroidal infarction: a case update. Am J Ophthalmol Case Rep. 2019;13:22–4.
133. Georgiadis O, Kabanarou SA, Batsos G, Feretis E, Xirou T. Bilateral hypertensive retinopathy complicated with retinal neovascularization: panretinal photocoagulation or intravitreal anti-VEGF treatment? Case Rep Ophthalmol. 2014;5(2):231–8.
134. Annesley WH Jr. Peripheral exudative hemorrhagic chorioretinopathy. Trans Am Ophthalmol Soc. 1980;78:321–64.
135. Vandefonteyne S, Caujolle JP, Rosier L, Conrath J, Quentel G, Tadayoni R, Maschi C, Le Mer Y, Dot C, Aknin I, Thariat J, Baillif S. Diagnosis and treatment of peripheral exudative haemorrhagic chorioretinopathy. Br J Ophthalmol. 2020;104(6):874–8.
136. Shields CL, Salazar PF, Mashayekhi A, Shields JA. Peripheral exudative hemorrhagic chorioretinopathy simulating choroidal melanoma in 173 eyes. Ophthalmology. 2009;116:529–35.
137. Huang J, Gajewski A, Cesaro T, Messina C, Mega JV Jr, Sellechio J. Peripheral exudative hemorrhagic chorioretinopathy in patients with nonexudative age-related macular degeneration. Fed Pract. 2017;34(5):20–2.
138. Alforja MS, Sabater N, Giralt J, Adán A, Pelegrín L, Casaroli-Marano R. Intravitreal bevacizumab injection for peripheral exudative hemorrhagic chorioretinopathy. Jpn J Ophthalmol. 2011;55:425–7.
139. Kumar V, Tewari R. Giant retinal pigment epithelium rip in a patient with peripheral exudative hemorrhagic chorioretinopathy. Indian J Ophthalmol. 2019;67:1164–5.
140. Badawi AH, Semidey VA, Magliyah M, Al-Dhibi H. Updated systematic review and clinical spectrum of peripheral exudative hemorrhagic chorioretinopathy. Middle East Afr J Ophthalmol. 2020;27(1):4–9.
141. Avashia JH, Fath DF. Bilateral central retinal vein occlusion in Waldenström's macroglobulinemia. J Am Optom Assoc. 1989;60(9):657–8.
142. Feman SS, Stein RS. Waldenstrom's macroglobulinemia, a hyperviscosity manifestation of venous stasis retinopathy. Int Ophthalmol. 1981;4(1–2):107–12.
143. Menke MN, Feke GT, McMeel JW, Branagan A, Hunter Z, Treon SP. Hyperviscosity-related retinopathy in waldenstrom macroglobulinemia. Arch Ophthalmol. 2006;124(11):1601–6.
144. Omoti AE, Omoti CE. Ophthalmic Manifestations of Multiple Myeloma. West Afr J Med. 2007;26(4):265–8.
145. Choi RY, Jacoby R, Shakoor A. Multimodality ocular imaging in a case report of hyperviscosity syndrome associated with lymphoplasmacytic leukemia: the images tell the story. Retin Cases Brief Rep. 2019 Summer;13(3):238–240.
146. Macedo MS, Figueiredo AR, Ferreira NN, Barbosa IM, Furtado MJ, Correia NF, Gomes MP, Lume MR, Menéres MJ, Santos MM, Meireles MA. Bilateral proliferative retinopathy as the initial presentation of chronic myeloid leukemia. Middle East Afr J Ophthalmol. 2013;20(4):353–6.
147. Lureau MA, Glacet-Bernard A, Coscas G. Occlusion de la veine centrale de la rétine bilatérale et anticoagulant circulant [Bilateral central retinal vein occlusion and circulating anticoagulant]. J Fr Ophtalmol. 1995;18(6–7):468–72.
148. Criswick VG, Schepens CL. Familial exudative vitreoretinopathy. Am J Ophthalmol. 1969;68(4):578–94.
149. Pendergast SD, Trese MT. Familial exudative vitreoretinopathy Results of surgical management. Ophthalmology. 1998;105(6):1015–102.
150. Shubert A, Tasman W. Familial exudative vitreoretinopathy: surgical intervention and visual acuity outcomes. Graefes Arch Clin Exp Ophthalmol. 1997;235(8):490–3.
151. Ikeda T, Fujikado T, Tano Y, et al. Vitrectomy for rhegmatogenous or tractional retinal detachment with familial exudative vitreoretinopathy. Ophthalmology. 1999;106(6):1081–5.
152. Tagami M, Kusuhara S, Honda S, Tsukahara Y, Negi A. Rapid regression of retinal hemorrhage and neovascularization in a case of familial exudative vitreoretinopathy treated with intravitreal bevacizumab. Graefes Arch Clin Exp Ophthalmol. 2008;246(12):1787–9.

153. Lin KL, Hirose T, Kroll AJ, Lou PL, Ryan EA. Prospects for treatment of pediatric vitreoretinal diseases with vascular endothelial growth factor inhibition. Semin Ophthalmol. 2009;24:70–6.
154. Buinauskiene J, Buinauskaite E, Valiukeviciene S. Incontinentia pigmenti (bloch-sulzberger syndrome) in neonates. Medicina (Kaunas). 2005;41(6):496–9.
155. Scheuerle A, Ursini MV. Incontinentia pigmenti. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. GeneReviews. Seattle (WA): University of Washington, Seattle;1993.
156. Goldberg MF, Custis PH. Retinal and other manifestations of incontinentia pigmenti (Bloch-Sulzberger syndrome). Ophthalmology. 1993;100(11):1645–54.
157. Goldberg MF. The blinding mechanisms of incontinentia pigmenti. Ophthalmic Genet. 1994;15(2):69–76.
158. Nakao S, Nishina S, Tanaka S, Yoshida T, Yokoi T, Azuma N. Early laser photocoagulation for extensive retinal avascularity in infants with incontinentia pigmenti. Jpn J Ophthalmol. 2020;64(6):613–20.
159. Nguyen JK, Brady-Mccreery KM. Laser photocoagulation in preproliferative retinopathy of incontinentia pigmenti. J AAPOS. 2001;5(4):258–9.
160. Wang X, Liang JH. Treatment of retinopathy of incontinentia pigmenti by anti-vascular endothelial growth factor. Zhonghua Yan Ke Za Zhi. 2019;55(4):294–301.
161. Sims KB. Updated:July 23,2009. NDP-Related Retinopathies. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). University of Washington, Seattle;1997–2012. http://www.genetests.org.
162. Drenser KA, Fecko A, Dailey W, Trese MT. A characteristic phenotypic retinal appearance in Norrie disease. Retina. 2007;27:243–6.
163. Smith SE, Mullen TE, Graham D, Sims KB, Rehm HL. Norrie disease: extraocular clinical manifestations in 56 patients. Am J Med Genet A. 2012.
164. Chow CC, Kiernan DF, Chau FY, Blair MP, Ticho BH, Galasso JM, Shapiro MJ. Laser photocoagulation at birth prevents blindness in Norrie's disease diagnosed using amniocentesis. Ophthalmology. 2010;117(12):2402–6.
165. Drenser KA, Walsh MK, Capone A Jr, Trese MT, Luo CK. Preterm treatment of Norrie disease. Ophthalmology. 2011;118(8):1694–5.
166. Walsh MK, Drenser KA, Capone A, Trese MT. Early vitrectomy effective for Norrie disease. Arch Ophthalmol. 2010;128(4):456–60.
167. Kiernan DF, Blair MP, Shapiro MJ. In utero diagnosis of Norrie disease and early laser preserves visual acuity. Arch Ophthalmol. 2010;128(10):1382.
168. Sisk RA, Hufnagel RB, Bandi S, Polzin WJ, Ahmed ZM. Planned preterm delivery and treatment of retinal neovascularization in Norrie disease. Ophthalmology. 2014;121(6):1312–3.
169. Shah VA, Cassell M, Poulose A, Sabates NR. Talc retinopathy. Ophthalmology. 2008;115(4):755-755.e2.
170. Fraser-Bell S, Capon M. Talc retinopathy. Clin Exp Ophthalmol. 2002;30(6):432–3.
171. Martidis A, Yung CW, Ciulla TA. Talc embolism: a static retinopathy. Am J Ophthalmol. 1997;124(6):841–3.
172. Gedde S, Regillo CD, Vander J. Advanced proliferative retinopathy and iris neovascularization in an intravenous drug abuser. Ophthalmic Surg. 1995;26(1):85–7.
173. Kresca LJ, Goldberg MF, Jampol LM. Talc emboli and retinal neovascularization in a drug abuser. Am J Ophthalmol. 1979;87(3):334–9.
174. Ruys J, de Smet MD, Van de Sompel W. Bilateral talc maculopathy and fibrovascular proliferation in a drug abuser. Retin Cases Brief Rep. 2010 Spring;4(2):123–4.
175. Brucker AJ. Disk and peripheral retinal neovascularization secondary to talc and cornstarch emboli. Am J Ophthalmol. 1979;88(5):864–7.
176. Tse DT, Ober RR. Talc retinopathy. Am J Ophthalmol. 1980;90(5):624–40.
177. Monroe AT, Bhandare N, Morris CG, Mendenhall WM. Preventing radiation retinopathy with hyperfractionation. Int J Radiat Oncol Biol Phys. 2005;61(3):856–64.
178. Durkin SR, Roos D, Higgs B, Casson RJ, Selva D. Ophthalmic and adnexal complications of radiotherapy. Acta Ophthalmol Scand. 2007;85(3):240–50.

179. Mason JO 3rd, Albert MA Jr, Persaud TO, Vail RS. Intravitreal bevacizumab treatment for radiation macular edema after plaque radiotherapy for choroidal melanoma. Retina. 2007;27(7):903–7.
180. Gupta A, Muecke JS. Treatment of radiation maculopathy with intravitreal injection of bevacizumab (Avastin). Retina. 2008;28(7):964–8.
181. Shields CL, Demirci H, Dai V, et al. Intravitreal triamcinolone acetonide for radiation maculopathy after plaque radiotherapy for choroidal melanoma. Retina Oct-Nov. 2005;25(7):868–74.
182. Finger PT, Kurli M. Laser photocoagulation for radiation retinopathy after ophthalmic plaque radiation therapy. Br J Ophthalmol. 2005;89(6):730–8.
183. Bianciotto C, Shields CL, Pirondini C, Mashayekhi A, Furuta M, Shields JA. Proliferative radiation retinopathy after plaque radiotherapy for uveal melanoma. Ophthalmology. 2010 May;117(5):1005–1012.
184. Hurtikova K, Gerding H. Combined laser photocoagulation and anti-VEGF injection treatment in radiation retinopathy. Klin Monbl Augenheilkd. 2017;234(4):515–519. English.
185. Seibel I, Vollhardt D, Riechardt AI, Rehak M, Schmied S, Schiller P, Zeitz O, Hellmich M, Joussen AM. Influence of Ranibizumab versus laser photocoagulation on radiation retinopathy (RadiRet)—a prospective randomized controlled trial. Graefes Arch Clin Exp Ophthalmol. 2020;258(4):869–78.

Chapter 12
Laser Treatment of Retinopathy of Prematurity

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The first data on the successful treatment of ROP became known in 1990 thanks to the multicenter CRYO-ROP study, where transscleral cryocoagulation was used as a treatment for the threshold stage of ROP [1]. This study compared the results of cryotherapy with no treatment. The follow-up of the study lasted for 15 years (examinations were carried out at 3 months, 1; 3.5; 5.5; 10 and 15 years), thus providing the first data on the long-term structural and functional parameters of ROP treatment [2]. CRYO-ROP data showed that in 3 months after cryotherapy, there were fewer undesirable structural outcomes, including retinal detachment in the treatment group than in the naturally occurring ROP group. However, the percentage of eyes with adverse outcomes increased over time in both groups: from 25.1% at one year to 30.0% at 15 years in the group of children receiving cryotherapy; from 44.7% to 51.9% in the group with natural ROP, which prompted the search for new more effective treatment methods [1, 2].

With the advent of laser technologies, a new method of ROP treatment—laser photocoagulation of avascular zones of the retina, gradually began to be introduced into practice [3]. According to long-term structural and functional results, laser coagulation was less traumatic and more effective treatment method than cryotherapy. According to a randomized study of patients with bilateral threshold ROP conducted by Connolly et al., in which cryocoagulation was performed in one eye and transpupillary diode laser photocoagulation—in the fellow eye, the effectiveness of laser treatment exceeded 6,91 times the effectiveness of cryocoagulation during the observation period of 4.3–7.6 years. At the same time, after laser photocoagulation of the retina, higher visual functions are noted, which was also a great advantage of using laser when treating ROP [4]. Differences between laser photocoagulation of the retina

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_12

and cryocoagulation were most noticeable in eyes with ROP localization in zone I; a favorable anatomical result was observed in 83% of cases of laser treatment, cryocoagulation—only in 25% of eyes with ROP in zone I. After laser photocoagulation, a significantly better indicator of visual acuity was achieved compared with cryotherapy [5]. When performing laser intervention, the risk of postoperative systemic and ocular complications is minimal compared to cryotherapy. In addition, laser applications are visible during treatment, which minimizes the risk of missing areas, that need treatment. Thus, laser photocoagulation of the avascular areas of the retina over the next 10 years almost completely supplanted cryotherapy.

Because of the development and introduction into clinical practice of less invasive methods of treatment, transconjunctival and transpupillary diode laser photocoagulation of the retina has become widely used. But in view of the fact, that a large number of complications were observed during treatment at the threshold stage of ROP, it became necessary to conduct a new large-scale study, during which results of ROP treatment using laser photocoagulation of avascular zones of the retina would be evaluated before the threshold stage of the disease sets in [6]. This is how the study on early treatment of ROP, ETROP, has evolved [6, 7].

The aim of ETROP was to study the effect of early ROP treatment on retinal structural changes and visual acuity. To do this, 401 children with a high risk of progression of bilateral ROP underwent laser photocoagulation of the retina in one eye at the prethreshold stage, in the pair - traditionally (the control group), that is, at the stage of the development of threshold ROP (in 84 cases of asymmetric ROP of high risk, eyes were randomized to early or conventional treatment). As a result of laser photocoagulation by the 9th month of life, functional (visual acuity according to Teller Table) and structural results of treatment were evaluated in 372 children (on 664 and 659 eyes). The highest percentage of ROP cases was recorded with stage 3 in zone II with “Plus” disease (42.1% in the group, where treatment was carried out at the prethreshold stage, and 43.7% in the control group), as well as with stage 1–2 in zone I with no “Plus” disease (27.4% in the group, where treatment was carried out at the prethreshold stage, and 26.1% in the control group). By 9 months of age, there was a significant functional and structural outcome in the high-risk ROP group treated at the prethreshold stage compared with the group treated later (14.3 and 19.8%, ($p < 0.005$); 9.0% and 15.6%, ($p < 0.001$)). When evaluating the functional result, a significant difference in the treatment performed at the prethreshold stage rather than at the threshold was noted in eyes with stage 3 ROP in zone I with or without “Plus” disease (30.8% had an unfavorable result versus 53.8%); a relatively significant difference was noted in children with stage 1–2 ROP in zone I without “Plus” disease (10.5% vs. 15.8%), with stage 3 ROP in zone II with “Plus” disease (15.3% vs. 18.0%), with stage 2 ROP in zone II with “Plus” disease (14.7% vs. 17.6%); insignificant difference in children with ROP stage 1–2 in zone I with “Plus” disease (22.2% of adverse outcome for both groups) and ROP stage 3 in zone II without “Plus” disease (no cases of adverse outcome for both groups). When evaluating the structural result, a significant difference in the treatment performed at the prethreshold stage rather than at the threshold was noted in eyes with stage 3 ROP in zone I with or without “Plus” disease (29.6% had an unfavorable result

versus 55.6%); a relatively significant difference was noted in children with stage 1–2 ROP in zone I without "Plus" disease (2.7% vs. 9.3%), with stage 3 ROP in zone II with "Plus" disease (7.3% vs. 10.9%); insignificant difference in children with stage 2 ROP in zone II with "Plus" disease (20.6% for both groups), stage 1–2 ROP in zone I with "Plus" disease (22.2% adverse outcome for both groups) [6].

After careful analysis of the data of the ETROP study, two groups of patients with prethreshold ROP were identified: type I (patients in need of early treatment), type II (patients, who can be observed). Such a division into types was not provided before the start of the study and was its result. The analysis of the obtained data became the basis for the creation of a clinical algorithm, where the type I and type II of prethreshold ROP is an indication for either treatment or observation. With the development of type I ROP (zone I, any stage of ROP with signs of "Plus" disease; zone I, stage 3 ROP with or without signs of "Plus" disease; zone II, stage 2 or 3 ROP with signs of "Plus" disease) laser photocoagulation of the retina should be performed. In cases of the development of type II ROP (zone I, stage 1 or 2 ROP without "Plus" disease or zone II, stage 3 ROP without "Plus" disease), it is recommended to continue monitoring and start laser photocoagulation only when the disease progresses into type I.

Clinical use of separating ROP cases into type I and II reduces the number of patients in need of treatment. For type I ROP, this indicator was 31.5%, for type II—77.3% of cases. Thus, the effectiveness of early treatment was statistically proved only for type I ROP [6].

Results of the state of the retina in 6 years confirmed the effectiveness of early treatment of ROP at the prethreshold stage of the disease (type I). Positive dynamics was noted at 6 and 9 months of age and persisted up to 6 years. Thanks to the use of early treatment, high rates of visual acuity were recorded. In 65.4% of cases, its number averaged 0.5. Whether this is due to retinal, cortical, or both groups of factors, it remains unclear.

Thus, early treatment of ROP is most preferable for a number of patients, although it is not always a guarantee of a favorable outcome of ROP and sufficient visual acuity [7].

According to Katsan, Pasyechnikova, Adakhovska and others, the effectiveness of the method of retinal laser photocoagulation in ROP is 95.3 ± 1.2% [8]. For treatment, laser with a wavelength of 532 nm was used. Coagulation was carried out throughout avascular retina in front of the ridge, and so that, burns were located at a distance of 0.5 of the width of the burn from each other, while achieving a confluent pattern of applying coagulates. Figure 12.1 shows confluent laser photocoagulation in zones II and III, performed using a diode-pumped Purepoint Laser semiconductor laser with a wavelength of 532 nm.

The model according to which laser photocoagulation of the retina is carried out depends on the choice of the doctor. There is no final consensus regarding the degree of intensity and the interval between applications. However, over time there is a tendency to perform denser retinal coagulation in ROP. In a number of studies, Banach et al. [9], performing laser photocoagulation of the retina in the localization of the pathological process in zone I and II at threshold stages of ROP, it was found

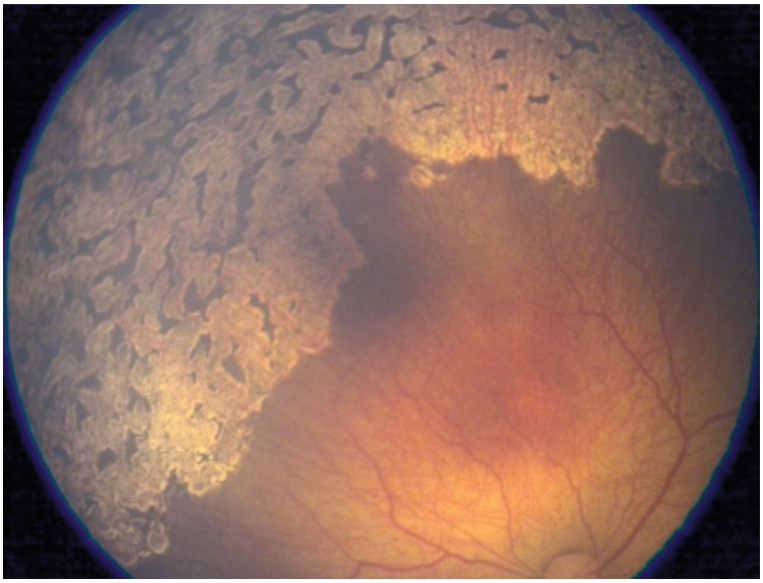

Fig. 12.1 Confluent laser photocoagulation in ROP

that during confluent laser photocoagulation of the retina, the frequency of ROP progression was 3.6% and when applying laser coagulates at a distance of 1–1.5 coagulate diameter—29%. The results indicated, that confluent laser photocoagulation of the retina leads to regression of ROP in a greater percentage of cases and reduces the rate of disease progression when the process is localized in zone II [9]. Similar data were obtained by Axer-Siegel et al. [10] in confluent laser photocoagulation of the retina with ROP localization in zone I and posterior part of zone II when disease regression was achieved in 85.4%. Eye complications—edema, chemosis and maceration of the conjunctiva, the development of cataract, hemorrhages both in the outer and inner membranes, the formation of preretinal membranes, proliferation in the optic disc, macula and rarely on the periphery of the retina, iridocyclitis, closure of the anterior chamber angle with increased intraocular pressure, are comparable for both confluent laser photocoagulation and coagulation with a scattered pattern [10]. The problem of this method is the violation of peripheral vision. According to Quinn et al., treatment at the prethreshold stage of ROP preserves peripheral vision with only a slight decrease in visual field than if treated at the threshold stage [11]. According to McLoon et al., the extent of the visual fields in the eyes using laser photocoagulation of the retina was 3–4% less compared to the eyes, when no intervention was performed [12]. While the concentric narrowing of the visual fields is associated, as a rule, with extensive areas of chorioretinal atrophy after confluent laser photocoagulation of the retina, when was the active phase of ROP, with the localization of the process in zone I-II of the fundus of the eye.

In addition, laser photocoagulation of the retina affects the development of refractive errors, mostly myopia [13], astigmatism [13] and anisometropia [14] usually within the first two years of child's life [15]. According to Quinn et al., myopia progressed in early ROP treatment and at the threshold stage at 3 years of age, the prevalence of myopia was similar in both groups, increasing from approximately 58 to 68% between 6 and 9 months of children's lives. At the same time, intensive progression of high-grade myopia was noted at the age of 6 months to 3 years [16]. According to Davitt et al., a randomized controlled clinical study of astigmatism in early ROP treatment and threshold stage at 3 years of age, the prevalence of astigmatism $\geq$ 1.00 dptr was similar in both groups, increasing from about 32% at 6 months up to 42% at 3 years of age, while the main changes were recorded, as a rule, in the period from 6 to 9 months. It should be noted, that regular astigmatism was more often recorded [17]. According to Wiecek et al., the progression of myopia is much faster in the eyes that underwent laser photocoagulation. The number of laser burns resulted in the progression of myopia by approximately 0.16 dptr/100 laser burns. The authors also noted, that the stage and zone of ROP had a significant influence on the progression of ROP, that is, a more severe disease led to a more rapid progression of myopia [18]. According to a study by Tafadzwa et al., by age 6, 50% of children treated with laser photocoagulation developed myopia compared with 19% of preterm infants who did not receive treatment ($p = 0.013$). In the eyes that had developed myopia, laser burns, on average, occupied 49% ($\pm$13) of the retinal area, compared with 43% ($\pm$10) in hypermetropia and 42% ($\pm$5) in emmetropia ($p = 0.030$). At the same time, a larger area of laser photocoagulation was associated with a higher degree of myopia and anisometropia ($p < 0.050$) [19]. It should also be noted, that, according to observations at the Filatov Institute, the risk of failure of laser treatment of ROP was significantly higher for patients with ROP localization in zone I and aggressive ROP. This category of patients has a severe general somatic condition, deep morphofunctional immaturity, are on a respirator for a long time, which aggravates the course of the disease and may affect the outcome of the treatment performed.

In 2007, the anti-VEGF drug, bevacizumab, was first used in the treatment of ROP in order to stop pathological vascular activity. Since then, a new direction in the treatment of ROP has appeared—the intravitreal use of anti-VEGF drugs: bevacizumab, ranibizumab, etc. [20, 21]. The mechanism of their action is based on the inhibition of the main vascular growth factor—VEGF, which significantly reduces the activity of the process and reduces the risk of developing retinal detachment. Thus, in 2011, BEAT-ROP study, among 75 patients with ROP in zone I who received bevacizumab, 6% had a relapse of proliferation versus 42% with disease progression with laser treatment [22]. At the same time, it should be taken into account, that this group of medicine affects only one vascular growth factor—VEGF and in some cases may not provide a complete cure, but lead to the suspension of vascular growth with subsequent neovascularization and, accordingly, the risk of developing retinal detachment at a later period (at postconceptual age up to 69 weeks). Thus, children who received intravitreal injections of anti-VEGF drugs require prolonged dispensary

observation due to long-term incomplete retinal vascularization and a high risk of late retinal detachment. Nevertheless, the suspension of ROP activity (especially in very preterm infants) makes it possible to delay the need for retinal coagulation for some time, during which the general condition of the child may improve significantly [23, 24].

The BEAT-ROP group did not observe systemic or local side effects due to the small sample size and short follow-up period. Jalali et al. described serious complications when intravitreal injection of bevacizumab as an adjuvant therapy for laser or surgical intervention, including macular retinal tear, retinal rupture caused by rhegmatogenous retinal detachment, bilateral vascular attenuation, perivascular exudation, optic neuropathy and progression to stage 5 ROP with bilateral retinal detachment. In addition, in one case, a side effect of the medicine was noted as a manifestation of liver dysfunction and a large choroidal rupture in one eye [24].

The VEGF factor is involved in the normal angiogenesis of other organs, that develop simultaneously with the retina. According to Sears (2008) the used dosage is 1000 times the concentration required to neutralize the maximum measured concentration of VEGF in the eye. At the same time, the serum concentration of VEGF in 2 weeks after intravitreal injection is 6 times lower than normal [25].

Undoubtedly, the method of intravitreal injection of anti-VEGF drugs is promising. However, including the potential risk of systemic absorption and subsequent adverse effects due to intravitreal administration of anti-VEGF drugs, evidence of safety outcomes is lacking and that is a major concern.

Laser photocoagulation of the peripheral avascular areas of the retina is a well-established treatment method of ROP. Despite extensive experience with the use of laser photocoagulation of the retina when ROP, discussions regarding indications for its implementation continue. According to Balasubramanian et al., there is no single protocol for laser treatment of ROP [26]. The solution to this problem is the objective monitoring of the disease and the search for accurate markers, the identification of which will be the right indication for laser photocoagulation of the retina. The effectiveness of the method may depend on many factors—the nature of the course of ROP, the localization of the process, the timing of treatment, the morphological and functional immaturity of the child, the presence of concomitant eye pathology, the nature of postoperative treatment [8, 27].

Thus, it is necessary to observe a differential approach in the choice of treatment tactics. The normal course of retinopathy of prematurity (zone II–III): a sparing approach, taking into account vascular activity, reducing trauma, which will reduce the frequency of late complications and improve functional results. Severe forms of ROP (threshold stage of the classic form of ROP and aggressive form of ROP) with extensive avascular zones, require not only to change the technique itself but it is necessary to work together with neonatologists and develop fundamentally new approaches to the prevention and treatment of this severe disease.

References

1. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. One–year outcome–structure and function. Arch Ophthalmol. 1990;108(10):1408–16.
2. Palmer EA, Hardy RJ, Dobson V, Phelps DL, Quinn GE, Summers CG. Cryotherapy for retinopathy of prematurity cooperative Group.15–year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. Arch Ophthalmol. 2005;123(3):311–18.
3. Cavalcanti RP, et al. Efficacy and safety of green laser photocoagulation for threshold retinopathy of prematurity. Arq Bras Oftalmol. 2008;71(1):49–51.
4. Connolly BP, McNamara JA, Sharma S. A comparison of laser photocoagulation with trans–scleral cryotherapy in the treatment of threshold retinopathy of prematurity. Ophthalmology. 1998;105(9):1628–31.
5. Connolly BP, Ng EY, McNamara JA, Regillo CD, Vander JF, Tasman WA. Comparison of laser photocoagulation with cryotherapy for threshold retinopathy of prematurity at 10 years: Part 2. Refractive outcome. Ophthalmology. 2002;109(5):936–41.
6. Good WV. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc. 2004;(102):233–48.
7. Good WV, Hardy RJ, Dobson V. Final visual acuity results in the early treatment for retinopathy of prematurity study. Arch Ophthalmol. 2010;128(6):663–71.
8. Adakhovska AA, Zaichko ES, Pasechnikova NV, Katsan SV. Risk factors for failure to achieve a positive result in the treatment of retinopathy of prematurity by confluent laser coagulation. Ophthalmol East Eur. 2018;8(1):97–107.
9. Banach MJ, Ferrone PJ, Trese MT. A comparison of dense versus less dense diode laser photocoagulation patterns for threshold retinopathy of prematurity. Ophthalmology. 2000;107(2):324–327.
10. Axer-Siegel R, Snir M, Cotlear D, et al. Diode laser treatment of posterior retinopathy of prematurity. Br J Ophthalmol. 2000;84(12):1383–86.
11. Quinn EG, Dobson V, Hardy RJ, et al. Visual field extent at 6 years of age in children who had high-risk prethreshold retinopathy of prematurity. Arch Ophthalmol. 2011;129(2):127–32.
12. McLoon E, O'Keefe M, McLoon S, et al. Effect of diode laser retinal ablative therapy for threshold retinopathy of prematurity on the visual field: results of goldmann perimetry at a mean age of 11 years. J Pediatr Ophthalmol Strabismus. 2007;44(3):170–3.
13. Quinn GE, Dobson V, Davitt BV et al. Progression of myopia and high myopia in the early treatment for retinopathy of prematurity study: findings at 4 to 6 years of age. J AAPOS. 2013;(17):124–8.
14. Gursoy H, Basmak H, Bilgin B, et al. The effects of mild-to-severe retinopathy of prematurity on the development of refractive errors and strabismus. Strabismus. 2014;(22):68–73.
15. Hsieh C, Liu J, Huang J, et al. Refractive outcome of premature infants with or without retinopathy of prematurity at 2 years of age: a prospective controlled cohort study. Kaohsiung J Med Sci. 2012;28(4):204–11.
16. Quinn GE, Dobson V, Davitt BV, et al. Progression of myopia and high myopia in the early treatment for retinopathy of prematurity study: findings to 3 years of age. Ophthalmology. 2008;115(6):1058–64.
17. Davitt BV, Dobson V, et al. stigmatism in the early treatment for retinopathy of prematurity study: findings to 3 years of age. Ophthalmology. 2009;116(2):332–9.
18. Wiecek E, Akula J, Vanderveen D, et al. Longitudinal change of refractive error in retinopathy of prematurity treated with intravitreal bevacizumab or laser photocoagulation. Invest Ophthalmol Vis Sci. 2021;(62):3253.
19. Tafadzwa Y-Z, Magdalena P, Hazel P, et al. Is the severity of refractive error dependent on the quantity and extent of retinal laser ablation for retinopathy of prematurity? Eye. 2020;(34): 740–5.

20. Gilbert CE, Zin A, Darlow B. Bevacizumab for retinopathy of prematurity. N Engl J Med. 2011;(364):2359–60.
21. Moshfeghi DM, Berrocal AM. Retinopathy of prematurity in the time of bevacizumab: incorporating the beat-rop results into clinical practice. Ophthalmology. 2011;(118):1227–28.
22. Mintz–Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011;(364):603–15.
23. Alba LE, Zaldua RA, Masini RA. Off–label use of intravitreal bevacizumab for severe retinopathy of prematurity. Arch Soc Esp Oftalmol. 2015;90(2):81–6.
24. Jalali S, Balakrishnan D, Zeynalova Z, Rani TRPK. Serious adverse events and visual outcomes of rescue therapy using adjunct bevacizumab to laser and surgery for retinopathy of prematurity. The Indian twin cities retinopathy of prematurity screening database. Report number 5. Arch Dis Child Fetal Neonatal Ed. 2013;98:327–33.
25. Sears JE. Anti–vascular endothelial growth factor and retinopathy of prematurity. Br J Ophthalmol. 2008;92(11):1437–38.
26. Balasubramanian M, Capone, A Jr, Hartnett ME, et al. Photographic screening for retinopathy of prematurity (Photo–ROP). Retina. 2006;26(7):4–10.
27. Katsan SV. Confluent laser coagulation of the retina in children with aggressive posterior retinopathy of prematurity. Ophthalmol J Kazakhstan. 2019;56(1–2):55–65.

Chapter 13
Laser Use for Hyaloidotomy

Maram E. A. Abdalla Elsayed and Igor Kozak

The vitreous membrane, or hyaloid membrane, is a layer of collagen separating the vitreous humour from the rest of the eye. Two parts identified anatomically have clinical significance. The posterior hyaloid membrane separates the rear of the vitreous from the retina. It is a false anatomical membrane. The anterior hyaloid membrane separates the front of the vitreous from the lens. Neodymium YAG laser (Nd:YAG laser) has adequate physical properties to disrupt the hyaloid membrane where clinically indicated. Nd:YAG laser posterior hyaloidotomy has been indicated for subhyaloid hemorrhages obscuring vision while anterior hyaloidotomy has been indicated to relieve malignant glaucoma.

Subhyaloid Haemorrhage

Subhyaloid hemorrhage is a localized vitreous detachment from the retina due to blood accumulation. Occurring at the macula, this haemorrhage causes deterioration of visual acuity within a short span of time and is seen on biomicroscopy as a dome-shaped bleed in the macular area. This is secondary to a multitude of pathologies:

- Retinal vascular disorders eg arteriosclerosis, hypertension, retinal artery or vein occlusion, diabetic retinopathy, retinal artery macroaneurysms, Eales' disease, arterio-venous communications of the retina; sickle cell disease
- Macular neo-vascularisation due to age-related macular degeneration, chorioretinitis, presumed ocular histoplasmosis syndrome

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_13

- Hematological disorders/coagulopathies eg aplastic anemia, leukemia
- Rupture of retinal vasculature eg trauma, Valsalva retinopathy, Terson syndrome, Purtscher retinopathy
- LASIK [1]
- Necrotic tumours

A conservative approach to treating subhyaloid hemorrhage is justifiable if the macula is not involved; however, macular involvement may result in epiretinal membrane formation, proliferative vitreoretinopathy, and permanent vision loss due to macular retinal pigment epithelium changes and toxic damage of the photoreceptors [2–4]. Epimacular membrane formation appears to be the most common complication and this is likely due to the stimulatory effect of growth factors on the entrapped cells along the internal limiting membrane and retinal surface [5, 6]. Spontaneous reabsorption of blood may take one to two months. Although treatment choices must pay careful consideration to the underlying aetiology, in clinical practice, the primary objective of treatment is elimination of the haemorrhage.

Therapeutic modalities described for treatment of premacular subhyaloid hemorrhages include pneumatic displacement of the hemorrhage (with or without tissue plasminogen activator) and pars plana vitrectomy. These procedures expose the patient to the known risks associated with retinal surgery including cataract formation and iatrogenic retinal tears or detachments. Choosing the ideal treatment may be challenging as there is sparse literature comparing the different treatment modalities - particularly in different age groups and in cohorts with different underlying disease.

Nd:YAG laser hyaloidotomy is a valid alternative approach that has the benefits of being a non-invasive, simple outpatient procedure that is less costly than a vitrectomy [7–11]. It involves perforation of the posterior hyaloid face or the internal limiting membrane by means of a pulsed laser, allowing the rapid drainage of blood from the obstructed macular area into the vitreous cavity. A macular lens is used to focus the laser just anterior to the inferior part of the detached hyaloid; and power is raised, in increments, from a starting point of approximately 4 mJ until the hyaloid breaks.

With regards considering Nd:YAG laser hyaloidotomy, it is of the upmost importance to good visualization, ensure ideal positioning of the hyaloidotomy and to be judicious with the amount of laser energy utilized. One must also take a careful history from the patient to elicit the timing of the haemorrhage (less than three weeks) as any delay in laser treatment may undermine the efficacy of the photo-disruptive procedure due to thrombus formation beneath the internal limiting membrane.

The main complications are the non-resolution of the haemorrhage in a third of the cases, macular hole or retinal detachment. The risk of macular hole increases in small hemorrhages since the blood absorbs the energy applied. It is recommended only in haemorrhages greater than 3 papillary diameters, in an area far from the fovea and with less than 9 mJ [12, 13] Ulbig et al.'s retrospective review conducted on 21 eyes reported a macular hole in one eye and a retinal detachment from a retinal break in a myopic patient [14].

Malignant Glaucoma

Another important use of laser hyaloidotomy (2–3 mJ energy) is in the disruption of the anterior hyaloid face in malignant glaucoma as an intact hyaloid face is a significant factor in the pathogenesis of this rare entity [15–17]. Malignant glaucoma is characterized by shallowing of the central as well as peripheral anterior chamber in the presence of a patent iridotomy and can induce permanent visual damage. It is known to be precipitated by wide range of medical or surgical interventions; including miotics, filtrating glaucoma surgeries, phacoemulsification, laser iridotomies or capsulotomies, bleb needling and laser cyclophotocoagulation. Initial management is medical involving topical and systemic hypotensive agents, topical cycloplegics and topical steroids and is effective in 50% of patients with malignant glaucoma [18]. Second-line treatment involves disruption of the anterior hyaloid face to create a conduit between the anterior vitreous and the anterior chamber in pseudophakic and aphakic patients with malignant glaucoma. In a pseudophakic patient with a large intraocular lens (IOL) optic, the outcome can be improved by making the capsular opening through a dialing hole, if present. In phakic patients, laser hyaloidotomy can potentially be performed through a peripheral iridotomy. Ultrasound biomicroscopy (UBM) imaging reveals that after laser disruption of the anterior hyaloid face, the anterior rotation of the ciliary body processes, iridocorneal touch and the decrease in anterior chamber depth normalize [18, 19]. Clinically, an improvement, with deepening of the anterior chamber, is usually seen within 24 h. UBM can facilitate both the diagnosis of malignant glaucoma and the monitoring of treatment effect [20].

Several studies have reported success with this anterior laser hyaloidotomy in eyes refractory to medical therapy. Debrouwere et al.'s retrospective case series of 24 eyes with malignant glaucoma reported a recurrence rate of 75% after a laser capsulotomy and a hyaloidotomy, 75% after a conventional vitrectomy and 66% after an anterior vitrectomy in combination with an iridectomy–zonulectomy [21]. The authors concluded that the reason for the short-term success and subsequent high relapse rate was that the primary mechanism of misdirection was not counteracted adequately and that new aqueous had accumulated in the vitreous cavity. In Dave et al.'s retrospective case series, Yag laser hyaloidotomy achieved resolution in 7 of 15 eyes (46.7%) with a median time to resolution of 11 days (range, 3–33 days) [22].

Nd:YAG laser anterior hyaloidotomy has also been used in a rare case of triamcinolone acetonide entrapment in Berger's space between the posterior lens capsule and the anterior hyaloid face after an intravitreal triamcinolone acetonide injection for clinically significant maculae oedema [23]. Anterior hyaloidotomy allowed the trapped fluid to flow into the vitreous cavity, restoring visual acuity in an effective and minimally invasive outpatient procedure avoiding more invasive surgical procedures such as pars plana vitrectomy with its associated risks. A significant limitation to this case report is its relatively short follow-up period of only one week. So even though no complications were observed during this short period, late complications such as diabetic macular oedema progression or cataractogenesis may occur (Fig. 13.1).

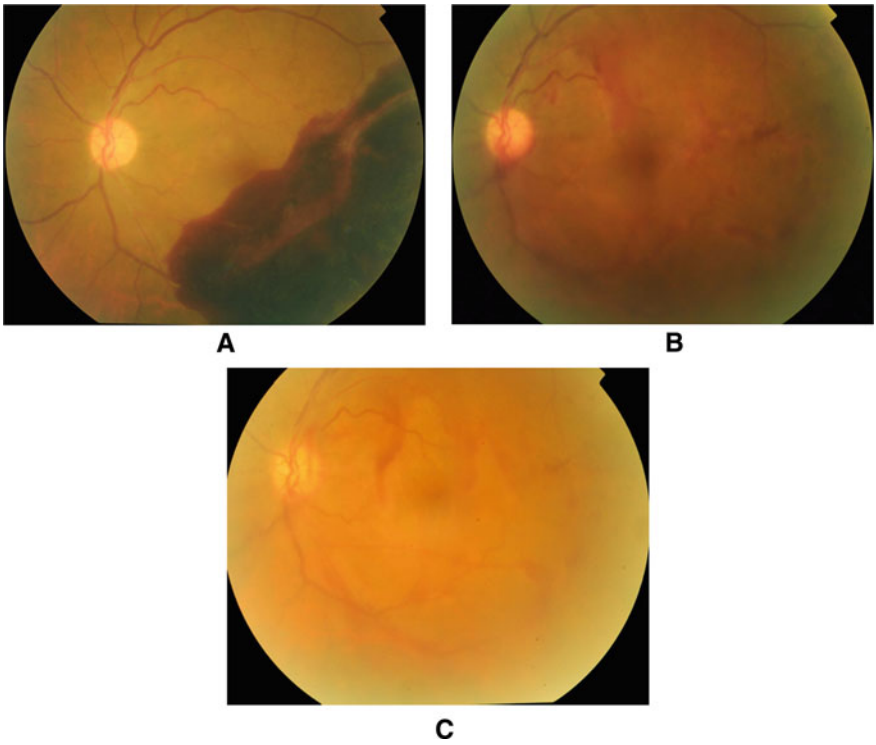

Fig. 13.1 **A** Color fundus photograph showing left eye with pre-retinal hemorrhage. Best corrected visual acuity was 20/100. **B** Color fundus photograph of the same eye 1 week following Nd:YAG laser hyaloidotomy. Best corrected visual acuity improved to 20/60. **C** Color fundus photograph of the same eye 1 month following the treatment. Best corrected visual acuity improved to 20/40. (*Source* Dr. Igor Kozak)

References

1. Mansour AM, Ojeimi GK. Premacular subhyaloid hemorrhage following laser in situ keratomileusis. J Refract Surg. 2000;16:371–2.
2. Khan MT, Saeed MU, Shehzad MS, Qazi ZA. Nd:YAG laser treatment for Valsalva premacular hemorrhages: 6 month follow up: alternative management options for preretinal premacular hemorrhages in Valsalva retinopathy. Int Ophthalmol. 2008;28(5):325–7.
3. Khadka D, Bhandari S, Bajimaya S, Thapa R, Paudyal G, Pradhan E. Nd:YAG laser hyaloidotomy in the management of premacular subhyaloid hemorrhage. BMC Ophthalmol. 2016;16:41.
4. Velikay M, Datlinger P, Stolba U, et al. Retinal detachment with severe proliferative vitreoretinopathy in Terson syndrome. Ophthalmology. 1994;10:135–7.
5. Meyer CH, Mennel S, Rodrigues EB, et al. Persistent premacular cavity after membranotomy in valsalva retinopathy evident by optical coherence tomography. Retina. 2006;26:116–8.
6. Russell SR, Hageman GS. Hemorrhagic detachment of the internal limiting membrane after penetrating ocular injury. Retina. 1992;12:346–50.
7. Kuruvilla O, Munie M, Shah M, Desai U, Miller JA, Ober MD. Nd: YAG membranotomy for preretinal hemorrhage secondary to valsalva retinopathy. Saudi J Ophthalmol. 2014;28:145–51.

8. Hazem HA, Shazly TA. Evaluation of pulsed Nd:YAG laser posterior hyaloidotomy as an emergency treatment for blinding premacular subhyaloid hemorrhage. Open Access Emerg Med. 2011;3:33–7.
9. Durukan AH, Kerimoglu H, Erdurman C, Demirel A, Karagul S. Long-term results of Nd:YAG laser treatment for premacular subhyaloid haemorrhage owing to Valsalva retinopathy. Eye. 2008;22:214–8.
10. Alarfaj MA, Hasen AA, Al-Yami SS. Traumatic sub-hyaloid macular hemorrhage with complete resolution following Neodymium-Doped Yttrium Aluminium Garnet Laser. Am J Ophthalmol Case Rep. 2018;9:85–7.
11. Bouladi M, Mghaieth F, Bouraoui R, Zerei N, Chaker N, El Matri L. Valsalva retinopathy occurring after general anesthesia. Tunis Med. 2019;97(4):595–8.
12. Burgos-Blasco B, Moreno-Morillo FJ, Hernández-Ruiz S, Valverde-Megías A, Sáenz-Francés F, Santos-Bueso E. Terson syndrome: vitrectomy vs Nd:YAG hyaloidotomy. J Fr Ophtalmol. 2019;42(6):e263–6.
13. Bypareddy R, Chawla R, Azad SV, Takkar B. Iatrogenic parafoveal macular hole following Nd-YAG posterior hyaloidotomy for premacular haemorrhage. BMJ Case Rep. 2016;2016:1–3.
14. Ulbig MW, Mangouritsas G, Rothbächer H, Hamilton AMP, McHugh JD. Long-term Results After Drainage of Premacular Subhyaloid Hemorrhage Into the Vitreous With a Pulsed Nd:YAG Laser. Arch Ophthalmol. 1998;116(11):1465–9.
15. Little BC. Treatment of aphakic malignant glaucoma using Nd:YAG laser posterior capsulotomy. Br J Ophthal. 1994;78(6):499–501.
16. Brown RH, Lynch MG, Tearse JE, Nunn RD. Neodymium-YAG vitreous surgery for phakic and pseudophakic malignant glaucoma. Arch Ophthalmol. 1986;104(10):1464–6.
17. Ruben S, Tsai J, Hitchings R. Malignant glaucoma and its management. Br J Ophthalmol. 1997;81:163–7.
18. Trope GE, Pavlin CJ, Bau A, Baumal CR, Foster FS. Malignant glaucoma: clinical and ultrasound biomicroscopic features. Ophthalmology. 1994;101(6):1030–5.
19. Tello C, Chi T, Shepps G, Liebmann J, Ritch R. Ultrasound biomicroscopy in pseudophakic malignant glaucoma. Ophthalmology. 1993;100(9):1330–4.
20. Sharma A, Sii F, Shah P, Kirkby GR. Vitrectomy–phacoemulsification–vitrectomy for the management of aqueous misdirection syndromes in phakic eyes. Ophthalmology. 2006;113:1968–73.
21. Debrouwere V, Stalmans P, Van Calster J, Spileers W, Zeyen T, Stalmans I. Outcomes of different management options for malignant glaucoma: a retrospective study. Graefe's Arch Clin Exp Ophthalmol. 2012;250(1):131–41.
22. Dave P, Senthil S, Rao HL, Garudadri CS. Treatment outcomes in malignant glaucoma. Ophthalmology. 2013;120(5):984–90.
23. Ascaso FJ, de Gopegui ER, Cascante JM. Neodymium: yttrium-aluminum-garnet laser anterior hyaloidotomy to treat trapped triamcinolone acetonide behind the crystalline lens after intravitreal injection. Middle East Afr J Ophthalmol. 2012;19(1):163–5.

Chapter 14
The Mechanism of Retinal Laser and Its End Result: Neuroprotecion

Jeffrey K. Luttrull

The therapeutic mechanism of retinal laser for the neurodegenerations of the chronic progressive retinopathies inevitably leads to discussion of neuroprotection because, as we will argue, neuroprotection is the end-result of retinal laser treatment (for other than cautery). In the following, the various modes of current retinal laser treatment will be examined weighing their differences and commonalities, safety and effectiveness, and suitability for the most important indication of retinal laser treatment, therapy and prevention of the most common causes of irreversible visual loss, via neuroprotection.

Current Thinking and Approaches to Neuroprotection

It has long been recognized that most patients with open angle glaucoma (OAG), the third most common cause of irreversible visual loss worldwide after age-related macular degeneration (AMD) and diabetic retinopathy (DR), continue to suffer progressive optic nerve dysfunction and visual loss despite intraocular pressure (IOP) reduction [1, 2]. This suggests the presence of an optic neuropathy associated with, but independent of, IOP in eyes with OAG. To address this optic nerve dysfunction, a treatment separate from IOP control is needed to protect the optic nerve against progressive degeneration. Such a treatment would be, by definition, "neuroprotective". Indeed, according to Levin, Crowe, and Quigley, "Within the field of glaucoma research, neuroprotection is defined as slowing the functional loss in glaucoma by a mechanism independent of lowering of intraocular pressure" [2]. While the cause of this neurodegeneration seemingly specific to OAG is unknown, Levin et al. suggest a number of anatomic targets for neuroprotection, all in the neurosensory retina.

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_14

These include retinal ganglion cells, microglia, astrocytes, Muller cells (macroglia), and the retinal vasculature. Only drug therapy is given serious consideration as the answer to achieving this goal [2].

This represents the dominant view of neuroprotection in ophthalmology. It is a narrow view, focused on the search for effective neuroprotection in glaucoma, on a narrowly defined target—the neurosensory retina—and narrowly defined solutions as well—drugs. However, neuroprotection is of widespread interest and concern in all of medicine. The search for solutions to the most common and prominent neurodegenerative diseases, such as Alzheimer's disease, is a search for neuroprotection. The search for measures to mitigate the effects of stroke is a search for effective neuroprotection. As noted by Sinclair and Schwartz, effective early and preventative treatment for diabetic retinopathy, which begins as a neuronal inflammatory degeneration, will be neuroprotection [3]. In fact, the search for effective treatment and prevention of visual loss from all chronic progressive retinopathies of all causes is the search for neuroprotection.

The focus on drug therapy as the ultimate answer to the problem of neuroprotection, and virtually every other medical problem, is *de rigeuer* and *au courant*. This is such as prevalent view across medicine and in ophthalmology that it sounds absurd to seriously consider anything else. It has risen to the level of the "self-evident". If not drug therapy, what? The focus on drugs as the answer to every problem is enhanced by the unparalleled influence of the pharmaceutical industry in medicine and ophthalmology, and in government and society as well. Anyone who has viewed television in the United States will have witnessed saturation of the airwaves by drug advertising. The drug focus is facilitated by the group-think common to many organizations, particularly those that are small and hierarchical, like ophthalmology, which tends to amplify and codify the views of a few "key opinion leaders". In such organizations, the influence of a few can go a long way [4].

Eroom's Law

Such a highly focused approach to problem solving, as in the search for effective neuroprotection, is thus problematic. First, we tend to limit our potential solutions to those at hand from a list of possibilities familiar to us. But if something from the menu of the known and familiar was effective, we would likely already have some indication of it. If there is nothing in the familiar that would appear to solve the problem, then the solution likely lies outside the familiar—"out of the box". Second, to focus narrowly is necessarily to simply neglect possibilities that lie outside that line of focus [4]. As an exercise in the preceding, consider the following assertion: "Drug therapy is the answer to AMD." Question: "OK, which drug?" Absent a clear answer to this question, it behooves us to question the assertion, and consider non-pharmacologic answers to the problem of AMD. Eroom's law suggests that, despite the heavy focus on pharmaceuticals, drug therapy may actually be the least promising avenue before us [5].

Moore's Law describes and for many years has accurately predicted the exponential increase in computing power over time. Eroom's Law is the pharmaceutical equivalent of Moore's Law. However, Eroom's (Moore spelled backwards) Law states that the development of new and effective drugs is *decreasing* at an exponential rate, even as the cost of these ever also less-effective drugs is exponentially increasing [5]. We have been spoilt by intravitreal anti-vascular endothelial growth factor (VEGF) drug therapy into thinking developing safe and effective drugs is simple and straightforward (and immensely profitable). In fact, intravitreal anti-VEGF therapy is the low-hanging pharmacologic fruit, an exception that proves the pharmacologic (Eroom's) rule. The challenge of binding extracellular factors floating in the vitreous is vastly simpler than targeted alteration of cell behavior in a specifically desired and clinically beneficial fashion, while also avoiding serious adverse treatment effects. Think of all the safe and highly effective drugs we have now to prevent just AMD, DR, and OAG. What drugs, you say? Exactly. Because of commercial pressures and public demand for cures, approvals of new drugs will be increasingly divorced from their safety and effectiveness [5–7]. Following on Eroom, new drugs will be increasingly less safe, less effective and more expensive. Aducanumab-avwa for Alzheimer's and brolucizumab for AMD are two recent examples of the phenomenon [6, 7]. Thus, we are best advised to cast a net wider than drug therapy in the search for useful neuroprotection.

Neuroprotection Candidates

A number of endogenous factors have been identified with potentially neuroprotective properties. These interact with cellular processes including autophagy and inhibition of aptoptosis, the unfolded protein response, anti-anoikosis, maintenance and repair of the cytoskeleton, and enhancement of mitrochondrial function [8]. Most clinical trials attempting to identify safe and effective neuroprotective agents have thus far failed. However, many candidates remain, and more will be identified. Additional endogenous candidates include human urinary kallidinogenase (HUK), statins, MCI-186 [3-methyl-1-phenyl-2-pyrazolin-5-one] (a low molecular weight free radical scavenger that can readily cross the blood–brain barrier and thus blood retinal barrier) NA-1 (nerinetide; TATNR2B9c), 3K3A-activated protein C (APC), GM6, Natalizumab, and Vinpocetine [9].

With regard to glaucoma, no biologic or pharmacologic agent has yet (June 2022) been proven to be neuroprotective. Topical brimonidine has a number of properties suggesting possible neuroprotective effects [10]. However, there is currently no good evidence of a clinically significant neuroprotective effect in glaucoma. Although an RCT of brimonidine vs timolol found significantly less visual field loss in the brimonidine compared to timolol patients treated over a two year study, the study was invalidated by premature loss to follow up of a large number of patients in the brimonidine group [10]. This may have been due to the high incidence of allergic conjunctivitis

and eye irritation associated with topical ocular brimonidine that may have discouraged continue use and trial participation. This illustrates the Achille's heel of even effective biologic and pharmacotherapy, encapsulated in Eroom's Law: the difficultly of avoiding unintended adverse treatment effects in targeted drug therapy that either limit or prevent clinical use [5].

Retinal Protection is Neuroprotection

It is helpful to remember that the retina, and optic nerve that originates from it, are parts of the central nervous system. Thus, chronic progressive diseases of the retina, like those of the optic nerve, are all neurodegenerations. This includes the most common causes of irreversible visual loss, AMD, DR, and OAG - the subject of greatest interest regarding neuroprotection. Thus, the need for effective neuroprotection applies equally to all [11].

To be neuroprotective a treatment must, by definition, either maintain or improve (restore, normalize) neurologic function in the face of dysfunction-inducing disease. Only maintained improved function can reduce or reverse the impetus toward progressive physical degeneration, which is the end result of chronic, progressive and/or severe dysfunction, and in the eye, visual loss [8]. If improved retinal function is retinoprotective and therefore also neuroprotective, and the optic nerve originates in the retina (mainly the macula), might improved retinal function also improve optic nerve function and thus be neuroprotective of the optic nerve in glaucoma? Possibly. But only if the abnormal retinal function was the cause of the optic nerve dysfunction and degeneration, and only if this retinal dysfunction was reversible.

Light, Laser, and the Retina

At this point it is useful to consider the effects of laser on the retina. There are two principal light-based retinal therapies, retinal laser and photobiomodulation (PBM). PBM employs visible light which is absorbed by electrons in the valences of the metal cofactor cations of the mitochondrial respiratory chain molecules. Absorption of the photon excites the electron into a higher orbital valence, after which this energy is radiated again as the electron decays back into its prior energy level valence. PBM is thus wavelength dependent, non-thermal, and the effects are dependent on the order of presentation if multiple different wavelengths are employed. The effect is photoelectric and, by mechanisms not entirely clear, PBM primarily improves mitochondrial function and thus cell metabolism [11–13]. However, as a rising tide lifts all ships, improved cell metabolism may pay many dividends. PBM can be anti-inflammatory and alter gene expression [9]. PBM appears quite safe, using visible light at normal environmental exposure intensities. The effect of PBM is generally short-lived, and treatment sessions somewhat prolonged and frequent. In

small clinical trials, PBM has shown modest effects in dry AMD, but no benefit in DME [13, 14].

Laser irradiation of the retina is mainly absorbed by melanin in the RPE and choroid [11–17]. This effect is thermal, rather than photoelectric. Wavelengths below 550um may be absorbed in the neurosensory retina as well, as ionizing radiation causing free-radical formation with photocytotoxic effects. At higher irradiances, and thus tissue temperatures, frank thermal photocoagulation may occur, destroying the retina and visual function, and causing inflammation and scarring [13, 14].

Shorter wavelengths are more energetic than longer laser wavelengths, and also generally better absorbed by melanin, further amplifying their tissue effects [15–17]. It is thus easier to produce thermal effects, and retinal burns, with shorter wavelength lasers. Despite this, because the therapeutic effects of retinal laser are mediated thermally, the clinical results of retinal laser treatment are wavelength independent, because, as in a statement attributed to the late HR Green regarding photocoagulation, "a burn is a burn is a burn." [18, 19].

By shortening the laser exposure duration, heat spread from the locus of absorption can be reduced. In the extreme, nanosecond lasers are simply photodisruptive to the RPE, concentrating the thermal effects at the RPE melanin to simply vaporize the cell as heat dissipation impossible due to the nanosecond laser exposure and temperature rise [15]. Slightly longer duration exposures, such in the range of 2 microseconds, produce gas bubble formation at the RPE melanin granules causing internal cavitation of the RPE and cell death with limited damage to collateral structures. Exposures longer still, in the range of 40–100 microseconds, such as used by microsecond pulsed lasers (MPL), may heat the RPE cell via melanin absorption without photodisruption or cavitation, allowing the cell to be affected by treatment, but survive [15–17, 20].

Because the clinical effects of retinal laser are wavelength independent, the therapeutic effects must necessarily reflect an essential commonality shared by all laser wavelengths [15–19]. While shorter wavelengths affect both the neurosensory retina and the RPE, longer wavelengths, like near-infrared 810 nm, are only absorbed by melanin in the RPE and choroid. The thermal effects of continuous wave (CW) 810 nm occur about 80% in the choroid, and 20% in the RPE, reflecting the generally higher melanin density in the choroid. By shortening the laser pulses to the MPL range to limit heat spread, but longer than the photodisruptive or photoablative range, the RPE can be preserved while increasing the localization of heating to the RPE (80%) rather than the choroid (20%), reversing the thermal distribution. Thus, by exclusion, the therapeutic effects of retinal laser treatment at all wavelengths arise from the commonality of thermal laser effects on the RPE which are sublethal to the RPE [15–21].

In the photocoagulation era, the universal presumption was that laser-induced retinal damage (LIRD), such as conventional photocoagulation (CPC), was the essential prerequisite to clinically effective treatment [15, 19, 21]. With time it became apparent that destruction of the neurosensory retina not only unnecessary, but undesirable [15, 16, 20–28]. This led to development of nanosecond and microsecond short-pulse laser modes (2RT, Ellex, Adelaide, Australia; Pattern Scanning Laser (PASCAL), Optimedica, Stanford, CA, USA; Selective Retinal Laser Treatment

(SRT), Lutronic, Bellerica, MA, USA), designed to better limit laser damage to the RPE and outer retina. Despite the presumed need for LIRD, no convincing and generalizable explanation of the mechanism of retinal laser treatment could be offered, based on this premise [15]. This was problematic, as all adverse effects of retinal laser treatment, of which there were many and some severe and sight-threatening, were the direct and sole result of LIRD.

Laser-Induced Retinal Damage (LIRD): Sufficient, but Unnecessary

The development of low-intensity/high-density subthreshold diode micropulse laser (SDM) represented a watershed in the understanding of retinal laser treatment, it's application, the mechanism of action, and potential treatment indications [22, 27, 28]. Prior to SDM, LIRD was considered both the necessary and sufficient cause of all therapeutic laser effects. SDM revealed that LIRD was sufficient, but necessary [22]. And, as the cause of all adverse treatment effects, SDM demonstrated that LIRD was, in fact, contraindicated and detrimental to optimal clinical effectiveness [20].

As noted above, the range of tissue effects achievable with microsecond pulse lasers is broad, from conventional suprathreshold full-thickness retinal photocoagulation, to sublethal thermal photostimulation. This is possible with other laser modes as well. The difference is that the microsecond pulsing makes possible treatment that is effective, but also *reliably* sublethal to the RPE and thus safe. It is this clinically reliable safety, evidenced by the ability to treat all eyes with identical ("fixed") laser treatment settings effectively and without LIRD, that appears to be a unique facility of MPL [15]. SDM describes a specific use of MPL that optimizes clinical effectiveness, while reliably avoiding LIRD of any kind [15, 22–28]. Following the Early Treatment of Diabetic Retinopathy Study (ETDRS) use of intense full-thickness suprathreshold retinal photocoagulation burns, retinal laser treatment gradually moved to less damaging, lower-intensity treatment [21]. However, LIRD continued to be considered essential. SDM was the first to eschew LIRD with an explicit intent to avoid, rather than cause, LIRD. The fact that this was successful is of inestimable importance [22, 25, 26]. Invocation of LIRD as a necessary precondition to effective treatment, because it was a false premise, prevented a useful and accurate understanding of the mechanism of action of retinal laser treatment, and thus optimal utilization [27, 28]. No explanation of retinal laser action presupposing LIRD as both necessary and sufficient could explain all observed laser effects in all clinical applications, or accurate predict new ones. SDM changed this [22, 27, 28].

Therapeutic laser effects are mediated by living cells, not destroyed (dead) tissue

By exclusion, the fact that the SDM low-intensity / high-density treatment paradigm was effective for treatment of the complications of DR without harming the RPE

provided three key pieces of information [22]. First, that the RPE is dysfunctional in DR that this function is correctable. Second, that correction of the RPE dysfunction in DR normalizes the function and structure of the neurosensory retinal. Third, that the therapeutic effects of treatment must necessarily arise from RPE affected but not killed by treatment. Thus, the therapeutic effects of retinal laser are mediated by living cells, not destroyed retina, redefining LIRD as a serious adverse effect and the most serious complication of treatment [11, 15, 20–28]. How?

Role of the RPE in Retinal Neurodegenerations is Central

So how does sublethal heating of the RPE lead to functional normalization and clinical improvement across a wide range of etiologically disparate neurodegenerations? First, the power and influence of the RPE on ocular and particularly retinal function must be appreciated. In addition to maintaining the blood-retinal barrier, the RPE is trophic for the choriocapillaris and neurosensory retina, as well as processing, maintenance, and toiletry of the outer retinal photoreceptors. Via numerous cytokines and other chemical factors elaborated into the extracellular space, the RPE supports normal retinal function and autoregulation [29]. Because these factors can be measured in the vitreous and aqueous, the influence of the RPE may extend throughout the entire eye [30].

Thermal activation of RPE Heat Shock Proteins is key to therapeutic laser response

Thermal heating of the RPE by laser exposures longer than photodisruption or photoablation results in some heat spread within the cell from the melanin granules resulting in generalized heating of the cytoplasm, and thus its contents [15–17, 24]. With MPL, average maximum temperature of the cell may take a hundred milliseconds or more to for the heat to accumulate to a therapeutic level [15–17, 24]. In addition, the microsecond pulses induce immediate, although brief and sublethal, repetitive temperature spikes on top of this average cell temperature rise [16, 24]. These acute and more severe but still sublethal temperature spikes may contribute to the biological effects of MPL over and above the average temperature rise [16, 24]. Analysis of the effects of sublethal hyperthermia on cellular proteins indicate that most are adiabatic, having no net effect. Activation of heat labile calcium channels has been identified in vitro [31]. The thermal activation temperature of these calcium channels is slightly higher than the lowest threshold for HSP 70 activation, but with sublethal thermal laser photostimulation, both are affected more or less simultaneously [17, 31]. However, only activation of RPE heat shock proteins, (HSPs), particularly HSP 70, can account for the therapeutic effects of retinal laser [27–47].

HSPs: Maintenance Versus Salvation

HSPs are highly conserved and ubiquitous intracellular proteins that play many roles essential for normal cell function. accounting for as much as 40% or more of all cell proteins. HSPs have a vast number of roles and essential functions, generally working in concert and integrated with a wide array of other cell functions relevant to the particular portfolio of actions characteristic of various HSPs. HSPs can be classified by their molecular weights in kilodaltons [33]. Of primary importance to retinal laser therapy is HSP 70KD. HSP 70 has two broad roles; a surveillance function to maintain cell homeostasis by repairing misfolded proteins and preventing protein aggregation along with other functions; and a salvific function, designed to preserve the cell in the face of an existential threat [29–41]. It is the salvific HSP reaction that is exploited by therapeutic retinal laser [41].

Sharp, Severe, but Sublethal

The most effective stimulus to the HSP salvific response is a stressor that is acute, severe, but sublethal to the cell [36–38]. In essence, therapeutic laser hyperthermia of the RPE causes the RPE cell "think" it is going to die, without harming it [41]. In response, a wide range of highly effective measures are triggered in an attempt improve the likelihood of surviving the perceived threat, starting with intracellular protein repair. While HSP activation is the key initiator of the therapeutic response, sublethal laser RPE HSP activation is relatively modest [17, 24, 31]. This is in part because only about 25% of free intracellular HSPs are available at any one time for activation [37–40]. In addition, measurement of HSP activation in vitro is generally indirect, using stains for the HSP promoter gene, rather than free HSP or the HSP.HSF complex [31]. Activation of the HSP.HSF complex results in marked upregulation of HSP transcription and HSP production. Thus, despite low levels of laser-induced free-HSP activation, the response to HSP activation is catalytic, acting like the fuse on a bomb. The fuse does not have to be big to lead to a big effect. An early (minutes) laser-induced effect thermal effect results in acceleration of HSP protein repair kinetics via a temperature induced conformational change in the heat sensitive molecule, that increases the rate of protein repair by 35% [17]. This response occurs only in sick cells with high levels of misfolded proteins in which the endoplasmic reticulum unfolded protein response is overwhelmed and proteostasis has failed [48]. In normal cells with low levels of protein misfolding, activation of the HSP salvific response has no significant effect, as a normal cell cannot be made more normal [17, 39–42]. This therapeutic selectivity for dysfunctional cells is consistent with of the effects of low-level tissue irradiation [42]. While enhanced protein repair kinetics promptly begin to improve cell function, HSP activation also triggers a broad range of cascades restorative to RPE cell and retinal function that extend over minutes, hours, days,

and weeks, reaching out from the RPE cell as far as systemic immunoactivation and recruitment of bone-marrow derived immune cells to the retina [42–47].

These restorative responses can be triggered in the RPE both by MPL directly sublethally to the retina, or indirectly in response to RPE destruction/LIRD [15, 24]. When there is LIRD, additional factors resulting from the response to tissue damage and the need for repair, as well as inflammation resulting from tissue destruction, are observed [32]. Because only living tissue can respond to a stimulus, the therapeutic effects of LIRD are entirely indirect from the stressors placed on the surviving cells at the margins of the LIRD [25]. Because the therapeutic effects arising from LIRD are entirely indirect, LIRD is unnecessary [22]. Further, the responses unique to LIRD are concerned with wound healing, phagocytosis, debridement, and tissue remodeling. These unique effects of LIRD are non-therapeutic, detrimental form and function, leading to a net reduction in the therapeutic response compared to the wholly therapeutic direct effects of sublethal laser hyperthermy [32]. Of the many effects of MPL sublethal to the retina that have been documented in vitro, in vivo, and in human studies, it is remarkable to note that all are restorative, anti-inflammatory, and therapeutic and none have been found to be adverse to retinal function [44–52]. A few of these effects include reduced in VEGF and increased (and neuroprotective) PEDF expression; increased superoxide dismutase function, decreased oxygen free radial formation and normalized retinal redox states; inhibition of apoptosis; local and systemic therapeutic immunoactivation; correction of protein misfolding and inhibition of protein aggregation; modulation of transcription and translation; increased markers of acute inflammation in the absence of tissue damage to reduce markers of disease driving chronic inflammation such as increased mRNA expression of RPE cytokines including *Ccl2, Cxcr4, Il1b, Il6,* and *Ifng*; improved mitochondrial function and energy utilization; down regulation of tumor necrosis factors NRF2 and Tnfsf, and interferon gamma; modification of glial fibrillary acidic protein (GFAP) and inwardly rectifying potassium (Kir) 4.1, aquaporin (AQP) 4, and modulation of retinal microglial and Mueller cells activity; reduced pro-inflammatory activation of normal T-cells and macrophage inflammatory proteins (MIP1α) and fas ligand (FasL); increased hematopoietic cells (CD4), reduced T cells and CD11b- and increased $L6C^{hi}$; and recruitment of bone-marrow immune and stem cells to the RPE [44–53].

Implications from Pathoselectivity for Laser Treatment Optimization

Arising from the mechanism of retinal laser is the property of pathoselectivity [25, 27, 28]. Because the result of laser is to functionally improve dysfunctional RPE cells, it has no effect on normally functioning cells [17]. Normal cannot be normalized. Because laser-induced enhancement of HSP protein repair kinetics is proportional to the load of misfolded proteins within the cell, improvements in cell function following

laser are proportional the degree of dysfunction prior to laser [17]. This has been well demonstrated clinically by the electrophysiologic and visual function responses to SDM MPL for dry AMD, IRDs including RP, and OAG. The greater the measurable dysfunction, the greater degree of improvement following SDM MPL. This does not mean a blind eye is restored to diamond-cutting status. This means that very poor function can be improved to less poor function. Such improvements may be reflected in improved vision. However, even in the absence of visual improvement, significant treatment associated improvements in retinal function should slow or prevent progressive degeneration and visual loss. Visual field testing in such eyes often demonstrates return of function to areas previously non-recordable. This suggests inhibition of apoptosis by MRT, and its ability to restore visual function to highly dysfunctional, likely pre-apoptotic, cells [11, 28, 48, 54, 55].

It can be helpful to test a proposition by taking it to its logical extremes. It is a given the sicker the retina, the greater the number of dysfunctional cells, and the more dysfunctional each cell is. Improving the function of a single RPE cell in such an eye, even to complete normality, would clearly have little to no effect on the disease process, clinical findings, or visual function. In contrast, if one could completely normalize the function of every cell, the effect of treatment would be maximized; slowing, preventing, or even reversing disease progression and possibly improving visual function as well [27, 28]. This is the logic behind the "high-density" treatment paradigm of SDM MPL, wherein confluent treatment of large areas of retina – such as panmacular treatment for macular disease – is performed to maximally recruit and improve all dysfunctional retina in the diseased area to optimize the clinical benefits of treatment [20, 22, 25]. Because treatment is pathoselective, meaning that only dysfunctional cells are affected while normal cells are undisturbed, this approach is simple, safe, and highly effective [20, 22, 27]. Because retinal-damaging treatment requires treatment limitation to focal and local treatment to limit treatment-associated visual loss, focal and local treatment is suboptimal and generally less effective, particularly when adverse treatment effects are factored in [56–58].

Protein Misfolding: The Currency of Neurodegeneration

The enzymatic machinery that makes every cell operate normally and effectively reflecting its particular bodily role are proteins folded into to highly specific shapes essential to their proper function [17, 31–40]. These specially folded proteins exist in the aqueous environment of the cytosol and maintain their shape primarily through the forces of hydrophobia and -philia, with the hydrophobic portions of the proteins seeking refuge from the polar aqueous surround by burying themselves in the interior of the folded protein; while the hydrophilic portions of the protein orient themselves outwardly toward the aqueous cytosol [33, 38–40]. Thus, the forces maintaining enzyme folding are much weaker than covalent bonds and are relatively easily broken, resulting in eventual loss of this tertiary structure and misfolding of the protein, and with misfolding, loss of function and the potential for polymeric aggregation with other misfolded proteins further compromising cell function [43, 48, 59–62]. Even

in a healthy cell the half-life of a normal enzyme is only on the order of 90 min. In a highly dysfunctional cell, the half-life declines to as little as 18 min [17]. This shorter the protein half-life results in accumulation of misfolded proteins and development of toxic aggregates within the cell, and increased cell dysfunction in a progressively increasing downward spiral. Dysfunction breeds dysfunction. Eventually, cell death will ensue with loss of tissue function and the development of chronic inflammation caused by the accumulation of failed cell debris and metabolic waste [11, 35, 36, 43, 48, 59–62]. This is the basis for every chronic disease, diseases of ageing, and neurodegeneration. In the eye, this is the basis for the visual loss that results from chronic progressive retinopathies.

Time

Age is a fundamental to all chronic progressive diseases, as all tend to worsen as a function of disease duration. As noted at the outset of this chapter, because the retina is nervous tissue, all chronic progressive diseases of the retina are neurodegenerations. Thus, any effective treatment of these diseases would be, by definition, retinoprotective and thus neuroprotective. The ideal treatment would improve all the chronic progressive retinopathies based on their shared status by addressing their commonalities as neurodegenerations. This facility has been demonstrated by SDM MPL and is the basis for the therapeutic effect of retinal laser treatment being described as a representing a physiologic "reset" phenomenon [11, 17, 20–28, 48, 54, 55].

The retinal laser "reset" effect: a non-specific trigger of disease-specific repair
Following on the mechanism of retinal laser as activated by RPE HSP activation, the effect of treatment can be described as a "non-specific trigger of disease-specific repair" [25, 27, 28]. This is really a restatement of the reset phenomenon, and the meaning of this phrase is central to the role of laser for neuroprotection. Every cell faces stressors that may lead to functional compromise. In all cells, this is compounded by time and thus age. In diabetics, it is metabolic dysfunction. In IRDs, genetic abnormalities. Each unique stressor affects the cell in a unique way, and thus particular enzymes more than others leading to disease-specific dysfunction that reflects the influence of the particular stressor. Thus, each stressor causes a disease-specific "menu" of enzyme and thus cellular dysfunction [27, 28]. This dysfunction is due to misfolding of the particular enzymes preferentially affected by a given stressor, leading to compromise and eventual failure of their role in cell function. Depending on the importance and a given enzyme and the health of the reparative mechanisms, this stressor induced enzyme misfolding may lead to cell death. The particular "menu" of disease-induced protein misfolding is what characterizes each clinical disease, its clinical signs, symptoms, and course [27, 28, 48]. Thus, while the instigator of cell dysfunction may be different for every disease (although there may be shared commonalities), the generic currency of the induced dysfunction—protein misfolding—and the end result—cell dysfunction and death,

functional loss and chronic inflammation—is the same [17, 20–28, 48, 52–54, 56, 59–65].

Interesting implications follow from the above. One is that therapies aimed at specifically correcting the primary abnormality require as many cures as there are diseases, and even individuals [65]. If nothing else, this is a highly inefficient approach to achieving public health. Retinal laser, as a non-targeted non-specific trigger of disease-specific repair via the reset phenomenon is largely agnostic to the cause of the disease process [52, 53]. Because the mechanism of retinal laser addresses protein misfolding and its downstream consequences generically and agnostically to the cause of the protein misfolding, retinal laser has demonstrated the potential address the entire class of retinal neurodegenerations [11]. These include all the major causes of irreversible vision loss [1]. Because retinal laser treatment can be reliably safe, durable, renewable, broadly applicable to a wide range of disparate disorders, and economical, it appears to offer the best prospect as an effective treatment and prevention of vision loss from the most common causes of irreversible visual loss worldwide, the chronic progressive retinopathies of AMD, DR, IRDs and OAG.

Retinal Laser and Open Angle Glaucoma: A Model of Neuroprotection

Open angle glaucoma is not typically thought of as a chronic progressive retinopathy [11, 55, 63]. For one reason, no retinopathy is clinically evident, other than by association with progressive glaucomatous optic neuropathy. However, the response to SDM MPL reveals that OAG is, in part, a retinopathy. This previously unrecognized retinopathy (the retinopathy of OAG, or "ROAG") appears to be the best current explanation for the observation of progressive optic neuropathy and visual loss in OAG despite maximal lowering of intraocular pressure (IOP) that occurs in the majority of patients with OAG. OAG, thus represents an iconic test of neuroprotection. An analysis of the treatment response to SDM MPL in OAG illustrates the fundamental mechanistic effects and principles of retinal laser for neuroprotection and establishes the benchmarks for neuroprotective treatments in OAG in general.

Diminished and worsening mesopic visual function (MVF), VA, visual fields, and pattern electroretinogram (PERG) have all been shown to identify and predict progression in all the major chronic progressive retinopathies, including OAG. In OAG, these abnormalities have been attributed to primary optic nerve dysfunction [11]. Thus, effective neuroprotection would be expected to demonstrate measurable improvement in some, if not all, of these prognostic indicators.

Acute IOP lowering has been shown to improve the PERG (a measure of ganglion cell layer function) and reduce nerve cupping in eyes with OAG and uncontrolled IOP [66]. Otherwise, treatment of OAG via IOP control alone seldom, if ever, results in

improvement in other findings or metrics. Measurable treatment-associated improvements in these key disease indicators would therefore represent strong and novel evidence of effective neuroprotection in OAG, and as prognostic indicators, a reduced risk of future vision loss [11, 27, 28].

In 2014, mesopic visual function testing and PERG were noted to improve significantly following SDM MPL in eyes with dry AMD [28]. In the absence of other effective treatment in high-risk dry AMD, panmacular SDM MPL was offered to patients in hopes of reducing progression and their risks of visual loss, with the retinal function improvements measured by PERG, and various visual function improvements, including MVF, acting as surrogate indicators for risk reduction. The PERG and MVF abnormalities in the eyes with dry AMD were noted to be similar to those reported in eyes with OAG [67–71]. If abnormal and/or worsening PERG and mesopic visual function in OAG predicted progression and visual loss, might improvement in these key indicators mean? Would improvements in such indicator as observed following SDM MPL in dry AMD, indicating reversal of disease progression and thus a reduced risk of future visual loss in OAG? [11, 28, 55]. In the absence of known adverse treatment effects and a reasonable expectation of possible benefit, panmacular SDM MPL was thus offered to patients with OAG and glaucomatous optic neuropathy with visual field loss in hopes of slowing disease progression via neuroprotection [55]. To attempt to achieve the most direct measure of optic nerve function, eyes with OAG were also tested by the visually evoked potential (VEP), in addition to PERG and mesopic visual function testing.

Retinal Laser Treatment for OAG

To try to discover if panmacular SDM MPL was evoking any potentially neuroprotective effects in eyes with OAG, the electronic medical record was searched for eyes with OAG that had undergone SDM treatment [55]. These were then screened to further identify those eyes that had undergone VEP, PERG, and mesopic visual function testing both before, and within 3 months after, SDM treatment. 89 eyes of 49 patients with OAG were identified having been tested prior to SDM treatment. One eye of one patient was lost to follow up prior to obtaining postoperative studies, leaving 88 eyes of 48 consecutive patients for study. These were 20 male and 28 female, aged 57–94 (avg. 79). All patients had glaucomatous optic neuropathy and visual field loss prior to treatment. Most eyes had coincident retinopathies as the primary indication for SDM treatment. These included dry AMD [15 eyes]; wet AMD [7 eyes]; high myopia [17 eyes]; non-proliferative diabetic retinopathy [11 eyes]; and retinitis pigmentosa [2 eyes]. Several eyes had more than one concurrent retinopathy. Twelve eyes of six patients had only OAG without any other notable retinopathy. Pretreatment, IOPs ranged 6–23 mmHg (average: 13) on 0–3 (average: 1.6) medications. 33 eyes had had prior glaucoma filtering and/or tube shunt surgery. Snellen visual acuities (VA) ranged 20/15 to count fingers (median 20/60). Prior to treatment, both VEPs and mesopic visual function of all eyes were abnormal. Following SDM

MPL, Snellen VA was improved ($p = 0.005$) and IOP was unchanged. All VEP indices were improved following SDM treatment, with VEP P1 amplitudes ($p = 0.001$) significantly improved. MVF ($p < 0.0001$) and PERG central field amplitudes were also significantly improved ($p = 0.05$). There was no significant difference in the responses of the eyes with OAG alone, compared to eyes with OAG and coincident conventional retinopathies [55].

Although a small retrospective study, the results are remarkable and because they are novel and unanticipated, and thus highly informative as well [72]. Supporting key tenets of the reset theory of retinal laser action, these findings demonstrate what appear to be clear and unambiguous signs of effective neuroprotection in OAG, and demonstrating, for the first time, that a previously unidentified retinopathy (ROAG) may lie at the heart of OAG and account for the common failure of treatment by IOP lowering alone.

The mechanism of retinal laser has been described as causing a physiological reset, like the "reset to default" function of electronic devices, restoring the "factory settings" when the system becomes corrupted. Part and parcel with such an effect is that the initiator of such a process, in this case laser, necessarily acts as a "non-specific trigger of disease specific repair" as described above [27, 28, 57] (Fig. 14.1). The results of SDM for OAG appear to confirm this assertion. The reset theory of retinal laser action predicts that treatment will improve all chronic progressive retinopathies, but each in a characteristic way reflecting the nature of dysfunction caused by the underlying disease process. This is particularly evident in the electrophysiologic responses to SDM MPL [51]. In classic phenotypic retinopathies such as AMD and IRDs, the predominant PERG responses to treatment are reflected in improvements in signal latency. In AMD, low-contrast PERG responses are most significantly improved. This is consistent with the tendency of AMD to reduce contrast sensitivity early, and more than photopic chart acuity. [51]. In the IRDs, signal latencies are also improved. In the macular IRDs, improvements reflect the geographic distribution of the disease process; either predominantly central (such as in Stargardt's disease or advanced RP), or peripheral (such as in early RP). Interestingly, and reflecting the "disease-specific" improvements elicited by retinal laser, electrophysiology in OAG, while also improving post SDM, improved differently [28, 55].

While improving all aspects of electrophysiology, the most significant responses to panmacular SDM MPL in OAG were improved signal amplitudes rather than latencies. This was true for both the PERG and VEP. While all PERG responses improved, only the central 16° field amplitudes significantly improved. Why signal amplitude improvement predominated over latencies in OAG is unknown. The macular predominance of the PERG appears to simply reflect anatomy. Approximately 95% of the nerve fibers that coalesce to form the optic nerve arise in the macula, and most of those from the fovea. Thus, if treatment of the retina, such as SDM MPL which is selective for the RPE, were to somehow improve optic nerve function and be neuroprotective in OAG, it would almost have to improve macular function. This is also consistent with the finding that both the PERG and mesopic visual acuity are early predictors of OAG, as is macular ganglion cell complex loss, indicating early macular involvement in OAG [66].

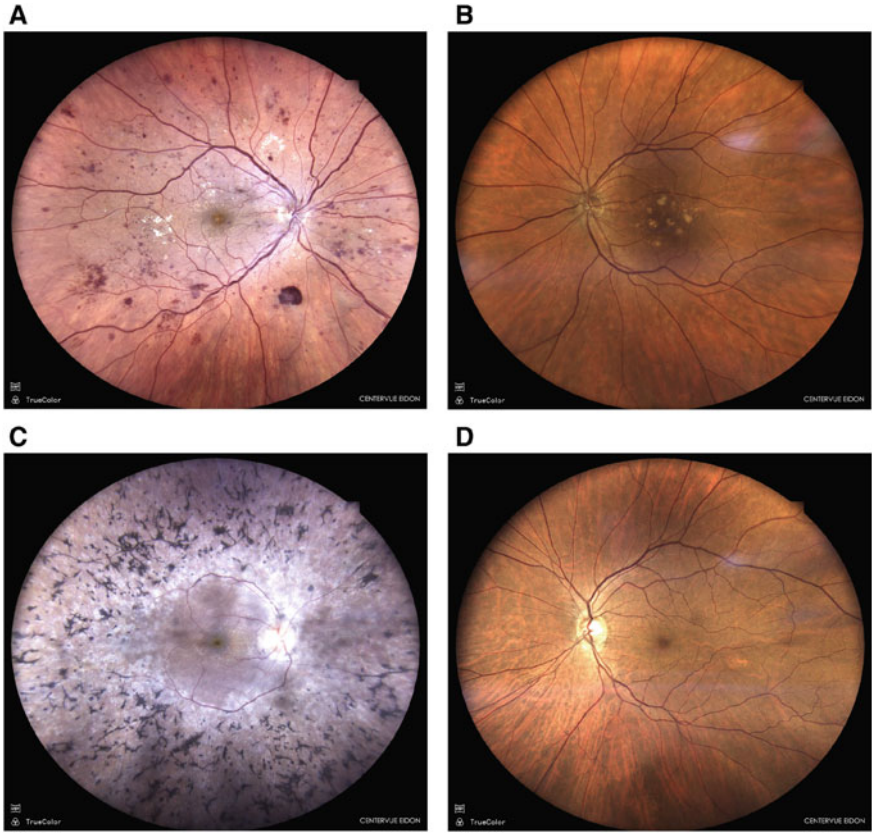
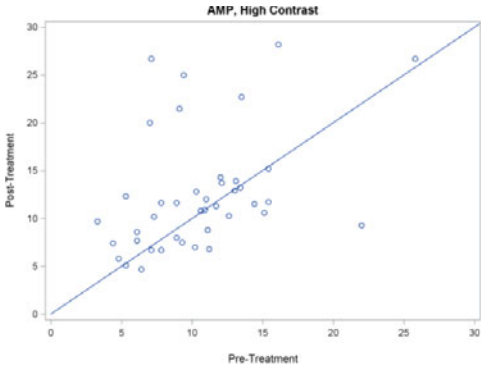


Fig. 14.1 **A** Diabetic retinopathy **B** Age-related macular degeneration. **C** Retinitis pigmentosa **D** Open angle glaucoma. All are neurodegenerations. The answer to each is neuroprotection

It is also very interesting is that SDM MPL improved the amplitudes of the high-contrast VEP P1 responses as well, and to a greater degree than the PERG. (Figs. 14.2 and 14.3) This finding is remarkable in that no treatment of any kind in any setting, laboratory or clinically, has previously been known to improve VEP responses. Thus, like the reversal of anti-VEGF drug tolerance in wet AMD, the ability of SDM MPL to improve VEP responses in OAG are unique in medicine, lending strong support to the reset theory of laser action and the restorative power of "low power" homeotrophic laser treatment in the macula [27].

Another point of interest is that despite concurrent conventional retinopathies in most of the eyes with OAG reported in this study, such as dry AMD, it was the OAG-specific electrophysiologic responses to treatment that predominated [55]. For example, in eyes with OAG and AMD, it was the OAG PERG signature (central 16° amplitude improvement) that predominated over the AMD-specific low-contrast signal latency improvement signature. It should be noted, however, that eyes with

A. Visually evoked potential (VEP) high-contrast amplitudes before and after panmacular subthreshold diode micropulse laser (SDM) treatment for open angle glaucoma.



B. VEP high contrast amplitudes, post – minus pre-treatment.

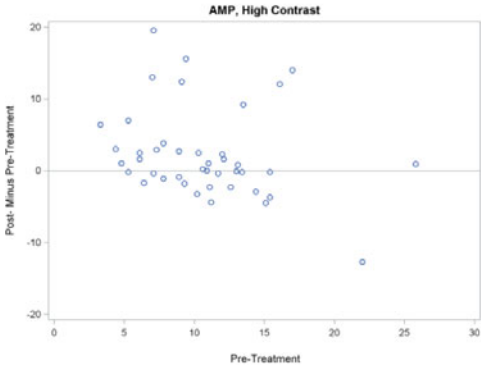


Fig. 14.2 **A** and **B** High-contrast visually evoked response amplitude responses to panmacular SDM laser in eyes with OAG and glaucomatous optic neuropathy. Note: significant improvements after treatment. From: Luttrull JK, Samples JR, Kent D, Lum BJ: Panmacular subthreshold diode micropulse laser (SDM) as neuroprotective therapy in primary open-angle glaucoma. Glaucoma Research 2018–2020, pp. 281–294 Edited by: John R. Samples and Paul A. Knepper © 2018 Kugler Publications, Amsterdam, The Netherlands

AMD and IRDs without OAG were not otherwise examined by VEP. Thus, it is possible, that VEP improvements may accompany treatment for the other, more conventional retinopathies, as well. One can argue that the best indicator of neuroprotection in the eye would be improved optic nerve function [2] Thus far, this effect appears to be unique to treatment of OAG with SDM MPL.

Finally, also reflecting the concept of retinal laser acting as a non-specific trigger of disease specific repair via the reset phenomenon, panmacular SDM MPL in OAG, like AMD and IRDs, produced highly significant improvements in MVF [11, 54] (Figs. 14.4 and 14.5) Because MVF is a more sensitive reflector of underlying macular function than high-contrast photopic chart acuity, it has been shown to abnormal

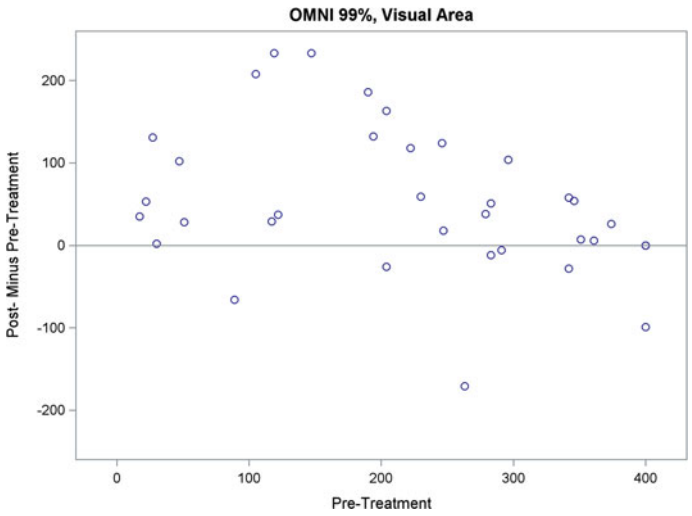


Fig. 14.3 Mesopic visual area before and after panmacular SDM laser in eyes with OAG and glaucomatous optic neuropathy. From: Luttrull JK, Samples JR, Kent D, Lum BJ: Panmacular subthreshold diode micropulse laser (SDM) as neuroprotective therapy in primary open-angle glaucoma. Glaucoma Research 2018–2020, pp. 281–294 Edited by: John R. Samples and Paul A. Knepper © 2018 Kugler Publications, Amsterdam, The Netherlands

early in OAG and all the other chronic progressive retinopathies. [68–71]. As visual function is the end result of retinal function, it would be expected to improve as the result of improvement in retinal function, regardless the nature of the retinal dysfunction and how that improvement was achieved. Thus, it is not surprising that retinal laser, improving AMD, IRDs, DR, and OAG each in different ways reflecting their different underlying disease processes, improves MVF in them all [11, 54, 55]. This makes MVF an especially useful and relatively simple and intuitive diagnostic test to not only detect early disease, but also to document and then follow to monitor treatment effects (Fig. 14.6).

Improvement in general retinal function, ganglion cell layer function, optic nerve function, mesopic and photopic visual function, and visual fields can only be described as reflecting neuroprotection [2]. The robust and predictable nature of these responses in all applications suggest that retinal laser, in the form of SDM MPL, is the first unambiguously neuroprotective treatment demonstrated in clinical ophthalmology. How were these neuroprotective effects produced, and what are the implications?

ROAG (the Retinopathy of Open Angle Glaucoma)

The mechanism of retinal laser treatment has been briefly reviewed above. Of all the findings of this study of retinal laser for neuroprotection in OAG, most interesting is that all improvements occurred in response to selective treatment of the RPE in

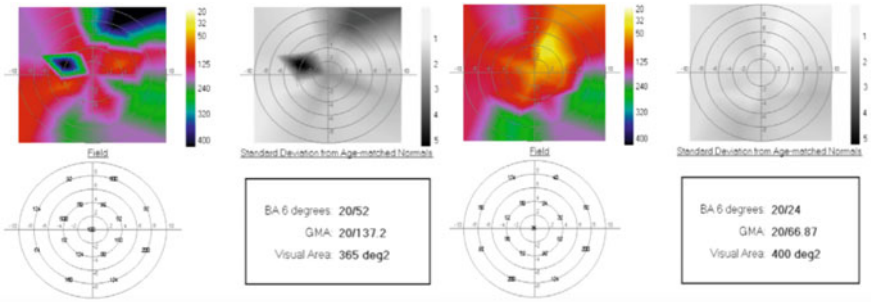


Fig. 14.4 Omnifield resolution perimetry (ORP) (Sinclair Technologies, Media, PA) of an eye with OAG and glaucomatous optic neuropathy before (**A**) and after (**B**) panmacular SDM MPL. ORP measures ETDRS VA at various intercepts in the posterior retina 10° surrounding fixation and builds a false color VA map to create a mesopic visual field. Note: improvement following SDM. From: Luttrull JK, Samples JR, Kent D, Lum BJ: Panmacular subthreshold diode micropulse laser (SDM) as neuroprotective therapy in primary open-angle glaucoma. Glaucoma Research 2018–2020, pp. 281–294 Edited by: John R. Samples and Paul A. Knepper © 2018 Kugler Publications, Amsterdam, The Netherlands

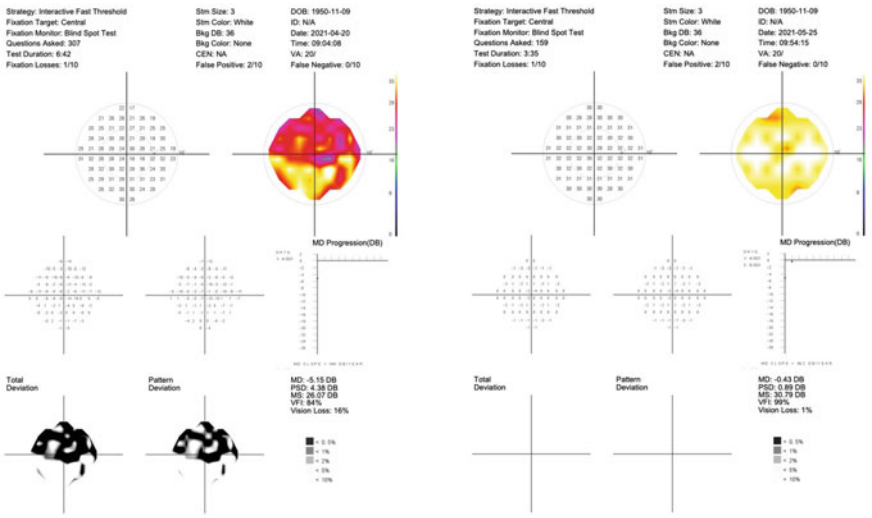


Fig. 14.5 10–2 automated perimetry modified to report as a false color map of retinal sensitivity, before (left) and after (right) panmacular SDM laser for an eye with OAG and glaucomatous optic neuropathy. Note improvement following treatment

eyes with no discernable retinopathy, other than glaucomatous optic neuropathy, by SDM MPL [11, 55]. The effect of retinal laser is homeotrophy—restoration of functional normality via the reset phenomenon [27, 28]. This is important because the response to laser treatment of the RPE in OAG reveals the presence of an acquired RPE dysfunction. Because normalization of this RPE dysfunction by laser improves

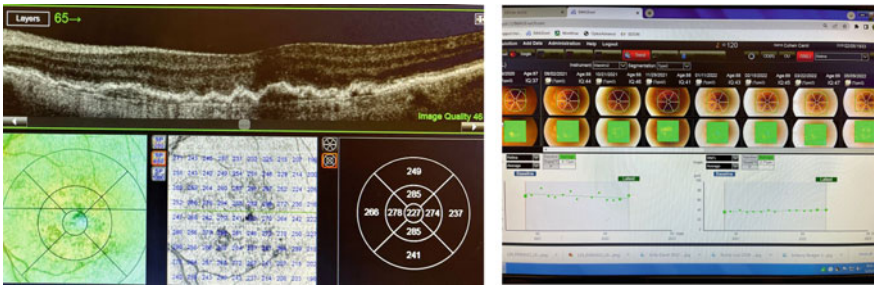


Fig. 14.6 Optic coherence tomography of an eye with AMD undergoing regular periodic panmacular SDM MPL for neuroprotection. Note thickening of the nerve fiber layer over time, while the average retinal thickness decreases due to thinning of the Bruch's membrane/RPE complex

ganglion cell and optic nerve function by electrophysiology, the laser treatment response suggests this retinopathy is a fundamental part of OAG and that a principal result of this retinopathy is insufficient retina-derived neurotrophy [11, 29, 55]. This may consist of either insufficient production of a neurotropic factor(s) essential to normal health and function of the optic nerve, overproduction of a factor(s) toxic to nerve function, or a pathologic imbalance of factors leading to premature nerve death. In any case, the response of OAG to SDM MPL treatment of the macular RPE indicates that OAG is a chronic progressive retinopathy and neurodegeneration, joining the ranks of AMD, DR, and IRDs. We can call it "ROAG", for Retinopathy of Open Angle Glaucoma" [11, 55]. This laser-induced neuroprotection may reflect normalization of abnormal retinal conditions already identified in glaucomatous eyes. These include the tumor necrosis factor TNF-alpha/TNFR1, complement component 1Q (C1Q), or some combination of both [11, 27, 28, 55, 73–80]. The mediators of this dysfunction, and functional normalization, are chemical. These are principally cytokines, interleukins, and other RPE mediated or modulated factors. In this, ROAG echoes the other neurodegenerations / chronic progressive retinopathies, in which disease states may either express, or arise from, an excess or paucity of a specific factor(s), or an imbalance of factors, such as the relative levels of VEGF and PEDF in diabetic retinopathy [3, 8, 81, 82].

Reset Non-fragility

The RPE is largely responsible for maintaining the day-to-day normal operation and autoregulation of the retina [29]. The power and elegance of the reset mechanism of retinal laser treatment is that rather than needing to identify and effectively target, block, enhance or replace specific chemical mediators to reverse a disease process, the reset effect retinal laser instead corrects the source of the chemical mediators of retinal function and dysfunction—the RPE [27–29]. By improving RPE function with little regard (agnosticism) to the primary cause of the dysfunction (age, diabetes,

a faulty gene), downstream abnormalities, such as cytokine expression, balance, and response, are also normalized. The reset phenomenon thus allows one to "fix" the problem without having to know exactly what the problem is, what is causing it, or how it is causing it. This is a powerful property of retinal laser called "anti-fragility" that sets it apart from targeted therapies, which are highly dependent on very narrowly defined but often highly variable conditions and circumstances, requiring a precise understanding of the pathophysiology, thus making targeted therapies vulnerable to innumerable factors that may compromise effectiveness [82].

Much more study on the utility and effects of retinal laser treatment for neuroprotection needs to be done. The surprising finding that optic nerve function can be improved, and improved by laser treatment of the macula, is just one of many examples of unprecedented and previously unanticipated findings resulting from understanding the reset mechanism of retinal laser action and following it to its various conclusions. For instance, progressive thickening of the nerve fiber layer over time in eyes receiving regular periodic panmacular SDM MPL ("vision protection therapy") for neuroprotection has been observed (JKL 2022, unpublished data), suggesting effective neuroprotection may result in anatomic improvement and restoration (neuroregeneration?) as a result of improved neuroretinal function. This is one of many apparently novel finding that warrants further exploration (Fig. 6).

Sometimes disruption takes time. The finding that photocoagulation was a complication, and not the essential property, of retinal laser treatment was disruptive. This led to an understanding of the mechanism of action of retinal laser treatment, and to the fact that retinal laser treatment could harmlessly improve retinal function directly where it was applied. Disruption. Where will the ability of retinal laser treatment to produce neuroprotection lead? Can effective neuroprotection improve anatomy, such as nerve fiber layer thickness, as well as function? Laser neuroprotection in classic chronic progressive retinopathies is clearly highly effective. Will it improve management and visual outcomes in eyes with ROAG? If so, more disruption. Time, open minds, and a great deal more study, will tell us.

References

1. GBD 2019 Blindness and Vision Impairment Collaborators; Vision Loss Expert Group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. Lancet Glob Health. 2021;9(2):e144–e160. https://doi.org/10.1016/S2214-109X(20)30489-7. Epub 2020 Dec 1. Erratum in: Lancet Glob Health. 2021 Apr;9(4):e408. PMID: 33275949; PMCID: PMC7820391.
2. Levin LA, Crowe ME, Quigley HA. Lasker/IRRF initiative on astrocytes and glaucomatous neurodegeneration participants. neuroprotection for glaucoma: requirements for clinical translation. Exp Eye Res. 2017;157:34–37. https://doi.org/10.1016/j.exer.2016.12.005. Epub 2016 Dec 9. PMID: 27955999; PMCID: PMC5413382.
3. Sinclair SH, Schwartz SS. Diabetic retinopathy-an underdiagnosed and undertreated inflammatory, neuro-vascular complication of diabetes. Front Endocrinol (Lausanne). 2019;10:843. https://doi.org/10.3389/fendo.2019.00843. eCollection 2019.PMID: 31920963.

4. Turner ME, Pratkanis AR. Twenty-five years of groupthink theory and research: lessons from the evaluation of a theory. Organ Behav Hum Decis Process.1998; 73 (2–3):105–115.
5. Hall J, Matos S, Gold S, Severino LS. The paradox of sustainable innovation: the "Eroom" effect (Moore's law backwards). J Clean Prod. 2018;172:3487–97. https://doi.org/10.1016/j.jclepro.2017.07.162.ISSN0959-6526.
6. Knopman DS, Jones DT, Greicius MD. Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. Alzheimers Dement. 2021;17(4):696–701. https://doi.org/10.1002/alz.12213. 2020 Nov 1 PMID: 33135381.
7. Baumal CR, Spaide RF, Vajzovic L, Freund KB, Walter SD, John V, Rich R, Chaudhry N, Lakhanpal RR, Oellers PR, Leveque TK, Rutledge BK, Chittum M, Bacci T, Enriquez AB, Sund NJ, Subong ENP, Albini TA. Retinal Vasculitis and Intraocular Inflammation after Intravitreal Injection of Brolucizumab. Ophthalmology. 2020;127(10):1345–59. https://doi.org/10.1016/j.ophtha.2020.04.017. 2020 Apr 25 PMID: 32344075.
8. Marmolejo-Martínez-Artesero S, Casas C, Romeo-Guitart D. Endogenous mechanisms of neuroprotection: to boost or not to be. Rev Cells. 2021;10:370. https://doi.org/10.3390/cells10020370
9. Paul S, Candelario-Jalil E. Emerging neuroprotective strategies for the treatment of ischemic stroke: an overview of clinical and preclinical studies. Exp Neurol. 2021 Jan;335:113518. https://doi.org/10.1016/j.expneurol.2020.113518. Epub 2020 Nov 2. PMID: 33144066; PMCID: PMC7869696.
10. Sena DF, Lindsley K. Neuroprotection for treatment of glaucoma in adults. Cochrane Database Syst Rev. 2013 Feb 28;2(2):CD006539. https://doi.org/10.1002/14651858.CD006539.pub3. Update in: Cochrane Database Syst Rev. 2017 Jan 25;1:CD006539. PMID: 23450569; PMCID: PMC4261923.
11. Luttrull JK, Kent D. Modern retinal laser for neuroprotection in open-angle glaucoma. In: Samples JR, Ahmed IIK, eds. New concepts in glaucoma surgery, vol 1. Amsterdam: Kugler Publications; 2019 ISBN-13: 978-1461483472, ISBN-10: 1461483476
12. Muste JC, Russell MW, Singh RP. Photobiomodulation therapy for age-related macular degeneration and diabetic retinopathy: a review. Clin Ophthalmol. 2021;2(15):3709–20. https://doi.org/10.2147/OPTH.S272327.PMID:34511875;PMCID:PMC8421781.
13. Markowitz SN, Devenyi RG, Munk MR, Croissant CL, Tedford SE, Rückert R, Walker MG, Patino BE, Chen L, Nido M, Tedford CE. A double-masked, randomized, sham-controlled, single-center study with photobiomodulation for the treatment of dry age-related macular degeneration. Retina. 2020;40(8):1471–82. https://doi.org/10.1097/IAE.0000000000002632.PMID:31404033;PMCID:PMC7392581.
14. Kim JE, Glassman AR, Josic K, Melia M, Aiello LP, Baker C, Eells JT, Jampol LM, Kern TS, Marcus D, Salehi-Had H, Shah SN, Martin DF, Stockdale CR, Sun JK; DRCR Retina network. a randomized trial of photobiomodulation therapy for center-involved diabetic macular edema with good visual acuity (Protocol AE). Ophthalmol Retina. 2022 Apr;6(4):298–307. https://doi.org/10.1016/j.oret.2021.10.003. Epub 2021 Oct 8. PMID: 34628066; PMCID: PMC9011341.
15. Chhablani J, Roh YJ, Jobling AI, Fletcher EL, Lek JJ, Bansal P, Guymer R, Luttrull JK. Restorative retinal laser therapy: Present state and future directions. Surv Ophthalmol. 2018;63(3):307–328
16. Dorin G. Subthreshold and micropulse diode laser photocoagulation. Semin Ophthalmol. 2003;18:147–53.
17. Chang DB, Luttrull JK. Comparison of subthreshold 577nm and 810nm micropulse laser effects on heat-shock protein activation kinetics: Implications for treatment efficacy and safety. Transl Vis Sci Tecnol. 2020;9(5):23. https://doi.org/10.1167/tvst.9.5.23.eCollection.
18. Krypton laser photocoagulation for neovascular lesions of age-related macular degeneration: results of a randomized clinical trial. Macular Photocoagulation Study Group. Arch Ophthalmol. 1990;108(6):816–24. https://doi.org/10.1001/archopht.1990.01070080058036. PMID: 1693496.

19. Blankenship GW. Red krypton and blue-green argon panretinal laser photocoagulation for proliferative diabetic retinopathy: a laboratory and clinical comparison. Trans Am Ophthalmol Soc. 1986;84:967–1003. PMID: 2438841; PMCID: PMC1298756.
20. Keunen JEE, Battaglia-Parodi M, Vujosevic S, Luttrull JK. International retinal laser society guidelines for subthreshold laser treatment. Transl Vis Sci Technol. 2020;9(9):15. https://doi.org/10.1167/tvst.9.9.15. eCollection 2020 Aug.PMID: 32879771.
21. Mainster MA. Decreasing retinal photocoagulation damage: principles and techniques. Semin Ophthalmol. 1999; 14:200e9
22. Luttrull JK, Musch MC, Mainster MA. Subthreshold diode micropulse photocoagulation for the treatment of clinically significant diabetic macular edema. Br J Ophthalmol. 2005;89(1):74–80.
23. Vujosevic S, Bottega E, Casciano M, Pilotto E, Convento E, Midena E. Microperimetry and fundus autofluorescence in diabetic macular edema: subthreshold micropulse diode laser versus modified early treatment diabetic retinopathy study laser photocoagulation. Retina. 2010;30(6):908–16. https://doi.org/10.1097/IAE.0b013e3181c96986. PMID: 20168272.
24. Luttrull JK, Sramek C, Palanker D, Spink CJ, Musch DC. Long-term safety, high-resolution imaging, and tissue temperature modeling of subvisible diode micropulse photocoagulation for retinovascular macular edema. Retina. 2012;32(2):375–86.
25. Luttrull JK, Dorin G. Subthreshold diode micropulse photocoagulation as invisible retinal phototherapy for diabetic macular edema a review. Current Diabetes Rev. 2012;8:274–84.
26. Luttrull JK, Sinclair SD. Safety of transfoveal subthreshold diode micropulse laser for intrafoveal diabetic macular edema in eyes with good visual acuity. Retina. 2014;34(10):2010–20.
27. Reza FM. An introduction to information theory. New York: Dover Publications, Inc.; (1994)[1961]. ISBN 0-486-68210-2
28. Luttrull JK, Chang DB, Margolis BWL, Dorin G, Luttrull DK. Laser re-sensitization of medically unresponsive neovascular age-related macular degeneration: efficacy and implications. Retina. 2015;35(6):1184–94.
29. Midena E, Bini S, Martini F, Enrica C, Pilotto E, Micera A, Esposito G, Vujosevic S. Changes of aqueous humor Muller cells' biomarkers in human patients affected by diabetic macular edema after subthreshold micropulse laser treatment. Retina. 2020;40(1):126–34. https://doi.org/10.1097/IAE.0000000000002356. PMID: 30300267.
30. Kern K, Mertineit CL, Brinkmann R, Miura Y. Expression of heat shock protein 70 and cell death kinetics after different thermal impacts on cultured retinal pigment epithelial cells. Exp Eye Res. 2018;170:117–26. https://doi.org/10.1016/j.exer.2018.02.013. 2018 Feb 16 PMID: 29454858.
31. Richert E, Papenkort J, von der Burchard C, Klettner A, Arnold P, Lucius R, Brinkmann R, Framme C, Roider J, Tode J. Selective retina therapy and thermal stimulation of the retina: different regenerative properties-implications for AMD therapy. BMC Ophthalmol. 2021;21(1):412. https://doi.org/10.1186/s12886-021-02188-8.PMID:34847865;PMCID:PMC8630886.
32. Kregel K. Invited review: heat shock proteins: modifying factors in physiological stress responses and acquired thermotolerance. J Appl Physiol. 2002; 5(92):2177±2186
33. Saibil H. Chaperone machines for protein folding, unfolding and disaggregation. Nat Rev Mol Cell Biol. 2013;14(10):630–42. https://doi.org/10.1038/nrm3658. Epub 2013 Sep 12. PMID: 24026055; PMCID: PMC4340576.
34. Dokladny K, Myers OB, Moseley PL. Heat shock response and autophagy–cooperation and control. Autophagy. 2015;11(2):200–13. https://doi.org/10.1080/15548627.2015.1009776.PMID:25714619;PMCID:PMC4502786.
35. San Gil R, Ooi L, Yerbury JJ, Ecroyd H. The heat shock response in neurons and astroglia and its role in neurodegenerative diseases. Mol Neurodegener. 2017;12(1):65. https://doi.org/10.1186/s13024-017-0208-6.PMID:28923065;PMCID:PMC5604514.
36. Hasday JD, Singh IS. Fever and the heat shock response: distinct, partially overlapping processes. Cell Stress Chaperones. 2000;5(5):471–80. https://doi.org/10.1379/1466-1268(2000)005%3c0471:fathsr%3e2.0.co;2.PMID:11189454;PMCID:PMC312879.

37. Beckham JT. The role of heat shock protein 70 in laser irradiation and thermal preconditioning. PhD dissertation, Vanderbilt University Biomedical Engineering (2008)
38. Rybinski M, Szymanska Z, Lasota S, Gambin A. Modeling the efficacy of hyperthermia treatment. J R Soc Interface. 2013;10(88):20130527.
39. Szymanska Z, Zylicz M. Mathematical modeling of heat shock protein synthesis in response to temperature change. J Theo Bio. 2009;259(3):562–9. https://doi.org/10.1016/j.jtbi.2009.03.021.
40. Richter K, Haslbeck M, Buchner J. The heat shock response: life on the verge of death. Mol Cell. 2010;40(2):253–66.
41. Gao X, Xing D. Molecular mechanisms of cell proliferation induced by low power laser irradiation. J Biomed Sci. 2009;16:4. Epub 2009/03/11. https://doi.org/10.1186/1423-0127-16-4. PubMed PMID: 19272168; PubMed Central PMCID: PMCPMC2644974.
42. Morimoto RI. Cell-nonautonomous regulation of proteostasis in aging and disease. Cold Spring Harb Perspect Biol. 2020;12(4): a034074. https://doi.org/10.1101/cshperspect.a034074.PMID:30962274;PMCID:PMC711124.
43. Caballero S, Kent DL, Sengupta N, Li S, Shaw L, Beli E, Moldovan L, Dominguez JM 2nd, Moorthy RS, Grant MB. Bone marrow-derived cell recruitment to the neurosensory retina and retinal pigment epithelial cell layer following subthreshold retinal phototherapy. Invest Ophthalmol Vis Sci. 2017;58(12):5164–76. https://doi.org/10.1167/iovs.16-20736.PMID:29049716;PMCID:PMC5636205.
44. De Cillà S, Vezzola D, Farruggio S, Vujosevic S, Clemente N, Raina G, Mary D, Casini G, Rossetti L, Avagliano L, Martinelli C, Bulfamante G, Grossini E. The subthreshold micropulse laser treatment of the retina restores the oxidant/antioxidant balance and counteracts programmed forms of cell death in the mice eyes. Acta Ophthalmol. 2019;97(4):e559–67. https://doi.org/10.1111/aos.13995. 2018 Dec 26 PMID: 30585429.
45. Iwami H, Pruessner J, Shiraki K, Brinkmann R, Miura Y. Protective effect of a laser-induced sub-lethal temperature rise on RPE cells from oxidative stress. Exp Eye Res. 2014;124:37–47. https://doi.org/10.1016/j.exer.2014.04.014. 2014 May 5 PMID: 24800654.
46. Frizziero L, Calciati A, Midena G, Torresin T, Parrozzani R, Pilotto E, Midena E. Subthreshold micropulse laser modulates retinal neuroinflammatory biomarkers in diabetic macular edema. J Clin Med. 2021;10(14):3134. https://doi.org/10.3390/jcm10143134.PMID:34300297;PMCID:PMC8304624.
47. Frizziero L, Calciati A, Torresin T, Midena G, Parrozzani R, Pilotto E, Midena E. Diabetic macular edema treated with 577-nm subthreshold micropulse laser: a real-life, long-term study. J Pers Med. 2021;11(5):405. https://doi.org/10.3390/jpm11050405.PMID:34067994;PMCID:PMC8152245.
48. Schroder M, Kaufman RJ. The mammalian unfolded protein response. Ann Rev Biochem. 2005;74:739–89.
49. Midena E, Bini S, Frizziero L, Pilotto E, Esposito G, Micera A. Aqueous humour concentrations of PEDF and Erythropoietin are not influenced by subthreshold micropulse laser treatment of diabetic macular edema. Biosci Rep. 2019;39(6):BSR20190328. https://doi.org/10.1042/BSR20190328. PMID: 31138761; PMCID: PMC6579974.
50. Midena E, Micera A, Frizziero L, Pilotto E, Esposito G, Bini S. Sub-threshold micropulse laser treatment reduces inflammatory biomarkers in aqueous humour of diabetic patients with macular edema. Sci Rep. 2019;9(1):10034. https://doi.org/10.1038/s41598-019-46515-y.PMID:31296907;PMCID:PMC6624368.
51. Lavinsky D, Chalberg TW, Mandel Y, Huie P, Dalal R, Marmor M, Palanker D. Modulation of transgene expression in retinal gene therapy by selective laser treatment. Invest Ophthalmol Vis Sci. 2013;54(3):1873–80. https://doi.org/10.1167/iovs.12-10933. PMID: 23422827.
52. Raina G, Mary D, Casini G, Rossetti L, Avagliano L, Martinelli C, Bulfamante G, Grossini E. The subthreshold micropulse laser treatment of the retina restores the oxidant/antioxidant balance and counteracts programmed forms of cell death in the mice eyes. Acta Ophthalmol. 2019;97(4):e559–67.

53. Luttrull JK, Margolis BWL. Functionally guided retinal protective therapy as prophylaxis for age-related and inherited retinal degenerations: a pilot study. Invest Ophthalmol Vis Sci. 2016;57(1):265–75. https://doi.org/10.1167/iovs.15-18163
54. Luttrull JK. Improved retinal and visual function following subthreshold diode micropulse laser (SDM) for retinitis pigmentosa. Eye (London) Feb 2018 PAP open access https://doi.org/10.1038/s41433-018-0017-3
55. Luttrull JK, Samples JR, Kent D, Lum BJ: Panmacular subthreshold diode micropulse laser (SDM) as neuroprotective therapy in primary open-angle glaucoma. In: Samples JH, Knepper PA, editors. Glaucoma Research 2018–2020. The Netherlands, Amsterdam: Kugler Publications, p 281–294
56. Van Rijssen TJ, van Dijk EHC, Scholz P, Breukink MB, Blanco-Garavito R, Souied EH, Kuenen JEE, MacLaren RE, Querques G, Fauser S, Downes SM, Hoyng CB, Boon CJF. Focal and diffuse chronic central serous chorioretinopathy treated with half-dose photodynamic therapy or subthreshold micropulse laser: place trial report No. 3. Am J Ophthalmol. 2019;205:1–10. https://doi.org/10.1016/j.ajo.2019.03.025. Epub 2019 Apr 3
57. Luttrull JK. "Comment on: van Rijssen TJ, van Dijk EHC, Scholz P, et al. PLACE Trial Report No. 3" (Letter). Am J Ophthalmol 2020;212:186–187
58. Battaglia Parodi M, Iacono P, van Dijk EH et al. Half-dose photodynamic therapy versus high-density subthreshold micropulse laser treatment in patients with chronic central serous chorioretinopathy: the PLACE trial (Ophthalmology. 2018; 125:1547–1555). Ophthalmology. 2019;126(4):e29–e30. https://doi.org/10.1016/j.ophtha.2018.11.004
59. Filadi R, Pizzo P. Key signalling molecules in aging and neurodegeneration. Cells. 2022;11(5):834. https://doi.org/10.3390/cells11050834.PMID:35269456;PMCID:PMC8909535.
60. Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Bendedictis G. Inflamm-aging: an evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244–54.
61. Smith HL, Mallucci GR. The unfolded protein response: mechanisms and therapy of neurodegeneration. Brain. 2016;139(Pt 8):2113–21. https://doi.org/10.1093/brain/aww101. Epub 2016 May 11. PMID: 27190028; PMCID: PMC4958893.
62. Melo EP, Konno T, Farace I, Awadelkareem MA, Skov LR, Teodoro F, Sancho TP, Paton AW, Paton JC, Fares M, Paulo PMR, Zhang X, Avezov E. Stress-induced protein disaggregation in the endoplasmic reticulum catalysed by BiP. Nat Commun. 2022;13(1):2501. https://doi.org/10.1038/s41467-022-30238-2.PMID:35523806;PMCID:PMC9076838.
63. Levkovitch-Verbin H, Vander S, Makarovsky D, Lavinsky F. Increase in retinal ganglion cells' susceptibility to elevated intraocular pressure and impairment of their endogenous neuroprotective mechanism by age. Mol Vis. 2013;19:2011–22. PMID: 24146536; PMCID: PMC3783363.
64. Romeo-Guitart D, Marmolejo-Martínez-Artesero S, Casas C. Is it the time of autophagy fine-tuners for neuroprotection? Autophagy. 2020;16(11):2108–2109. https://doi.org/10.1080/15548627.2020.1794355. Epub 2020 Jul 17. PMID: 32677502; PMCID: PMC7595645.
65. Fan YY, Hu WW, Nan F, Chen Z. Postconditioning-induced neuroprotection, mechanisms and applications in cerebral ischemia. Neurochem Int. 2017;107:43–56. https://doi.org/10.1016/j.neuint.2017.01.006. 2017 Jan 11 PMID: 28087295.
66. Yang X, Luo C, Cai J, et al. Neurodegenerative and inflammatory pathway components linked to TNF-alpha/TNFR1 signaling in the glaucomatous human retina. Invest Ophthalmol Vis Sci. 2011;52(11):8442–54. https://doi.org/10.1167/iovs.11-8152. PMID:21917936.
67. Ventura LM, Porciatti V. Restoration of retinal ganglion cell function in early glaucoma after intraocular pressure reduction: a pilot study. Ophthalmology. 2005;112:20–7.
68. Stockman A, Sharpe LT. Into the twilight zone: the complexities of mesopic vision and luminous efficiency. Ophthalmic Physiol Opt. 2006;26:225–39.
69. Lin RJ, Ng JS, Nguyen AL. Determinants and standardization of mesopic visual acuity. Optom Vis Sci. 2015;92(5):559–65.

70. Puell MC, Barrio AR, Palomo C, Gómez-Sanz FJ, Clement-Corral A, Pérez-Carrasco MJ. Impaired mesopic visual acuity in eyes with early age-related macular degeneration. Invest Ophthalmol Vis Sci. 2012;53(11):7310–4. https://doi.org/10.1167/iovs.11-8649
71. Puell MC, Pérez-Carrasco MJ, Palomo AC. Macular thickness and mesopic visual acuity in healthy older subjects. Curr Eye Res. 2018;10:1–7. https://doi.org/10.1080/02713683.2018.1522648.
72. Kolomyer AM, Zarbin MA. Trophic factors in the pathogenesis and therapy for retinal degenerative diseases. Survey Ophthalmol. 2014; (59):135±165.
73. Kuehn MH, Kim CY, Jiang B, Dumitrescu AV, Kwon YH. Disruption of the complement cascade delays retinal ganglion cell death following retinal ischemia-reperfusion. Exp Eye Res. 2008;87(2):89–95. https://doi.org/10.1016/j.exer.2008.04.012. PMID:18572163.
74. Kuehn MH, Kim CY, Ostojic J, Bellin M, Alward WL, Stone EM, et al. Retinal synthesis and deposition of complement components induced by ocular hypertension. Exp Eye Res. 2006;83(3):620–8. https://doi.org/10.1016/j.exer.2006.03.002. PMID:16677633.
75. Sawada H, Fukuchi T, Tanaka T, Abe H. Tumor necrosis factor- alpha concentrations in the aqueous humor of patients with glaucoma. Invest Ophthalmol Vis Sci. 2010;51(2):903–6. https://doi.org/10.1167/iovs.09-4247. PMID:19737888.
76. Stasi K, Nagel D, Yang X, et al. Complement component 1Q (C1Q) upregulation in retina of murine, primate, and human glaucomatous eyes. Invest Ophthalmol Vis Sci. 2006;47(3):1024–9. https://doi.org/10.1167/iovs.05-0830. PMID:16505037.
77. Steele MR, Inman DM, Calkins DJ, Horner PJ, Vetter ML. Microarray analysis of retinal gene expression in the DBA/2J model of glaucoma. Invest Ophthalmol Vis Sci. 2006;47(3):977–85. https://doi.org/10.1167/iovs.05-0865. PMID:16505032.
78. Tezel G, Li LY, Patil RV, Wax MB. TNF-alpha and TNF-alpha receptor-1 in the retina of normal and glaucomatous eyes. Invest Ophthalmol Vis Sci. 2001;42(8):1787–94 PMID:11431443.
79. Tezel G, Yang X, Luo C, Cai J, Powell DW. An astrocyte-specific proteomic approach to inflammatory responses in experimental rat glaucoma. Invest Ophthalmol Vis Sci. 2012
80. Zhang SX, Wang JJ, Gao G, Parke K, Ma JX. Pigment epithelium-derived factor downregulates vascular endothelial growth factor (VEGF) expression and inhibits VEGF-VEGF receptor 2 binding in diabetic retinopathy. J Mol Endocrinol. 2006;37(1):1–12. https://doi.org/10.1677/jme.1.02008. PMID: 16901919.
81. Kaviarasan K, Jithu M, Arif M, Sharma T, Sivasankar S, Das UN, Angayarkanni N. Low blood and vitreal BDNF, LXA4 and altered Th1/Th2 cytokine balance are potential risk factors for diabetic retinopathy. Metabolism. 2015;64(9):958–66. https://doi.org/10.1016/j.metabol.2015.04.005. 2015 May 1 PMID: 26004392.
82. Taleb NN. Antifragile: things that gain from disorder. New York: Random House; 2012. p. 430. ISBN 9781400067824.

Chapter 15
Laser in Treatment of Retinal Artery Occlusions

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Introduction

Retinal artery occlusion (RAO), including its two major entities central (CRAO) and branch retinal artery occlusion (BRAO), which was first described by the German ophthalmologist von Graefe in 1859 [1], is an acute interruption of blood flow in the blood supply system to the retina and its branches. It imposes a high risk for development of infarction in the inner retinal layers. Sudden decrease of visual function as low as hand movement or light perception is a very common presenting sign. The condition usually affects only one eye and requires an urgent ophthalmic care,

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Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/978-3-031-25779-7_15.

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_15

especially when the macular area is involved [2, 3]. Most often the event occurs in patients with atherosclerotic changes in the cardiovascular system, or presence of hypertension, temporal artery- and/or rheumatic heart- disease [2–4]. In the case of impaired blood flow for more than 100 min, an extensive irreversible damage to the retina occurs with significant loss of vision [2, 5–7]. Majority of people have solely the central retinal artery as the only artery feeding the inner retina. Only 15–30% of people have a cilioretinal artery—a backup source that can provide adequate blood flow to the macula in case of acute CRAO [8, 9]. The latter patients have for that reason the best visual prognosis [10]. In 70–85% of the people without a cilioretinal artery, CRAO most often leads to irreversible vision loss [5, 8–10]. Spontaneous vision recovery after CRAO is also described, but appears to be extremely rare. Occlusion of the central retinal artery is found in 1 in 100,000 people. Males are twice as likely to have it as females. People over 60 are at risk. CRAO is present in 56% of the cases, while BRAO and cilioretinal artery occlusion is found in 40% and 4%, respectively [5, 9–12].

Etiology. Emboli that are carried into the central retinal artery or one of its branches are suspected to be the cause of RAO. These emboli may be thrombi, cholesterol plaques, or calcified emboli originating from the heart valves or carotid plaques [13, 14]. Hollenhorst was able to identify orange-yellow plaques at the vascular bifurcations in 11% of the patients with RAO [15]. To the main causes of RAO belong atherosclerotic thrombosis at the level of the lamina cribrosa (80%), carotid embolism with cholesterol, fibrinous or calcified emboli in the bifurcation of the common carotid artery, giant cell arteritis, rheumatoid arthritis, periarteritis and thrombophlebitis [9, 12–14]. Retinal migraine is a rare condition which is possibly related to CRAO in young people [11]. CRAO is associated with ipsilateral stenosis of the internal carotid artery. A study of 103 cases of CRAO have shown that 37% of the patients had $\geq$70% stenosis, arterial dissection, or intraarterial thrombus [16]. In the EAGLE study, 77 out of 84 patients who underwent a thorough examination, 31 (40%) had carotid artery stenosis with $\geq$ 70% of vascular occlusion [17–19]. During the vascular examination, it was concluded that emboli in the CRAO cases could arise from the heart, aortic arch or large vessels. The EAGLE study identified high cardiovascular risk factors: obesity (82%), hypertension (73%), smoking (49%), hypercholesterolemia (49%) and diabetes (14%) in the 77 patients. Among all examined subjects, 67% had at least 1 risk factor for CRAO. It is also important to note that 20% of patients had cardiac arrhythmia, 17% had heart valve disease, and 5% had heart failure [17, 18].

Diagnosis and ophthalmic examinations. CRAO is manifested by a sudden, painless and extensive violation of the field of view or the relevant sector. Having varying degrees of vision loss, more than 80% of patients have best corrected visual acuity (BCVA) counting finger or worse [8–10, 12]. In the case the blood supply of a cilioretinal artery is preserved, the central visual acuity is maintained, but the peripheral visual field is constricted [8]. Visual field testing can show the defects of central and peripheral vision: sectoral or central scotomas corresponding to the ischemic area of the retina, as well as concentric narrowing of the visual field. However, the central visual field testing is usually not reproducible at the time of presentation.

Biomicroscopy of the eye allows to pre-determine the degree of occlusion of the CRAO. For example, in incomplete arterial occlusion, an afferent pupillary defect (Marcus-Gunn pupil) could be detected. In the case of total arterial occlusion—the pupil's response to light is absent or sharply reduced. Ophthalmoscopy examination of the fundus helps to detect retinal edema, its loss of transparency, and paleness of the retina in the affected area. Typical signs of CRAO are a cherry red spot fundoscopic finding—a bright colored appearance of *fovea centralis* due to choroidal blood supply and slow segmental blood flow in the retinal arteries, with direct visualization of emboli being possible in <10% of the cases. The optic disc usually looks normal. Additionally, retinal arterioles could be narrowed and the emboli of different origin could be seen in the area of occlusion.

Fluorescence angiography (FA) of the retina is used to clarify the location of the occlusion and to understand the degree of blockage of a vascular circulation. Usually, FA imaging shows delay of the filling of arteries and indistinct borders of background (choroidal) fluorescence within the involved area with retinal edema being observed [20]. Optical coherence tomography (OCT) is being used to assess the severity of the acute phase of CRAO or BRAO, which presents with increased thickness and reflectivity of the inner retina layers and a decreased reflectivity of the outer retinal layers, the outer layer of the retina and the retinal pigmented epithelium/choriocapillaris layer. Unlike acute onset RAO, chronic occlusion is characterized by diffuse atrophy and thinning of the inner retinal layers [21].

Beside ophthalmologic examination, the patients should be referred to a stroke center and cardiologist, where they will undergo duplex scanning of the carotid arteries, ultrasound of the heart to determine their cardiovascular disorder risks. Presently, CRAO is treated as a micro-stroke [22]. According to a recent study, 12.1% of the patients had evidence of an acute stroke on MRI, and 27.5% have ipsilateral internal carotid artery stenosis >50% [23].

Overall, the diagnosis is based on the collected anamnesis and results of the general and ophthalmic examination. These patients usually have cardiovascular, systemic, inflammatory, metabolic diseases, eye injuries, stroke, myocardial infarction, superficial and deep thrombosis of the veins of the lower extremities or obliterating endarteritis, among the few [2, 4, 14, 24].

Therapeutic Approaches

Standard therapeutic methods to treat RAO and natural partial restoration of the blood flow poses limited efficiency in terms of restoration of visual function [8, 10, 25]. Usually, irreversible vision loss can drastically impact the quality of life of patients with RAO [26]. Thus, urgent implication of the most effective therapeutic modalities should be mandatory in order to try to restore the blood circulation in occluded retinal arteries. Improvement of the perfusion of the retina, dissolution, fragmentation, displacement and/or removal of the intravascular emboli and restoration of the blood flow in the damaged area are the main endpoints of the RAO treatment

[27–29]. Manual massage of the eyeball in an acute stage of RAO will increase the retinal perfusion, lower the eye pressure and even support the displacement of the emboli to the more peripheral artery branches, which can renew blood circulation in the central area. Application of anterior chamber paracentesis together with antiglaucoma medication and hemodilution measurements will improve blood flow in the impacted arteries and retinal capillaries [29]. Pharmacological induction of vasodilation and hyperbaric oxygenation can target the small caliber arteries by increasing the volume and oxygenation of the blood passing through them [29, 30]. The clinical efficacy of systemic lysis has been evaluated by many groups, but it remains only the treatment of choice due to insufficient data, as emboli in over 80% of RAO case are cholesterol or calcium compound and there is no lysis agent for that [3]. Still the duration of the RAO, its localization and timing of the therapy application remain the most important issues to handle, which determine the final visual outcome. The severity of the pathological changes often can diminish the treatment efficacy. That is why alternative treatment approaches have been developed, and studies aiming to address the most important causes of RAO, such as occlusion of the artery by the emboli, have been carried out to improve the visual recovery. Among these, a surgical method of embolectomy and intrasurgical massage of the arteries with displacement of the emboly to the periphery, as well as neodymium-doped yttrium aluminum garnet (Nd: YAG) laser embolysis of the occluded arteries at the site of visible emboli have been applied before [31–34]. When the risk for surgical embolectomy or arterial massage reaches that of a typical vitreoretinal intervention, the consideration for doing transluminal application of Nd: YAG laser to restore the blood flow in the occluded arteries with minimally invasive approach becomes viable [32–34]. A number of groups have described the efficacy of translumenal Nd: YAG laser embolysis as well as its rationale for benefits and risks [32–43].

In spite the progress in development and improvement of the Nd: YAG technique, there are still discussions regarding the parameters used and sites of the laser application. The following section is dedicated to the description of the surgical setting, laser modes and treatment results used at Department of Ophthalmology od Bogomolets National Medical University (Kyiv, Ukraine) since 2015. We have so far treated 69 eyes of 67 patients with a Nd: YAG laser embolysis due to CRAO or BRAO (unpublished data). Based on our experience, three main mechanisms of restoration of the retinal blood flow could be distinguished after the application of laser energy: fragmentation of the emboli (embolysis), displacement/rotation of the emboli inside the vessel, and laser vasotomy with displacement of the emboli into the vitreous (embolectomy).

Translumenal Nd: YAG Laser Embolysis

Surgical technique and pulse energy. The main indication and requirement for the patient to apply Nd: YAG laser embolysis lays in the appearance of the intraarterial visible emboli. The main treatment endpoint is considered the appearance of one of

the following effects: fragmentation of the embolus, building gas bubbles, migration of the embolus into the vitreous cavity or bleeding. According to the literature review, the mean maximum pulse energy used for YAG-laser fragmentation of the emboli was 2.56 mJ (range: 0.1 to 9 mJ) with double impulse (l2) in 96% of cases [34]. The average number of pulses used during the treatment was 31 (range: 2–164 mJ, l2 = 94%). Opremcak et al. presented 21 cases where they applied in average 53 pulses per case, the weighted mean was 5.9 pulses (n = 19 cases, I2 = 96%) [34]. In majority of the studies, the initial energy used was rather low (<0.5–1 mJ) with subsequent increase in small steps (0.2–0.8 mJ) until the appearance of the one of the treatment effects occurred.

Our own experience. Since 2015, we have implicated the Nd: YAG laser embolysis/embolectomy approach to treat cases with CRAO and BRAO caused by visible intralumenal emboli as well as cases with CRAO without visible emboli and performed an observational study of the treatment results. In our setting, we used Lightlas YAG laser system 1064 nm (Lightmed, San Clemente, CA, USA) with Singh MidVitreous (Volk, Mentor, OH, USA). During visualization of the embolus in the middle of the vessel, the laser beam was focused directly at the embolus itself (Fig. 15.1a). In CRAO cases without visible emboli, the laser beam was focused at the central retinal artery on the optic disc in the area of its bifurcation. The range of laser energy used in our patient cohort was 0.3 to 5.0 mJ, with an average number of pulses being 3 to 60 (Table 15.1). The treatment starts with a low laser energy of 0.1 mJ followed by a gradual energy increase by 0.1–0.2 until the response from the embolus in the form of fragmentation, restoration of blood flow or rupture of the vessel with subsequent hemorrhage into the vitreous (CRAO cases without visible emboli) occurs. In order to reach fragmentation of the emboli within the vessel without compromising the integrity of the vascular wall, the aiming beam is usually displaced by 150 μm in the direction of the vitreous from the area of localization of the emboli. Hemorrhages in the area of laser exposure are undesirable events and can significantly complicate further manipulation or force a stop of the intervention. In case of small hemorrhage, application of pulse laser energy onto the hemorrhage site can displace the blood and restore the visualization of the embolus for further treatment. Significant vitreous hemorrhage is usually an indication to stop laser surgery. Laser induced vitreous hemorrhages can be controlled by increasing the intraocular pressure with contact lens pushed against the eyeball (Fig. 15.1b–d).

The endpoint treatment criteria in our patient cohort were BCVA, restoration of blood flow on FA, decrease of the retinal thickness and restoration of the integrity of the retinal layers on OCT, as well as subjective improvements in the patients' visual field within 1–2 weeks after the treatment.

In 49 cases (71.1%) visible emboli were detected during ophthalmoscopy, and in 20 CRAO cases (28.9%) there were no visible intravascular emboli. The mean duration of the RAO in the entire group was 16 days (range 5–30 days). The mean BCVA at presentation was 0.17 decimal (range 0.001–1.0 decimal). At the 2 weeks follow-up, the mean BCVA was 0.37 decimal (range 0.001–1.0 decimal) (Table 15.1). The increase of the BCVA in the group with BRAO was documented in 11 cases (91.7%), and in the group with CRAO in 8 cases (14%). Complete

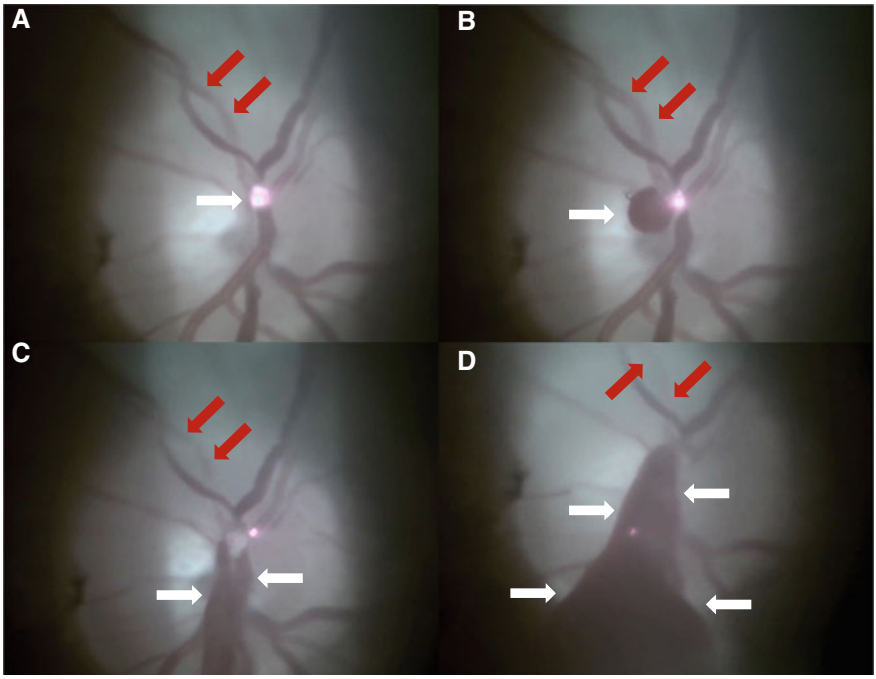

Fig. 15.1 ND: YAG laser embolysis in a patient with BRAO with a visible embolus. **a** aiming beam was focused on the embolus (white arrow). Thinning of the upper branch of the retinal artery (red arrows) is shown. **b** preretinal hemorrhage (white arrow) occurred as complication after laser application with restoration of the blood flow in the upper branch of the retinal artery (red arrows). **c, d** elevation of the intraocular pressure was achieved by pushing the contact lens against the eyeball in order to control hemorrhage (white arrows). Repeated transient decrease of the vascular flow due to iatrogenic increase of the intraocular pressure is also shown (red arrows)

restoration of the blood flow as determined by FA was documented in 65 cases (94%) (Fig. 15.2a, b). The regression of the retinal edema on OCT was observed in all cases (100%) with variable preservation of the integrity of the retinal layers. All patients from the CRAO group who did not observe an increase in the BCVA reported subjective improvement of their visual field. However, it was not possible to evaluate objectively the dynamics of these changes.

Case Presentation

Case 1. Male 48 y.o. presented with BRAO on his RE with visible intraluminal embolus within the optic nerve. His initial BCVA was 0.65 decimal. The duration of BRAO was 7 days (Fig. 15.3a). After standard ophthalmic examination, a Nd: YAG laser embolysis was performed under local anesthesia. During the treatment, partial

Table 15.1 Epidemiologic data of the patients, settings of the Nd: YAG laser and dynamic of the visual function after the treatment

Total number of cases	**Patients, n**	**67**
	Eyes, n	69
Gender	Male, n	42
	Female, n	25
Type of RAO	CRAO, n	57
	BRAO, n	12
Age, y.o	**Average**	**62.1**
	Min	26
	Max	85
Laser energy, mJ	**Average**	**2.7**
	Min	0.3
	Max	5.0
Pulses, n	**Average**	**30.6**
	Min	3
	Max	60
Presence of the emboli, n (%)	Visible	49 (71.1%)
	Not visible	20 (28.9%)
BCVA before treatment, decimal	**Average**	**0.17**
	Min	0.001
	Max	1
BCVA after treatment, decimal	**Average**	**0.37**
	Min	0.001
	Max	1

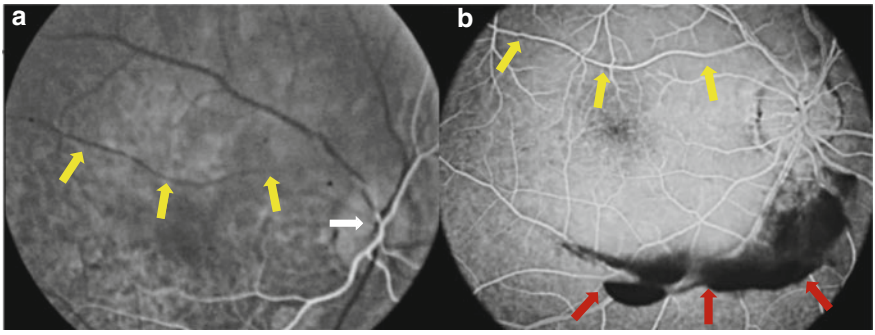

Fig. 15.2 Fluorescence angiography before (**a**) and after ND: YAG laser embolysis (**b**). **a** localization of the embolus is indicated with a white arrow. Yellow arrows depict the occluded artery as well as ischemic retinal area. **b** restoration of the blood flow in the occluded artery (yellow arrows) is shown, as well as a post-surgical vitreous hemorrhage (red arrows)

fragmentation of the embolus was observed, as well as intravascular formation of air bubbles and restoration of the blood flow in the occluded artery (Fig. 15.4c, d, e, f, and Video 1). There was no vitreous hemorrhage at the end of the intervention (Fig. 15.3b). The paleness of the retina disappeared within 1 week after the treatment (Fig. 15.3c). The BCVA increased from 0.65 preoperatively to 1.0 decimal within 2-weeks of follow-up.

Case 2. Female 72 y.o. was referred to our facility with BRAO on her LE with duration of 10 days caused by an embolus in the macular area (Fig. 15.5a). Her BCVA decreased to 0.3 decimal. Nd: YAG laser embolysis was indicated in order to

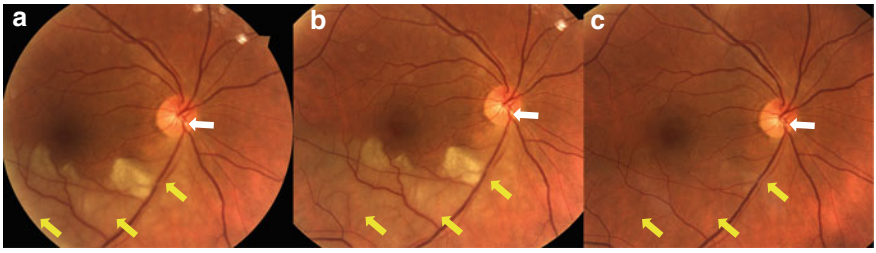

Fig. 15.3 Case 1 from case presentation. Patient with BRAO caused by visible intraluminal embolus within the optic nerve (white arrow in **a**, **b**, **c**). Yellow arrows depict the macular area in **a** and **b**, and resolution of the ischemia within 2 weeks after fragmentation of the embolus in panel **c**

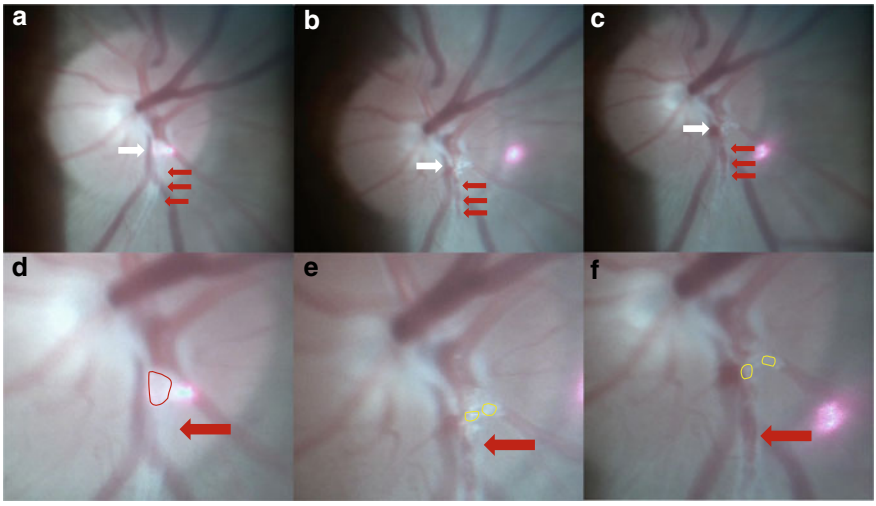

Fig. 15.4 Case 1 from case presentation. Solid intravascular embolus (**a**—white arrow, **b**—delineation with red), which occluded a branch of the retinal artery (**a—**red arrows, **b**—red arrow). Fragmentation of the embolus after initial (**c**, **d**) and repeated (**e**, **f**) ND: YAG laser embolysis with appearance of air bubbles (**c**, **e**—white arrow, **d**, **e**—delineated with yellow) with subsequent restoration of the blood flow (**c**, **d**, **e**, **f**—red arrows)

restore retinal perfusion. Application of the laser energy induced focal intraretinal hemorrhage (Fig. 15.5b). At the 1- and 2- weeks follow-up, a complete involution of the retinal paleness was noticed. OCT images revealed reduction of the retinal edema in the affected area at the 1-week follow-up, with preserved integrity of the retinal layers (Fig. 15.6a, b). Her BCVA improved from 0.3 to 0.6 decimal within 2 weeks after the intervention. In spite the intralumenal embolus was still visible at the 1- and 2- weeks follow-up, the blood flow seemed to be restored (Fig. 15.6c, d).

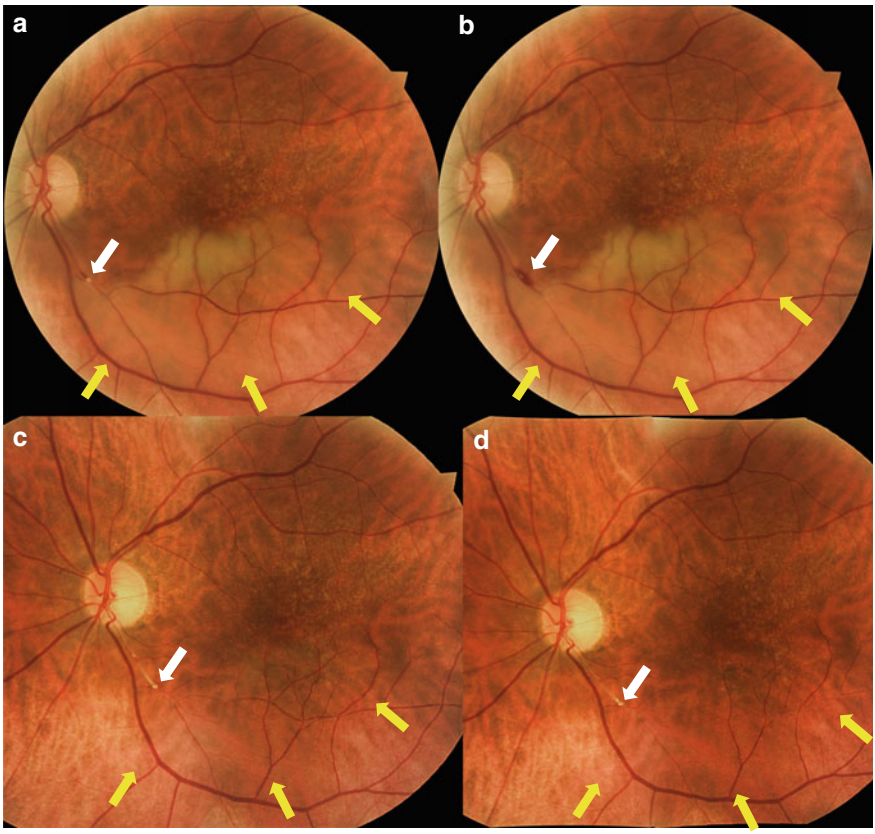

Fig. 15.5 Case 2 from case presentation. Patient with BRAO with retinal ischemia (**a**—yellow arrows) caused by visible intraluminal embolus (**a**—white arrow). After ND: YAG laser embolysis, a small intraretinal hemorrhage has occurred (**b**—white arrow) and retinal ischemia was still significant. At the 1-(**c**) and 2-weeks (**b**) follow-up, retinal ischemia has resolved (yellow arrows). Partial fragmentation of the embolus (**c**, **d**—white arrow) allowed for restoration of the retinal perfusion

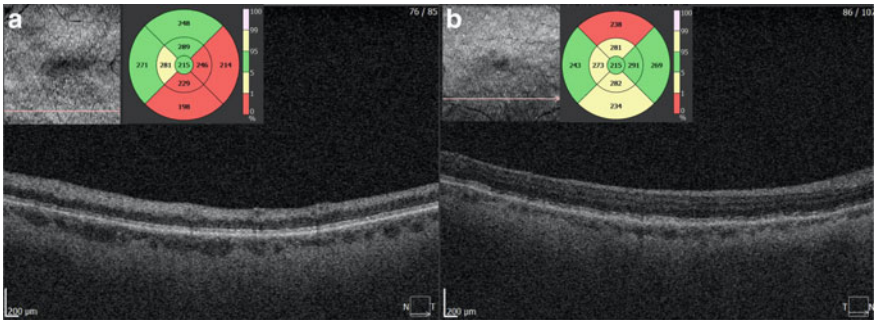

Fig. 15.6 Case 2 from case presentation. **a** OCT image of the edema of the inner retinal layers caused by BRAO. **b** OCT image at the 1-week follow-up showed involution of the retinal edema in the affected area and preserved integrity of the retinal layers and resumed normal retinal thickness

Complications

The most common complication following Nd: YAG laser embolysis remains being getting a hemorrhage, which occurred in 35 (57%) of the cases, comparable to the results published in all reviewed studies [34, 36, 37]. Hemorrhages typically were localized preretinal or in the central vitreous (Figs. 15.1 B–D and 2B). Vitreous hemorrhage immediately following the procedure can obscure the visualization of the embolus and prevent further laser surgery. It was reported that application of the Nd: YAG laser with focusing it on the hemorrhage site will displace the blood and clear up the preretinal space enabling the further procedure [34]. Additionally, bleeding can be controlled by applying pressure using a contact lens for several minutes. Resolution of the vitreous hemorrhage can last up to 1–4 weeks. In most severe cases, vitrectomy is considered necessary. Subretinal and choroidal hemorrhages, retinal holes, false aneurisms and choroidal neovascularization have been among the other potential complication that required additional treatment.

Preretinal and subretinal hemorrhages in our group were observed in 9 cases (16.3%). The total number of cases with intraoperative vitreous hemorrhages was 29 (59%). However, in 20 CRAO cases without visible emboli, vitreous hemorrhage was considered to be a desired treatment response. Therefore, the vitreous hemorrhage as undesired post-treatment event was documented only in 9 patients (18.4%). In our cohort, none of the patients with a vitreous hemorrhage required vitrectomy, as vitreous bleeding resolved spontaneously within 1–2 weeks. Additionally, the formation of retinal holes or microaneurysms of the vascular wall in the area of laser exposure was not observed.

Discussion

RAO is one of the most severe ophthalmic emergencies, which management remains challenging [2–4, 44]. Prolonged ischemia of the inner retinal layers usually leads to irreversible loss of vision. Thus, the implication of an effective treatment approach in patients with RAO is crucial [45]. There have been many different treatment modalities proposed to treat RAO, but none of them have demonstrated significant efficacy to become a best treatment approach [9, 16, 29]. The use of systemic fibrinolytics, intra-arterial fibrinolysis, surgical embolectomy or Nd: YAG laser embolysis/embolectomy or combination of these methods have been applied in order to help patients. The role of hyperbaric oxygenation in the treatment of BRAO and CRAO is being discussed as well [30]. Surgical removal of the embolus appears to be the most reasonable option in regards to the pathophysiology of the RAO. However, this approach requires a vitreoretinal intervention, which is associated with a number of other risks on its own.

Attempts to use a laser for embolization have been described as early as 1989 by Dutton and Craig [33]. An argon laser has been used to treat lipid emboli in case of BRAO, but to no avail. Opremcak et al. described their experience with laser embolysis and raised the discussion of retinal endurance in ischemia [35]. It is believed that after 100 min of occlusion of the arterial bed in the retina there are irreversible changes, but our experience generally indicates that recovery is possible much later than this time within 24 h or even days and weeks [45]. Most likely, this happens as a result of incomplete occlusion of blood vessels by the embolus and the preservation of minimal partial blood flow in the affected area or presence of smaller collateral vessels [5, 7]. Nevertheless, it is no doubt that rapid restoration of retinal perfusion will lead to restoration of visual function.

It has been shown that application of Nd: YAG laser embolysis/embolectomy is associated with a rapid recovery of retinal blood flow and improved vision in patients with CRAO and BRAO [32–43]. The most common complication when applying laser energy is the occurrence of vitreous hemorrhage, but this appeared to be an insignificant complication and only in a few cases required vitrectomy [34]. In our cohort of patients, we have found that BCVA in patients with RAO treated with this very technique increased significantly during the first week after laser embolysis as a result of almost complete restoration of the blood flow in the obstructed arteries. Cases with BRAO usually responded more promptly and significantly to the treatment as the central vision in many patients could be preserved in part. Additionally, in case of BRAO, the lesion of the central part of the macula is not obvious in the acute phase, but the BCVA worsens, and ischemic retinal edema develops afterwards, which can be detected by OCT. The paleness of the retina as a sign of intercellular edema successfully disappears after Nd: YAG laser embolysis/embolectomy with the restoration of blood flow in the artery.

We suspect that in cases of CRAO with no visible emboli, the occlusion occurs behind the lamina cribrosa of the optic nerve. The aim of the laser assisted damage to the retinal artery wall is to induce the fluctuation of the intravascular pressure,

giving the opportunity to the emboli to pass through the lamina cribrosa and either to be displaced into the vitreous cavity or to get visible and consequently fragmented by further application of the laser.

The results of our observational study allowed us to hypothesize and distinguish three main mechanisms which could explain the restoration of retinal blood flow after Nd: YAG laser embolysis/embolectomy: 1. fragmentation of the emboli (laser-assisted embolysis); 2. displacement/rotation of the emboli inside the vessel (with possible dilation of the artery); 3. laser-induced angiotomy with evacuation of the embolus from the artery into the vitreous (laser-assisted embolectomy).

In general, Nd: YAG laser embolysis/embolectomy demonstrates promising results compared to other treatments of CRAO and BRAO. Applying this method, one can achieve a rapid restoration of the blood flow and a significant improvement in the visual acuity, which is the main aim of the treatments. Nevertheless, application of laser energy in patients with RAO shall be investigated further, as this procedure can be a double-edged sword in regards to the risks for vitreous, preretinal or subretinal hemorrhage. As a rule, small vitreous or other hemorrhages resolve spontaneously and do not require vitreoretinal intervention. However, application of the laser energy at the embolus in a large vessel on the optic disc can cause significant vitreous hemorrhage that may require vitrectomy.

Conclusions

CRAO and BRAO belong to ophthalmic emergencies, as the prognosis for vision recovery depends on the speed of care. It is important to determine which etiological risk factors may be the causes of CRAO/BRAO: atherosclerosis (80% of cases), occlusion by an embolus detached from a parietal thrombus in the carotid artery, cases exacerbated by retinal artery spasm, arterial hypertension or heart disease, ulceration of the heart valves (infectious endocarditis), thrombosis of the lumen of the vessel in the background of retinovascular disease, spasms with neurocirculatory dystonia, exogenous and endogenous intoxication of the body, and rarely temporal giant cell arteritis and drug use. Treatment should be aimed at the immediate resumption of blood flow of the central retinal artery.

Implication of the ND: YAG laser embolysis/embolectomy as an alternative approach to treat CRAO and BRAO is a minimally invasive procedure and can be applied in any eye care unit by qualified laser specialists.

References

1. Von Graefe A. Ueber Embolie der Arteria centralis retinae als Ursache plötzlicher Erblindung. Albrecht von Graefes Arch Ophthalmol. 1859;5:136–57.
2. Hayreh SS, Podhajsky PA, Zimmerman MB. Retinal artery occlusion: associated systemic and ophthalmic abnormalities. Ophthalmology. 2009;116(10):1928–36.
3. Varma DD, Cugati S, Lee AW, et al. A review of central retinal artery occlusion: clinical presentation and management. Eye. 2013;27(6):688–97.
4. Leisser C. Risikofaktoren retinaler Arterienverschlüsse. . Spektrum Augenheilkd. 2012;26:202–4.
5. Hayreh SS, Zimmerman B. Central retinal artery occlusion: visual outcome. Am J Ophthalmol. 2005;140(3):376–91.
6. Dunlap AB, Kosmorsky GS, Kashyap VS. The fate of patients with retinal artery occlusion and Hollenhorst plaque. J Vasc Surg. 2007;46(6):1125–9.
7. Hayreh SS, Weingeist TA. Experimental occlusion of the central artery of the retina. IV: Retinal tolerance time to acute ischaemia. Br J Ophthalmol. 1980;64(11):818–825.
8. Yuzurihara D, Iijima H. Visual outcome in central retinal and branch retinal artery occlusion. Jpn J Ophthalmol. 2004;48(5):490–2.
9. Sharma S, Brown M, Brown GC. Retinal artery occlusions. Ophthalmol Clin North Am. 1998;11:591–600.
10. Augsburger JJ, Magargal LE. Visual prognosis following treatment of acute central retinal artery obstruction. Br J Ophthalmol. 1980;64:913–7.
11. Brown GC, Magargal LE, Shields JA, et al. Retinal arterial-obstruction in children and young-adults. Ophthalmology. 1981;88(1):18–25.
12. Hayreh SS, Podhajsky PA, Zimmerman MB. Branch retinal artery occlusion. Ophthalmology. 2009;116(6):1188-1194.e1184.
13. Schmidt D, Hetzel A, GeibelZehender A, SchulteMönting J. Systemic diseases in noninflammatory branch and central retinal artery occlusion – an overview of 416 patients. Eur J Med Res. 2007;12(12):595–603.
14. Leisser C. Hyperlipidämie und erhöhte systemische Blutdruckwerte – gibt es einen Zusammenhang zu retinalen Arterienverschlüssen? Spektrum Augenheilkd. 2010;24(3):154–6.
15. Selaru D, Radocea R, Stanca H. Inferior temporal branch arterial occlusion–acute form. Oftalmologia. 2008;52(1):64–71.
16. Hayreh SS. Acute retinal arterial occlusive disorders. Prog Retin Eye Res. 2011;30(5):359–94.
17. Feltgen N, Neubauer A, Jurklies B et al. EAGLE-Study Group. Multicenter study of the European Assessment Group for Lysis in the Eye (EAGLE) for the treatment of central retinal artery occlusion: design issues and implications. EAGLE Study report no. 1 : EAGLE Study report no. 1. Graefes Arch Clin Exp Ophthalmol. 2006 Aug;244(8):950–6.
18. Schumacher M, Schmidt D, Jurklies B et al. EAGLE-Study Group. Central retinal artery occlusion: local intra-arterial fibrinolysis versus conservative treatment, a multicenter randomized trial. Ophthalmology. 2010;117(7):1367–75.e1.
19. Mueller AJ, Neubauer AS, Schaller U et al. European Assessment Group for Lysis in the Eye. Evaluation of minimally invasive therapies and rationale for a prospective randomized trial to evaluate selective intra-arterial lysis for clinically com- plete central retinal artery occlusion. Arch Ophthalmol 2003;121: 1377– 81.
20. Gong H, Song Q, Wang L. Manifestations of central retinal artery occlusion revealed by fundus fluorescein angiography are associated with the degree of visual loss. Exp Ther Med. 2016;11(6):2420–4.
21. Falkenberry SM, Ip MS, Blodi BA et al. Optical coherence tomography findings in central retinal artery occlusion. Ophthalmic Surg Lasers Imaging. 2006;37(6):502–5.
22. Mac Grory B, Schrag M, Poli S, et al. Structural and functional imaging of the retina in central retinal artery occlusion—current approaches and future directions. J Stroke Cerebrovasc Dis. 2021;30(7): 105828

23. Lee KE, Tschoe C, Coffman SA, et al. Management of acute central retinal artery occlusion, a “retinal stroke”: an institutional series and literature review. J Stroke Cerebrovasc Dis. 2021;30(2): 105531.
24. Mead GE, Lewis SC, Wardlaw JM, et al. Comparison of risk factors in patients with transient and prolonged eye and brain ischemic syndromes. Stroke. 2002;33(10):2383–90.
25. Altmann M, Ertl M, Helbig H, Schömig B, et al. Low endogenous recanalization in embolic central retinal artery occlusion-the retrobulbar ‘spot sign.’ J Neuroimaging. 2014;25:251–6.
26. Weger M, Pichler T, Franke GH, et al. Wedrich A and Rabensteiner DF: Assessment of vision-related quality of life in patients with central retinal artery occlusion. Retina. 2014;34:539–45.
27. Cugati S, Varma DD, Chen CS, et al. Treatment options for central retinal artery occlusion. Curr Treat Options Neurol. 2012;15(1):63–77.
28. Schumacher M, Schmidt D, Jurklies B, et al. Central reti nalartery occlusion: local intraarterial fibrinolysis versus conservative treatment, a multicenter randomized trial. Ophthalmology. 2010;117(7):1367–75.
29. Watson PG. The treatment of acute retinal arterial occlusion. In: Cant JS, editors. Proceedings of the Wm Mackenzie centenary symposium on the ocular circulation in health and disease, Glas- gow, 1968. London: Kimpton; 1969:234–45.
30. Beiran I, Goldenberg I, Adir Y, et al. Early hyperbaric oxygen therapy for retinal artery occlusion. Eur J Ophthalmol. 2001;11(4):345–50.
31. Lytvynchuk L. Embolectomy for branch retinal artery occlusion: a case report. Acta Ophthalmol. 2017;95(5):e428–9.
32. Reynard M, Hanscom TA. Neodymium: yttrium-aluminum-garnet laser arteriotomy with embolectomy for central retinal artery occlusion. Am J Ophthalmol. 2004;137(1):196–8.
33. Dutton GN, Craig G. Treatment of a retinal embolus by photocoagulation. Brit J Ophthalmol. 1989;73(7):580–1.
34. Man V, Hecht I, Talitman M, Hilely A, et al. Treatment of retinal artery occlusion using transluminal Nd:YAG laser: a systematic review and meta-analysis. Graefes Arch Clin Exp Ophthalmol. 2017;255(10):1869–77.
35. Opremcak E, Rehmar AJ, Ridenour CD, et al. Restoration of retinal blood flow via translumenal Nd:YAG embolysis/embolectomy (TYL/E) for central and branch retinal artery occlusion. Retina. 2008;28(2):226–35.
36. Feist RM, Emond TL. Translumenal Nd:YAG laser embolysis for central retinal artery occlusion. Retina. 2005;25(6):797–9.
37. Opremcak EM, Benner JD. Translumenal Nd : YAG laser embolysis for branch retinal artery occlusion. Retina J Ret Vit Dis. 2002;22(2):213–6.
38. Lu N, Yang QS, Ma K, et al. Preliminary report of Nd: YAG laser embolysis for branch retinal artery occlusion. Zhonghua Yan Ke Za Zhi. 2006;42(4):326–9.
39. Mason JO, Nixon PA, Albert MA. Trans-luminal Nd : YAG laser embolysis for branch retinal artery occlusion. Retina J Ret Vit Dis. 2007;27(5):573–7.
40. Lim JY, Lee JY, Chung HW, et al. Treatment of branch retinal artery occlusion with transluminal Nd:YAG laser Embolysis. Korean J Ophthalmol. 2009;23(4):315.
41. Solans Pérez-Larraya AM, Ortega-Molina JM, Salgado-Miranda AD et al. Branch retinal artery occlusion in a patient with one eye. Laser Nd:YAG approach. Arch Soc Esp Oftalmol. 2016
42. Stanca HT, Petrovic Z, Munteanu M. Transluminal Nd:YAG laser embolysis-a reasonable method to reperfuse occluded branch retinal arteries. Vojnosanit Pregl. 2014;71(11):1072–7.
43. Haritoglou C, Wolf A, Ulbig MW. Laser embolectomy for central retinal artery occlusion. Ophthalmologe. 2010;107(5):465–7.
44. Fraser SG, Adams W. Interventions for acute non-arteritic central retinal artery occlusion. Cochrane Database Syst Rev 2009;(1):CD001989.
45. Hayreh SS, Kolder HE, Weingeist TA. Central retinal artery occlusion and retinal tolerance time. Ophthalmology. 1980;87:75–8.

Chapter 16
Laser Treatment of Submacular Hemorrhages

Lyubomyr Lytvynchuk, Stanislav Saksonov, Goran Petrovski, and Andrzej Grzybowski

Introduction

Submacular hemorrhage (SMH) remains one of the most vision threatening complications of the retinal and choroidal vascular disorders [1]. Among the causes of SMH, traumatic choroidal rupture, pathologic myopia, angioid streaks, intake of anticoagulants, systemic cardiovascular and infectious diseases have been determined so far [2, 3]. The geographic and exudative forms of age-related macular degeneration

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Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/978-3-031-25779-7_16.

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_16

(AMD) belong to the most frequent reasons for development of choroidal neovascularization (CNV) and retinal angioid proliferation (RAP) with subsequent SMH [4–6]. Bennett et al. analyzed the visual function of 29 patients with massive SMH involving the fovea centralis region and found the following risk factors to determine a poor visual prognosis: great thickness of the hemorrhage, AMD, diameter of the hemorrhage, choroidal rupture [7]. While tiny or thin SMH usually do not require treatment and may only be observed, thick or large in diameter SMH shall be promptly treated in spite the efficacy of the existing therapeutical and surgical approaches is limited. Massive SMH are associated with exudative detachment of the photoreceptor layer (PRL) from the retinal pigment epithelium (RPE), and RPE detachment caused by choroidal bleeding. Thick SMH obscures the RPE, decreasing significantly the visual function and possibility to examine the underlying retina for potential causes [4]. The application of the spectral-domain/swept source optical coherence tomography (OCT) and OCT angiography into everyday use allows the scanning beam to penetrate the SMH and reach the RPE and the Bruch's membrane, and even visualize the choroid in order to differentiate the pathology from other causes [8, 9].

Accumulation of the blood in the subretinal space initiates a cascade of damaging mechanisms, which in turn determine the future postoperative prognosis [4, 10]. The mechanical detachment of the photosensory retina from RPE induces atrophic changes in the outer retina. The toxic action of hemosiderin, iron ions and fibrin on the RPE and PRL deteriorates the retinal damage. Additionally, tangential traction caused by the blood clots and subretinal scars can tear the RPE and PRL accordingly. Development of these pathological changes requires some time. Hence, earlier treatment can be beneficial and increase the chances for improvement of the visual function [4, 10–12]. To date, a number of treatment concepts and modalities have been proposed and applied in clinical practice [13–15]. Amid most applied therapeutic approaches, photodynamic therapy of the bleeding vessels (PDT), intravitreal injection (IVI) of tissue plasminogen activator (TPA) and anti-VEGF agents, IVI of gas and vitrectomy with subretinal injection of TPA [16–20], have all been described. The PDT approach belongs to the minimally invasive ambulatory procedures. However, it targets the bleeding vessels but not the hemorrhage itself.

The use of Nd: YAG laser as minimally invasive approach has been reported only for the treatment of preretinal subhyaloidal hemorrhages, and hemorrhages under the internal limiting membrane [21–24]. However, the use of the Nd: YAG laser induced retinotomy to treat SMH has not yet been proposed so far. Moreover, laser-induced retinotomy has been reported to be among the undesired complications of Nd: YAG hyaloidotomy or membranotomy [24].

In this chapter, we present the novel approach for the treatment of SMH using Nd: YAG laser developed and applied at the Department of Ophthalmology, National Medical University (Kyiv, Ukraine) since 2015. All treated patients were informed about the standard treatment methods as well as the novel approach **using** Nd: YAG laser retinotomy for SMH.

Surgical technique and pulse energy. Nd: YAG laser retinotomy to treat SMH is similar to the concept of Nd: YAG laser embolysis and Nd: YAG laser membranotomy

where the laser energy is applied onto the surface of the retina [23]. Performance of a retinotomy in order to release the trapped hemorrhage laying in the subretinal space is the main novelty of this approach. One to three laser-induced retinotomies shall be performed. Immediately after the laser procedure, the SMH gains a way to escape into the vitreous cavity. Slight vitreous opacification due to SMH migration is possible, but it reabsorbs within few weeks.

Our own experience with the technique. With this approach ten cases (10 patients) were treated who presented with late stage exudative (AMD). The presence of fibrovascular retinal detachment caused by SMH were among the inclusion criteria to perform Nd: YAG laser retinotomy. Before treatment, all patients underwent standard ophthalmological examination including fundus photography and OCT, which were performed before, and immediately after the procedure, as well as in 1-, 3- and 6-months post-treatment. In our setting, we used a Lightlas YAG laser system (dysrapter) with wavelength 1064 nm (Lightmed, San Clemente, CA, USA) and Singh MidVitreous contact lens (Volk, Mentor, OH, USA). After the eye surface was anesthetized and the contact lens was applied onto the cornea, we performed one to three laser retinotomies in the area of SMH outside the fovea centralis to obtain a small leackage of the SMH from the subretinal space into the vitreous cavity. Additionally, an IVI of anti-VEGF agent was performed on the same day or shortly after, and repeated at 1-month intervals. Gradual hemorrhage resorption appeared in 1 to 2 weeks after the surgery. Fibrin plaques in the subretinal space were noticed during the reabsorption period with significant decrease in their size by the 3rd month of observation.

The initial best corrected visual acuity (BCVA) in the treated cohort was 0.16 decimal (range 0.1–0.4) (Table 16.1). Improvement of the BCVA coresponded to the resorption of the hemorrhage. After the maximal reabsorption of the blood in the foveal area, approximately in 2–3 months after the surgery, the average BCVA in the treated group increased to 0.31 decimal (range 0.05–0.5).

In six cases after the SMH reabsorbtion, a RPE detachment and folding was observed, which limited the increase in BCVA, although the patients noticed significant improvement of vision. All patients reported a subjective recurrence of the central visual field.

Table 16.1 Data of the patients with submacular hemorrhage and settings of the Nd: YAG laser, as well as dynamics of the visual function after the treatment

Total number of cases	**Patients, n**	**10**
	Eyes, n	10
Gender	Male, n	6
	Female, n	4
Age, y.o	**Average**	**66.7**
	Min	56
	Max	87
Laser energy, mJ	**Average**	**2.1**
	Min	0.7
	Max	3.0
Pulses, n	**Average**	**15.5**
	Min	2
	Max	40
BCVA before treatment, decimal	**Average**	**0.16**
	Min	0.01
	Max	0.4
BCVA after treatment, decimal	**Average**	**0.31**
	Min	0.05
	Max	0.5

Complications

Slight central vitreous opacification was noticed in all cases, but it was not significant and resolved within few weeks. Reabsorption of the SMH in 8 cases was accompanied by local exudative retinal detachment (RD) in the macular zone with distinct adhesion between RPE and PRL along the edge of the hemorrhage. However, the subretinal fluid resolved spontaneously and those events required no additional therapy. Subtotal RD developed in one case after 3 months of positive dynamics due to persistent subretinal fluid (SRF). This patient was treated by pars plana vitrectomy.

Case Presentation

Case 1. Male 66 y.o. presented with SMH due to exudative AMD on his LE (Fig. 16.1). The duration of SMH was 6 days (Fig. 16.1A) and the BCVA before the treatment was 0.01 decimal. After standard ophthalmic examination, Nd: YAG laser retinotomies (n = 2) were performed under local anesthesia (Fig. 16.1B). During the laser treatment, the following parameters were used: energy—1.1 mJ, pulses—12. The same day, an IVI of anti-VEGF was instilled. Resolution of the SRF was noticed within 3–4 weeks, with clearing of the fovea centralis and presence of residual fibrin plaque

in the temporal paramacular area (Fig. 16.1D). BCVA improved to 0.2 decimal within 4-weeks from treatment. Preoperative OCT imaging showed SMH with RPE detachment and choroidal hemorrhage (Fig. 16.2A). At 4 weeks after the treatment, OCT revealed reabsorption of the SMH and involution of the RPE detachment and choroidal bleeding (Fig. 16.2B). There was only slight hyperpigmentation at the site of the laser retinotomies on fundus imaging (Fig. 16.1D).

Case 2. Male 87 y.o. complained on sudden decrease of vison in the last 4 days. Diagnosis at the admission: exudative AMD with SMH of the RE (Fig. 16.3A). The BCVA on his RE was 0.05 decimal. Single Nd: YAG laser retinotomy was performed

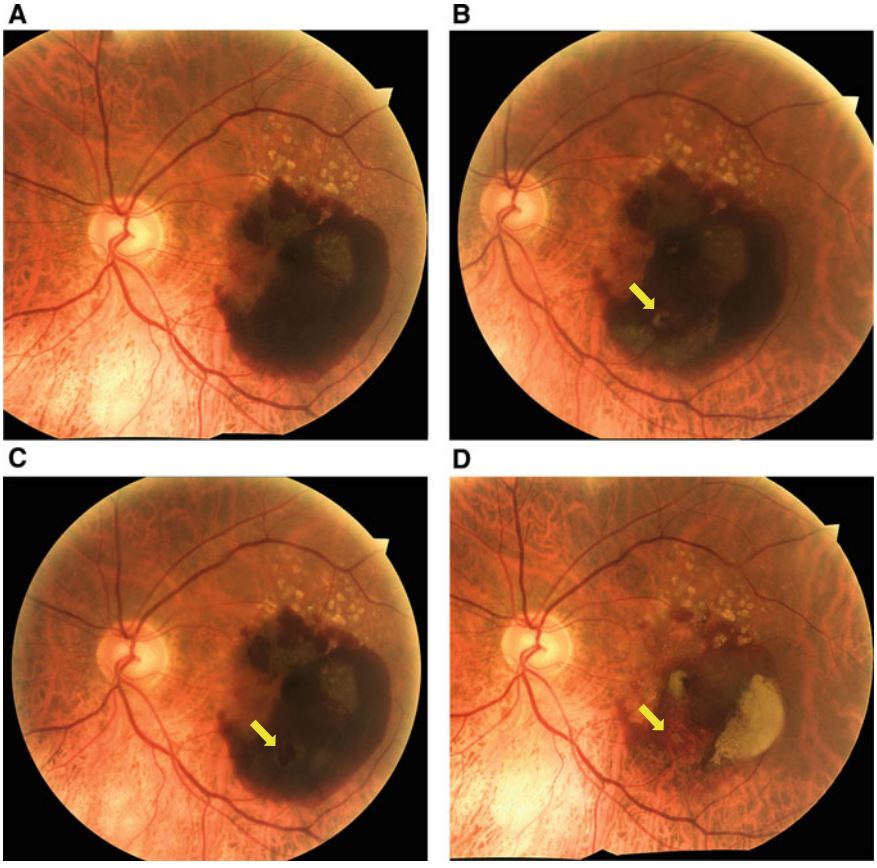

Fig. 16.1 Case 1. 66 y.o. RE: submacular hemorrhage due to exudative AMD, BCVA (decimal). **A**—surbetinal and choroidal hemorrhage covering almost entirely the macula at the time of presentation. **B**—yellow arrow indicates a small perifoveal retinotomy with whitish swollen edges performed by ND: YAG laser (yellow arrow) immediately after the surgery. **C**—slow evacuation of the subretinal blood into the vitreous cavity (yellow arrow) was seen 1 h after the surgery. **D**—significant involution of the subretinal blood in 4 weeks after the surgery is observed. Yellow arrow depicts barely visible retinal changes at the site of the laser retinotomy

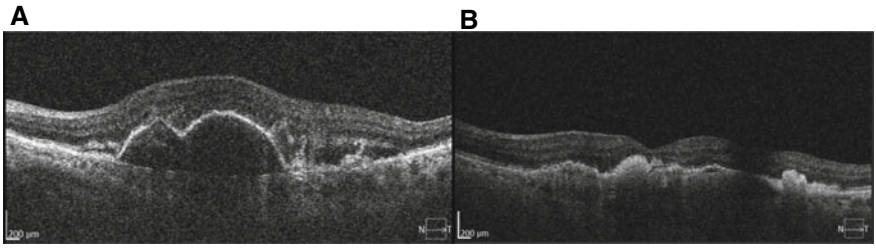

Fig. 16.2 Case 1. 66 y.o. RE: submacular hemorrhage due to exudative AMD, BCVA (decimal). **A**—optical coherence tomography of the foveal area before the surgery with subretinal and choroidal hemorrhage associated with RPE detachment. **B**—resolution of the subretinal and choroidal bleeding with decrease of RPE detachment

in the upper temporal area within the macula with energy of 1.0 mJ and number of pulses of 17. Partial resolution of the SMH with two residual subretinal fibrin plaques with no scaring of the laser retinotomy site were observed in 4–5 weeks after the surgery (Fig. 16.3B). Subretinal fibrin reabsorption was documented at the 8-weeks follow-up (Fig. 16.3C). BCVA improved to 0.4 decimal at 4 weeks after the Nd: YAG laser retinotomy.

Discussion

SMH in exudative AMD complicates the course and radically reduces the patient's visual function as well as nullify the achievements of the anti-VEGF therapy [4, 5]. Massive SMHs occur suddenly and usually are associated with worsening of the disease and/or with detachment and/or duplication of the RPE [4, 10]. The separation of the RPE itself remains masked by the hemorrhage and becomes available for visualization after resorption or removal of the hemorrhage [11]. In the cases of massive SMHs with large prominence into the vitreous cavity during blood resorption, a retinal detachment within the hemorrhage is also formed.

Standard recommendation in such cases is to continue giving anti-VEGF therapy [25]. Vitrectomy with intravitreal or subretinal TPA application is also an option, which shows good visual results, but is not always associated with a subjective improvement of BCVA and requires much skills [19]. The complex vitreoretinal procedure has always a risk for intra- and postoperative complications including iatrogenic retinal holes [26]. Retinal holes in the macular are undesired events which usually do not lead to the development of retinal detachment and do not require laser photocoagulation [27]. Similarly, laser hyaloidotomy for preretinal hemorrhage can also be associated with the risk of iatrogenic retinal rupture at the site of laser exposure [27–30]. Such openings rarely lead to retinal detachment. Therefore, we consider the targeted laser-induced retinal hole formation for the treatment of SMH to be a relatively safe procedure. Moreover, laser energy required to perform a small

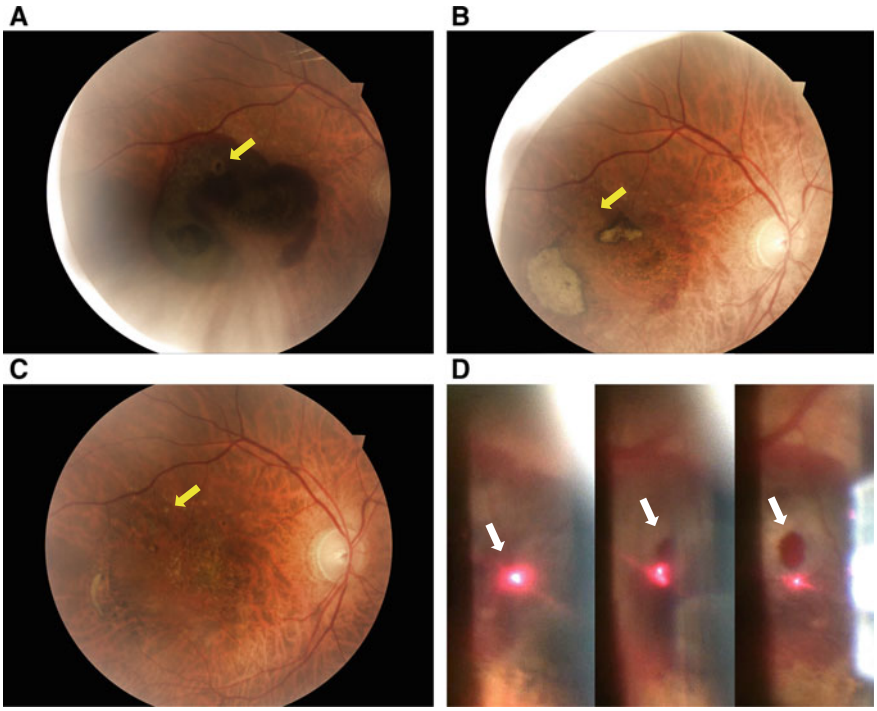

Fig. 16.3 Case 2. 87 y.o. RE: submacular hemorrhage due to exudative AMD, BCVA (decimal). **A—**submacular hemorrhage at the time of treatment. Yellow arrow depicts a small perifoveal retinotomy with swollen edges performed by ND: YAG laser. **B**—gradual involution of the blood with residual subretinal fibrin plaques in 4–5 weeks with slight pigmentation of the area of laser retinotomy (yellow arrow). **C**—complete resolution of the subretinal hemorrhage in 8-weeks period. The site of laser retinotomy shows no further chorioretinal scarring (yellow arrow). **D**—intraoperative view of the retinal surface. White arrow indicates the site of future laser retinotomy (white arrow). **E**—the flow of the subretinal blood into the vitreous cavity (white arrow). **F**—slow progression of the blood evacuation towards the vitreous cavity at the end of the laser surgery (white arrow)

retinotomy above the SMH does not reach the pigmented epithelium layer as it is absorbed by the blood cells. Therefore, otherwise typical for laser photocoagulation, chorioretinal scaring does not develop with Nd: YAG laser retinotomy.

The data obtained from this observational study consider the performance of Nd: YAG laser retinotomy to be a useful and minimally invasive treatment method for rapid hemorrhage resorption. The idea behind it is to include the subretinal, and in some cases sub-RPE cavity filled with blood, to the hemodiluting activity of the vitreous body and its enzymes available for that. Quick resorption of the SMH after a Nd: YAG laser retinotomy facilitates a positive result, improves prognosis and prevents the deposition of the fibrin plaques in the subretinal space. Implementation of this methods has shown that even massive hemorrhages can be reabsorbed quickly with minimal risk for secondary atrophy of the RPEs.

Conclusions

SMH in geographic and exudative AMD remains the most vision threatening complication, which can significantly deteriorate an already compromised central vision; if untreated, it has a poor prognosis [1, 7]. To date, there is no state-of-the-art therapeutical approach which could be reproducible, well tolerated and highly effective in treating SMH. Blood toxicity, mechanical damage of the inner retinal layers and complexity of the pathologic changes in the case of SMH are time-dependent. Therefore, an ambulatory and minimally invasive therapeutic method would be of use as an alternative treatment modality in this vulnerable elderly group of patients. Clinical application of Nd: YAG laser retinotomy to treat SMH appears to be novel, effective, safe and minimally invasive method, and it can be used in an out-patient eyecare units by ophthalmologists having experience with laser treatment. The efficacy of this method, however, remains to be investigated in larger patients' cohorts in order to evaluate its long-term effects.

References

1. Avery RL, Fekrat S, Hawkins BS, Bressler NM. Natural history of subfoveal subretinal hemorrhage in age-related macular degeneration. Retina. 1996;16:183–9.
2. Bloome MA, Ruiz RS. Massive spontaneous subretinal hemorrhage. Am J Ophthalmol. 1978;86(5):630–7 PubMed PMID: 717519.
3. Gillies A, Lahav M. Absorption of retinal and subretinal hemorrhages. Ann Ophthalmol. 1983;15(11):1068–74.
4. Avery RL, Fekrat S, Hawkins BS, Bressler NM. Natural history of subfoveal subretinal hemorrhage in age-related macular degeneration. Retina. 1996;16(3):183–9.
5. Nasrallah F, Jalkh AE, Trempe CL, McMeel JW, Schepens CL. Subretinal hemorrhage in atrophic age-related macular degeneration. Am J Ophthalmol. 1989;107(1):38–41.
6. Shultz RW, Bakri SJ. Treatment for submacular hemorrhage associated with neovascular age-related macular degeneration. Semin Ophthalmol. 2011;26(6):361–71.
7. Bennett SR, Folk JC, Blodi CF, Klugman M. Factors prognostic of visual outcome in patients with subretinal hemorrhage. Am J Ophthalmol. 1990;109(1):33–7.
8. Sampangi R, Chandrakumar HV, Somashekar SE, Joshi GR, Ganesh S. SD-OCT to differentiate traumatic submacular hemorrhage types using automatic three-dimensional segmentation analysis. Ophthalmic Surg Lasers Imaging. 2011 Mar 3;42 Online:e32–6.
9. Hua R, Ning H. Using optical coherence tomography angiography to guide the treatment of pathological myopic patients with submacular hemorrhage. Photodiagnosis Photodyn Ther. 2019;28:105–9.
10. Toth CA, Morse LS, Hjelmeland LM, Landers MB 3rd. Fibrin Directs Early Retinal Damage After Experimental Subretinal Hemorrhage. Arch Ophthalmol. 1991;109(5):723–9.
11. Bopp S. Subretinale Blutungen. Spontanverlauf und Stadieneinteilung [Subretinal hemorrhage. Natural course and staging]. Ophthalmologe. 2012 Jul;109(7):635–43.
12. Feltgen N. Submakuläre Blutungen [Submacular hemorrhage]. Ophthalmologe. 2012;109(7):633–4.
13. Hochman MA, Seery CM, Zarbin MA. Pathophysiology and management of subretinal hemorrhage. Surv Ophthalmol. 1997 Nov-Dec;42(3):195–213.
14. Lauritzen DB, Weiter JJ. Management of subretinal hemorrhage. Int Ophthalmol Clin. 2002 Summer;42(3):87–95.

15. McCabe CM, Flynn HW Jr, McLean WC, Brod RD, McDonald HR, Johnson MW, Williams GA, Mieler WF. Nonsurgical management of macular hemorrhage secondary to retinal artery macroaneurysms. Arch Ophthalmol. 2000;118(6):780–5.
16. Woodburn KW, Engelman CJ, Blumenkranz MS. Photodynamic therapy for choroidal neovascularization: a review. Retina. 2002 Aug;22(4):391–405; quiz 527–8.
17. Tennant MT, Borrillo JL, Regillo CD. Management of submacular hemorrhage. Ophthalmol Clin North Am. 2002;15(4):445–52.
18. Chew GWM, Ivanova T, Patton N, Dhawahir F, Jasani KM, Turner G, Charles S, Jalil A. STEP-WISE APPROACH TO THE MANAGEMENT OF SUBMACULAR HEMORRHAGE USING PNEUMATIC DISPLACEMENT AND VITRECTOMY: The Manchester Protocol. Retina. 2022;42(1):11–8.
19. Meyer CH, Scholl HP, Eter N, Helb HM, Holz FG. Combined treatment of acute subretinal haemorrhages with intravitreal recombined tissue plasminogen activator, expansile gas and bevacizumab: a retrospective pilot study. Acta Ophthalmol. 2008.
20. Bardak H, Bardak Y, Erçalık Y, Erdem B, Arslan G, Timlioglu S. Sequential tissue plasminogen activator, pneumatic displacement, and anti-VEGF treatment for submacular hemorrhage. Eur J Ophthalmol. 2018;28(3):306–10.
21. Puthalath S, Chirayath A, Shermila MV, Sunil MS, Ramakrishnan R. Frequency-doubled Nd:YAG laser treatment for premacular hemorrhage. Ophthalmic Surg Lasers Imaging. 2003 Jul-Aug;34(4):284–90.
22. Matonti F, Donadieu V, Hoffart L, Dornadin A, Nadeau S, Roux S, Denis D. Traitement précoce par laser Nd:YAG de la rétinopathie de Valsalva : résultats à propos de cinq cas et revue de la littérature [Early treatment with Nd:YAG laser for Valsalva retinopathy: results of five cases and literature review]. J Fr Ophtalmol. 2013;36(7):604–9.
23. Raymond LA. Neodymium:YAG laser treatment for hemorrhages under the internal limiting membrane and posterior hyaloid face in the macula. Ophthalmology. 1995;102(3):406–11.
24. Goker YS, Tekin K, Ucgul Atilgan C, Kosekahya P, Yilmazbas P. Full Thickness Retinal Hole Formation after Nd:YAG Laser Hyaloidotomy in a Case with Valsalva Retinopathy. Case Rep Ophthalmol Med. 2018;3(2018):2874908.
25. Kauffmann Y, Isaico R, Lefebvre A, Bron AM, Creuzot-Garcher C. Relation entre injection intravitréenne d'anti-VEGF et hématome sous-rétinien chez des patients atteints de dégénérescence maculaire liée à l'âge exsudative [Relationship between intravitreal anti-VEGF therapy and subretinal hemorrhage in patients with exudative age-related macular degeneration]. J Fr Ophtalmol. 2014;37(3):195–201
26. An JH, Jang JH. Macular Hole Formation Following Vitrectomy for Ruptured Retinal Arterial Macroaneurysm. Korean J Ophthalmol. 2021;35(3):248–50.
27. Alsakran WA, Alsulaiman SM, Ghazi NG. Delayed spontaneous closure of blue laser-induced full thickness macular hole. Am J Ophthalmol Case Rep. 2019;9(13):154–6.
28. Bypareddy R, Chawla R, Azad SV, Takkar B. Iatrogenic parafoveal macular hole following Nd-YAG posterior hyaloidotomy for premacular haemorrhage. BMJ Case Rep. 2016 Nov 23;2016:bcr2016217234.
29. Thach AB, Lopez PF, Snady-McCoy LC, Golub BM, Frambach DA. Accidental Nd:YAG laser injuries to the macula. Am J Ophthalmol. 1995;119(6):767–73.
30. Khadka D, Bhandari S, Bajimaya S, Thapa R, Paudyal G, Pradhan E. Nd:YAG laser hyaloidotomy in the management of Premacular Subhyaloid Hemorrhage. BMC Ophthalmol. 2016;18(16):41.

Chapter 17
Retinal Laser Telephotocoagulation and Teleeducation

Igor Kozak

The field of teleophthalmology has evolved from a research tool to a useful clinical service in many areas of ophthalmic diagnostics and care. Teleophthalmology has been shown to be a valuable means for extending care to larger populations of high-risk patients with diseases such as diabetic retinopathy, glaucoma, and/or retinopathy of prematurity [1–4]. Pertinent to retinal care, the most recent developments include retinal "telephotocoagulation" and "teleeducation". Telephotocoagulation describes the ability to prepare and guide retinal laser treatments (teleguidance) by an expert from a remote location. Teleeducation enables learners to gather more practical experience and feedback during their laser training through digital channels. Both concepts may help overcome the lack of experts in retinal laser care as well as the challenges in laser training while allowing clinics to respect social distancing when in-person trainings are to be minimized as much as possible.

The Concept of Telephotocoagulation with Navigated Laser

The navigated laser, camera based laser delivery system, uses the concept of preplanning treatments on either fundus photo and/or overlaid diagnostic images such as fluorescein angiogram or optical coherence tomography thickness map [1, 2]. As the transfer of images and its subsequent analysis is the basic concept of telemedicine/teleophthalmology, the laser system NAVILAS (OD-OS Inc., Teltow, Germany) is an ideal system to use for distant planning and retinal telephotocoagulation. The original concept of retinal telephotocoagulation based on "offline" image-based treatment planning and using a navigated laser system was introduced in 2017 by Kozak et al. In their study, Clinic 1 (located at the King Khaled Eye

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_17

Specialist Hospital, Riyadh, Saudi Arabia) collected retinal images and fundus fluorescein angiogram. Clinic 2 (located at the Palmetto Retina Center, West Columbia, SC, USA) created image based treatment plans based on which macular laser photocoagulation with motion-stabilized laser delivery was performed back at clinic 1. The teleretinal treatment plan was able to be successfully completed in all eyes thus demonstrating the feasibility and safety of using telemedicine to perform navigated retinal laser treatments regardless of geographical distance [3].

Chen H et al. have further advanced this concept and shown ability to plan the treatment online while having an expert available for consulting in real-time. Retinal telephotocoagulation operations were performed on all eyes without any noticeable delay during treatment. The study concluded that applying novel technologies may continue to ensure that remote patients with DR and other conditions have access to essential health care [4].

Teleeducation

Retina laser treatment is a critical task which requires experience and intense training to be performed safely and efficiently. Expert knowledge is needed to define the best treatment approach and to perform a precise treatment—especially when using a manually operated slit lamp based laser. However, the retina laser expertise is becoming scarce as retina experts face growing numbers for diabetic retinopathy and other retina diseases worldwide leaving less time for education. In addition, resident physicians have less chances opportunities to gather practical experiences with laser as some diseases have used intravitreal injections as the primary care. Thus, less patients are available for residents to study "correct" laser treatments by observation of more experienced colleagues. At the same time, trainers have little opportunity to accompany the practical learning process and provide regular feedback. In addition to this, the potential pandemic situation also complicates several steps such as "observation" as the goal is to minimize number of persons within the treatment room.

Feasibility of teleguided treatment with navigated laser opens up the opportunity of teleguided education (distant learning) which can help overcome current restraints in the learning of retinal laser care, such as lack of practical experience under expert guidance. At the same time, remote guidance and distant learning help respect social distancing during the pandemic times when in-person trainings are to be minimized as much as possible.

Retinal laser teleeducation module developed by OD-OS Inc. has three main components: distant learning, distant guidance and distant planning (Fig. 17.1). *Distant learning* enables learners to observe live laser treatments from a remote location. With typical slit lamp laser treatments only 1 person is able to observe the application of laser spots via an ocular tube. With the possibility to tele-wire the digital treatment screen of a navigated laser treatment, a larger group of residents may benefit from seeing an expert practically perform a variety of cases of laser

treatments. *Distant guidance* allows an expert sitting in a remote location to observe, interfere through remote control and guide less experienced doctors in performing a retinal laser treatments. This way, learners may benefit from more frequent feedback and improve skills and quality of their treatments. *Remote planning* makes expert knowledge available also in underserved areas. It allows an experts to create laser plans which are then performed in the local region with the knowledge that the treatment approach has been designed by a physician with experience in the field.

There are, naturally, challenges for wider practical implementation of retinal telephotocoagulation. Despite the feasibility of the technical realization of telephotocoagulation, there is a barrier of device cost which needs to be addressed. Although expert knowledge might be used highly efficient over country borders, the laser equipment to perform controllable telephotocoagulation needs to be purchased regionally. In economically challenged countries, this can be an issue. An important aspect to remember is also the technical set-up of telephotocoagulation that needs to comply with regulatory as well as information technology (IT) safety and data protection requirements for particular clinics and countries. Finally, the liability for the treatment requires a careful agreement between both treating parties, as well as the patient. As of current regulatory understanding, the medical liability remains with ophthalmologist who is sitting in front of the laser and activates it for treatment. This, however, may change with the broader adoption of teleophthalmological solutions

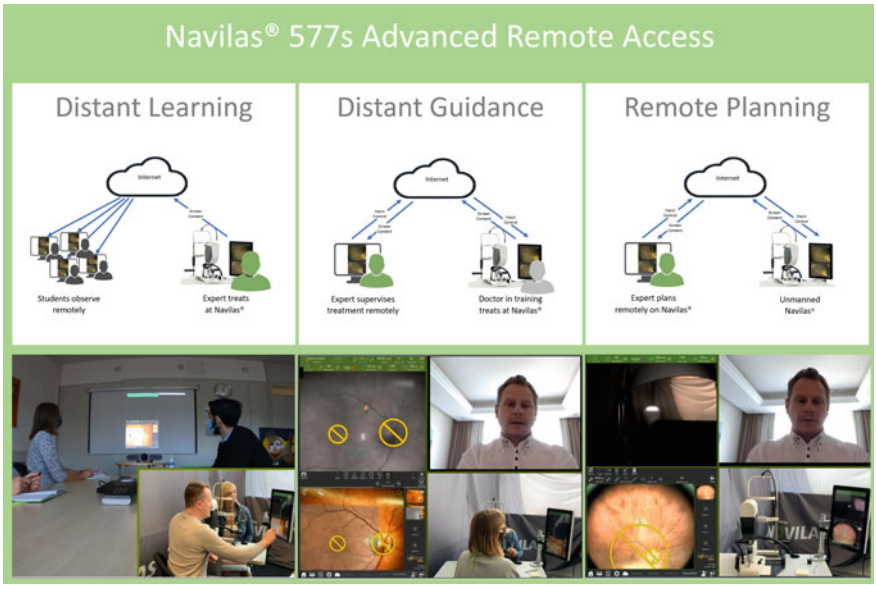

Fig. 17.1 The retinal laser teleducation module using navigated laser technology shows distant learning, distant guidance and remote planning modules in scheme (upper panels) and in practice (lower panels)

in the future. More studies and practical experiences are need to define the best approach on how to efficiently integrate these concepts in daily clinical care.

References

1. Kozak I, Oster SF, Cortes MA, Dowell D, Hartmann K, Kim JS, Freeman WR. Clinical evaluation and treatment accuracy in diabetic macular edema using navigated laser photocoagulator NAVILAS. Ophthalmology. 2011;118(6):1119–24.
2. Kernt M, Cheuteu R, Vounotrypidis E, Haritoglou C, Kampik A, Ulbig MW, Neubauer AS. Focal and panretinal photocoagulation with a navigated laser (NAVILAS®). Acta Ophthalmol. 2011;89(8):e662–4.
3. Kozak I, Payne JF, Schatz P, Al-Kahtani E, Winkler M. Teleophthalmology image-based navigated retinal laser therapy for diabetic macular edema: a concept of retinal telephotocoagulation. Graefe's Arch Clin Exp Ophthalmol. 2017;255(8):1509–1513. https://doi.org/10.1007/s00417-017-3674-1.
4. Chen H, Pan X, Yang J, Fan J, Qin M, Sun H, Liu J, Li N, Ting DSW, Chen Y. Application of 5G technology to conduct real-time teleretinal laser photocoagulation for the treatment of diabetic retinopathy. JAMA Ophthalmol. 2021;139(9):975–982.

Chapter 18
Diabetes Mellitus Associated Progressive Neurovascular Retinal Injury

Stephen H. Sinclair

Abstract Diabetes mellitus is now recognized as a systemic, autoimmune, microvascular disorder, which, in the retina results in severe, multifocal injury now recognized as a leading cause, world-wide, of progressive vision loss. To address this problem in the prediabetic and overt diabetic states, it must be realized that, although the injury processes may be system wide, there are varying responses, effector, and repair mechanisms that differ from organ to organ or within varying cell structures. Specifically, within the "neurovascular unit" of the retina, lesions occur of focal microvascular occlusions, inflammatory endothelial and pericyte injury, and small vessel leakage resulting in injury to astrocytes, Müller cells, microglia, and causing progressive neuronal apoptosis and death. Such lesions are now recognized to occur before the first microaneurysms are visible by fundus camera imaging or before detectable symptoms or signs recognizable to the patient or clinician. Treatments, therefore, which currently are not initiated until edema develops or progressive vascular occlusion, are applied relatively late with some reduction in progressive cellular injury but with minimal vision improvement. Desperately needed are newly developed imaging and functional testing methods that detect the early stages of microvascular injury and neuronal apoptosis when the processes are potentially reversible, not following severe, widespread atrophy. Treatment, when applied at such early stages, therefore can preserve far better functional vision. However, to be acceptable, such interventions must be minimally invasive with patient appreciated improvement in vision. Micropulsed applications of laser retinal phototherapy appear to offer treatment for such early intervention, not just to reverse the early alterations, but also for later stages of the progressive neurovascular and vision degradation when patients will continue to present.

Keywords Diabetic retinopathy · Neurovascular degeneration · Micropulse laser retinal therapy

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_18

Introduction

There are 463 million persons worldwide with diabetes mellitus, representing 9.3% of the adult population. This is expected to double in the next 25 years [1], with approximately 37% of adults older than 20 years and 51% older than 65 having prediabetes with predicted high rates of conversion to type 2DM with aging [2]. It is now recognized that diabetes, along with prediabetes, presents a severe risk for the development and progression of retinal, optic nerve, and brain neurovascular dysfunction [3–8], resulting in severe vision loss [9, 10]. The focus of the medical industry predominantly has been to examine the effect of hyperglycemia control along with other aggravating comorbid factors (hypertension, hyperlipidemia, smoking, obesity, and sleep apnea) on the progression of large vessel occlusive disease, because of the rising incidence of stroke and myocardial infarction [11–13]. However, it is now recognized that the small vessel disease is 20–30 times more common, resulting in severe disabling neuronal injury with resultant progressive vision and cognitive impairment [14–21].

To address this problem, it must be realized that, although some of the injury processes associated with diabetes are system wide and, therefore, possibly amenable to systemic therapy, there are varying response, effector, and repair mechanisms that differ from organ to organ or within varying cell structures within an organ tissue. For instance, inflammatory processes in the pancreas that result in beta cell death and reduced insulin production, are different from those in the adipose tissue that increase insulin resistance and are also different from responses within tissues of neurons, astrocytes, microglia, pericytes, and endothelia of the retina, now termed the "neurovascular unit" and, as well, with genetically defined variable susceptibility [22].

The Normal Human Retinal Neurovascular Unit and the Lesions Associated with Diabetes

The inner retina and brain neuroparenchyma demonstrate organization of a microvasculature supplied by small, perforating, independent vascular units that demonstrate little ability to provide collateral flow [23, 24] but, rather, demonstrate an intensive balance between tissue metabolism and vascular regulation of blood flow, termed autoregulation. The local precapillary arterioles are very sensitive to local extravascular oxygen levels. Because of the tendency of the intense light focused on the retina to potentially generate oxygen-free radicals within the tissue [25], the blood flow is maintained at critically low oxygen levels, therefore requiring extremely careful regulation of flow, moment to moment, despite changes in arterial inflow or venous outflow pressures. While the choriocapillaris supply to the outer retina manifests a high flow rate to provide high oxygen delivery for the intense oxygen consumption of the immediately overlying photoreceptors, as well as stabilizing generated heat, little

oxygen diffuses through into the middle and inner retina. At night the photoreceptor and middle nuclear layer neurons become hyper-polarized (termed "dark current") in order to reduce spontaneous transmissions (flashes of light), also requiring sensitive adjustment of flow within the middle nuclear and parenchymal layers. In humans, non-invasive flow measurements allow assessment of baseline flow by laser doppler velocimetry along with autoregulatory changes that can be induced by alterations of inhaled oxygen and/or perfusion pressure [26].

Astrocytes in the inner retina synapse on blood vessels to control such autoregulation [27], while Müller cells, which span all retinal layers, coordinate the vascular responses to meet the metabolic demand of neurons, interchange metabolites, recycle neurotransmitters and glutamate, and control extracellular ion homeostasis. Microglia, which normally reside within the plexiform retinal strata, exhibit ramified processes responsible for immune surveillance along with monitoring noxious insults such as oxidative stress, hypoxia, or inherited mutations, that trigger proliferation and migration of the cells to the sites of injury [28, 29]. Coordinated activity among neurons, Müller cells, astrocytes, and microglia, together with the microvasculature, is essential for the maintenance of normal metabolic function and visual perception. Although the local autoregulatory mechanisms pre-eminently attempt to maintain flow aligned with metabolism, it is recognized that certain conditions, such as vasospasm induced in the peripheral limbs due to cold exposure also produce coexistent transient reductions in retinal blood flow in susceptible individuals (termed systemic vascular dysregulation, SVD) [30]. Although these are thought to be transient, SVD has been associated with a risk for anterior ischemic optic neuropathy, retinal venous occlusion, central serous chorio-retinopathy, and especially for glaucomatous disc nerve-fiber-layer progressive loss [31, 32]. More recently SVD has been associated with a more chronic, reduced parapapillary, microvascular density in what were thought to be normal eyes [32]. This may be only one manifestation of system-wide disorders that alone, or perhaps in conjunction with local ocular abnormalities, may result in more prolonged injury to the microvasculature.

The coordination of blood flow to metabolic demand, synaptic activity, and waste removal is coordinated through neurotransmitter-mediated signaling, particularly through glutamate release of nitric oxide from neurons and of arachidonic acid derivatives from astrocytes (and possibly from neurons) and by ATP conversion to adenosine [33–35]. The blood-retinal barrier is formed by the continuous microvascular endothelium and its underlying basement membrane with pericytes that tightly encircle the endothelium, and astrocytes in the surrounding tissue space that extend their cell processes between the endothelia to insert on the basement membrane. Pericytes are noted to be highly susceptible to damage in ischemic conditions (when ATP levels are low) suggesting the possibility that pericytes are the cause of the prolonged constriction of capillaries at the start of a stroke [36] as they remain in rigor (because no ATP is available to relax their contractile filaments), causing the capillaries to remain too narrow for the passage of blood cells, predominantly leukocytes. In agreement with this, pericytes are noted to remain constricted even for hours after the re-opening of an occluded parent artery (in brain models [37]) that results in endothelial damage and capillary leakage. Suppression of oxidative and

nitrosative stress prevents this pericyte constriction, restoring the patency of capillaries and tissue recovery [37]. This has important implications to the understanding of tissue reactions to prolonged ischemia due as well to chronic small vessel disease, as well as with the occurrence of vacillations in oxygen levels or in blood pressure (as occurs with sleep apnea in which transient drops in oxygen induce autoregulatory dilation of the retinal arterioles resulting in capillary hypertension that is severely aggravated with the sudden rise in blood pressure occurring at the "reprise" end of each apneic episode and has been associated with capillary occlusion even in normal, non-diabetic individuals suffering sleep apnea [38]).

The mechanisms by which the retinal microvasculature in the diabetic individual is more susceptible to large, as well as small vessel abnormalities of flow regulation are now better understood. In the human diabetic eye, increased blood flow has been measured associated with elevations of serum glucose, known to occur as well in the eye of the "prediabetic" with hyperglycemia variation [39]. This results in capillary hypertension [40, 41] along with a reduced capability of autoregulation, [26, 41–43], apparently worse in the middle retinal layer than that in the inner, more superficial layers [44], but, in both, due to abnormalities of the nitric oxide (NO) messenger within the arteriolar musculature [45]. These mechanisms, as well the recognized additional factors of hypertension, smoking, sleep apnea, and others that will be discussed below, result in aggravation of both retinal small vessel ischemic lesions in the diabetic and prediabetic populations [46, 47] with progressive vision loss (and in the brain, which shares similar outcomes, resulting in microvascular cognitive impairment and dementia [48]). While arteriolar oxygen reactivity and its match with metabolism have been the primary focus of investigations into the aberrant cause of the retinopathy, it is also now recognized that toxic byproducts which accumulate in the interstitial, perivascular space result as well in neuronal apoptosis. Such toxic products have been thought to be eliminated primarily via the veins. However, more recently perivascular accumulated fluid, and metabolic byproducts, have been demonstrated to exit also via the lamina cribrosa and a hypothesized glymphatic CSF drainage [49]. While the importance of this aspect of toxic removal is now better recognized in the pathogenesis of glaucomatous nerve fiber layer injury, its causation in other retinal and brain neurodegenerations at this time remains only hypothetical.

Diabetic retinopathy (DR) has traditionally been considered to be a microcirculatory disease caused by the deleterious metabolic effects of hyperglycemia per se and the metabolic pathways triggered by hyperglycemia, including the polyol [50], hexosamine, and DAG-PKC pathways [51, 52], resulting in advanced, glycation end-products [53] and the induction of oxidative stress [54]. The primary retinal lesions, however, are now recognized as small neurovascular lesions composed of both focal vascular occlusions mixed with varying degrees and types of inflammatory endothelial and pericyte injury. These produce small vessel leakages that result in injury to structural astrocytes, Müller cells, and microglia, with both processes causing progressive focal neuronal apoptosis that has been noted to occur in diabetic as well as many prediabetic individuals. The earliest structural change appears to be a loss of microvascular pericytes via apoptosis or migration, which then leads

to weakening of the blood-retinal barrier [55] through loss of the inter-endothelial tight junction proteins [56]. This precedes, but results as well, in apoptosis of the endothelial cells, resulting in loss of endothelial nitric oxide (NO) production. NO is the primary vasodilator that provides for the normal small arteriolar autoregulatory capabilities discussed above. Furthermore, capillary hypertension, caused by the elevated flow levels in the remaining patent vessels, is recognized to stimulate the endothelial cell production of inter-cellular adhesion molecules (ICAMS) that slow and obstruct the normal passage of white blood cells through those capillaries [57] with subsequent WBC breakdown and endothelial injury [58, 59]. Studies of retinal vessel oxygen saturations indicate a reduction in oxygen delivery, confirming such focal occlusions with increased flows that occur within the surrounding microvasculature units early within diabetics [60], but resulting in significant focal variations in delivery of oxygen, nutrients, and waste removal.

For the past 50 years, however, the clinical focus for detecting and grading diabetic retinopathy (DR), as well as considering the instigation of treatment, has been the viewing on examination of secondary retinal vascular lesions of microaneurysms, hemorrhages, intra-retinal and epiretinal microvascular proliferation, arterial wall thickening and venular irregular dilation, with varying degrees of intracellular and extracellular edema and irregularly scattered lipid [61, 62]. Of greater significance, is that neuronal and Müller cell death occurs in focal patterns within multiple retinal layers much earlier (in both diabetic and prediabetic individuals) [63, 64], even prior to the pericyte and endothelial cell apoptosis [64–69]. These alterations, however, are not visible on examination or appreciated with standard imaging by fundus cameras or ocular coherence tomography (OCT) until there is fairly severe, wide spread neuronal death and atrophy that is appreciated structurally as progressive layer thinning on OCT of the inner retinal nuclear layers and nerve fiber layer [64, 66–68, 70–72]. This occurs in 20% of diabetics even prior to observation of microaneurysms [71] and in prediabetics as well [73]. In addition, the Müller cells (macroglia) and microglia appear to play key roles in what is considered to be an inflammatory process [74] via activation of their endoplasmic reticulum from the stress of hyperglycemia [75]. The stressed Müller cells express vimentin and glial fibrillary acidic protein (GFAP) that have multiple effects upon both neural [76, 77] and capillary regeneration [78]. As well it should be understood that Müller cells act as living optical fibers that guide red and green light through the inner retinal tissue to specialized cone photoreceptors [79], minimizing intra-retinal light scatter to support high resolution vision [80, 81]. Therefore, reactive gliosis of and by Müller cells [74] contributes to the early visual abnormalities that have been detected in diabetic subjects via multifocal ERG [82–84], as well as when tested at fixation via blue-sensitive acuity or contrast sensitivity at low light levels [65, 85, 86] as well as throughout the macula with resolution perimetry conducted under low illumination, low contrast conditions [87].

Unfortunately, these functional and electrophysiologic tests are seldom performed in the standard ophthalmologist's or optometrist's office and are not recommended in current evaluation guidelines [88], resulting in the relatively late discovery of injury when macular edema or the more severe lesions of DR are recognized [89]. This delays intervention, currently consisting primarily of repeated intravitreal injections

of antiVEGF or steroid medications that result in marginal vision improvement. In multiple studies, only 25–34% demonstrate improvement of ≥3 ETDRS lines of high contrast, photopic visual acuity, and primarily only among the eyes with severe retinopathy and severely reduced initial vision, and with 23% considered non-responders and 27% having only a moderate response [62, 90–93]. Recent methods of OCT derived microvascular analysis (termed OCTangiography, OCTangio) have provided analysis of the retinal microvasculature. These demonstrate that reductions in microvascular density occur prior to the development of the traditional retinopathy lesions and progressively worsen over time, correlated with worsening grades of the retinopathy [94–97]. The microvascular disease, however, is not uniform through the retinal layers, but occurs in a focal process primarily or earliest within the superficial ganglion cell layer with a slower decline in the deeper internuclear, plexiform, and middle neuronal layers [95–98], as well as within the radial peripapillary capillaries of the nerve fiber layer [99]. However, owing to the limitations of this new imaging modality and the great variety of algorithms utilized for vascular layer segmentation and flow evaluation, much debate continues over which vascular plexus is primarily affected, especially within the parafoveal area of the central vision where the layers merge [100]. No consensus has been reached on the ideal set of quantitative metrics, whether parafoveal vascular density or total avascular area or a derivative "adjusted flow index", would best quantitate microvascular occlusive progression [98] as well as the adequacy of the remodeling that is known to occur [101]. As well, it must be understood that flows and diameters are not quantitated, only the microvascular grid structure. In addition, the indices derived have represented averages within the perifovea; diabetes is a focal microvascular disease process, and, with this understanding, evaluations must reflect this.

Simultaneous with the microvascular alterations, there is neuronal apoptotic injury with death and tissue fluid that appear as darkened regions of the retina on adaptive optics scanning laser ophthalmoscopy [101] and then with eventual diffuse atrophy of the various layers noted on OCT beta scans as discussed above [95, 97, 102–105]. It remains unknown whether the microvascular occlusions, with degradation of the endothelia, pericytes, and Müller cells, occurs prior to, and causes the neuronal apoptosis, or whether the microvascular changes are the consequence of prior neural tissue inflammation and cellular injury proximal to the vessels. It is now recognized that the current, commonly utilized imaging methods fail in this regard. What is required are improved methods to detect and grade the progression of both processes that compromise the neurovascular integrated function with then the hopeful development of treatments applied early in the course, before the irreversible death and atrophy occur [87, 96, 106, 107].

Pathologic Mechanisms Implicated in the Development of Retinal Lesions in Diabetic Patients

Diabetes mellitus, therefore, is now recognized to involve a systemic, autoimmune, inflammatory disorder causing focal microvascular occlusions and alterations of the blood-retinal and blood–brain barriers, that occur in the "pre-diabetic" as well as diabetic individuals [1, 87, 108, 109]. In the Diabetes Prevention Program (DPP), 7.9% of subjects with impaired glucose tolerance had retinopathy [110], similar to the 8.1% prevalence of retinopathy observed among individuals with prediabetes in the Gutenberg Health Study [111] with the variability of the glycemia a significant recognized risk factor for both development and progression [112, 113]. HbA1c has been the primary criteria differentiating the diagnosis of diabetes from prediabetes, but it must be stressed that there are many recognized problems of this measurement [114]. Although DR or its progression is recognized to be related to HgbA1c or associations with HTN and hyperlipidemia, studies across the globe have observed that the risk of many of the associated co-morbidities are the same in diabetics and prediabetics and affect all age groups indicating these are complicated interactions [5]. Across the straie of hyperglycemia definitions, the increasing requirement for insulin, brought about by the progressive insulin resistance of peripheral fat, together with the pancreas Beta cell loss (both a product of the autoimmune reactions) is associated in itself with aggravated risk of vascular induced retinal as well as cognitive dysfunction [115]. It is important to recognize that, in this regard, the retina is the window to the brain.

Microvascular Injury, Dysregulation, and Occlusion

One proposed mechanism of vascular injury associated with diabetes is through impairment in the regulation of the transient receptor potential cation channel (TRPC). Under physiologically healthy conditions, the vascular wall responds to high pressure by upregulating TRPC, triggering reactive vasoconstriction. However, continuous stimulation ultimately results in poor flow autoregulation to the variations of the stimulant (studied in the brain) [116]. Both aging and deficiencies in insulin-like growth factor 1 (IGF-1) in the presence of hypertension have been shown to impair upregulation of TRPC [117, 118], a proposed mechanism of vascular injury associated with diabetes[119]. Failure to upregulate TRPC leaves the microcirculation vulnerable to damage caused by the variation in pressures within the microvasculature resulting in increased blood-retinal and blood–brain barrier leakage and neuroinflammation [120, 121]. There is also a gradual accumulation of multiple molecular fractures of the intima and internal, elastic lamina of the microvasculature. The accumulation of such patches eventually transforms the elastic lamina to a stiffened, friable wall. The resulting array of structural, degenerative events in the vessel wall, including death of endothelial cells, basal membrane thickening, and atrophy of the

smooth muscle cells [122, 123] all lead to rupture (microbleeds), microinfarcts, and loss of tight junctions with reduced retinal barrier integrity. In addition, within the retinal capillaries of the diabetic, leukocyte drag and adhesion occur due to leukocyte increased stiffness in diabetes with the upregulation of endothelial derived adhesion molecules (ICAMS and VCAMS) that adhere with the leukocyte integrins resulting in the adherence of the leukocyte to the endothelium and with degradation result in focal microvascular occlusion and leakage [124–126]. The resultant increased permeability of the blood-retinal barrier then results in interstitial accumulation of water and cytokine proteins with further worsening of the inflammatory/oxidative stress events that, with gliosis, damage the parenchyma. Pericytes and oligodendrocytes are extremely vulnerable to these ischemic and toxic insults [127, 128] also resulting in impaired normal tissue repair [129].

Inflammatory Mechanisms Associated with the Neurovascular Injury

Systemic inflammatory mechanisms certainly appear active in a number of the recognized neurodegenerative processes of diabetes, with microglia and astrocytes as the primary contributors to the inflammation. Normally quiescent, such activated cellular components begin to secrete cytotoxic substances that contribute to neuronal cell death [103]. As discussed above, in the diabetic or prediabetic patient, there is chronic, systemic, low-grade systemic inflammation [87] that is reflected by elevated serum cytokines such as tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP), and the interleukin cytokines IL-6, IL-8, IL-1B, and the receptor antagonist, C5a [130, 131] along with granulocyte and monocyte elevations [130, 132]. While this inflammatory state is thought to be the mechanism by which metabolic disorders such as diabetes are associated with the development of small vessel organ failure, there is significant variability of the cytokines that indicates this is a complex process among the various organ tissues [133–137].

As discussed above the neuronal apoptosis within the inner retina appears to be preceded by loss of the microvascular pericytes and then endothelia, resulting in loss of reactivity with very early vasodilation along with early increased permeability [40, 55]. Chronic, variable hyperglycemia has been observed to cause an increase in release of glutamate with loss of neuroprotective factors due to oxidative stress with the accumulation of the waste products of glycolysis that trigger the apoptosis [65]. However, it must be acknowledged that all of the supporting structures of the neurons, including the Müller cells, astrocytes, pericytes, and infiltrating monocytes (microglia), have also been defined as critical participants in the neuroinflammatory and protection processes [138]. Activated Müller cells mediate both protective and detrimental effects upon the ganglion cell layer neurons of the retina through a variety of receptors that result in the expression of multiple factors affecting neuronal survival [139] including glial fibrillary acidic protein (GFAP),

vimentin [140, 141] and growth factors, such as brain-derived neurotrophic factor (BDNF) and platelet-derived growth factor B (PDGF-B) [64, 74, 142]. Müller cells also manifest a protective role by absorbing glutamate, reducing the extracellular glutamate cytotoxic effects [143, 144]. Diabetes not only reduces the Müller uptake of glutamate within the neuro-retina [145] but also reduces the activity of glutamine synthetase, hindering it's ability to convert the excess glutamate to inactive glutamine [146] or to oxidize the glutamate to a-ketoglutarate [143]. Activated Müller cells, therefore, serve not only as rapid sensors of neuronal damage to initiate repair and neural regeneration [147, 148], but they may also initiate a deleterious inflammatory process with release of proinflammatory cytokines, such as activating transcription factor 4 (results in release of ICAM-1 and VEGF [75, 149]) as well as TNFα, IL-1, and other cytokines known to exacerbate apoptosis of adjacent neurons [69, 139, 150]. Such cytokines, as mentioned above, have been detected in aqueous humor samples of diabetic eyes with varying grades of retinopathy [151, 152]. This dual action, therefore, is certainly a double-edged sword and should be accounted for in the design of therapeutic approaches addressed to abrogate Müller glial and activation with gliosis.

Microglia within the retina are the principal immune effector cells, constantly surveying their environment in preparation to react to insult or injury. When activated, for example in diabetes, microglia become ameboid, and migrate within the inner and outer retina, releasing pro-inflammatory and vasoactive substances, contributing to the local inflammatory response that results in increased vascular permeability. The microglia are normally phagocytic, clearing damaged myelin to allow neuronal repair. However, a chronic pro-inflammatory state, such as that induced with variable hyperglycemia, alters the response, preventing remyelination. In human diabetic retinas, activated microglia are often observed associated with the vasculature as discrete hyper-reflective foci on SD-OCT [153], leading to the term "microglial perivasculitis", even in diabetic eyes without clinical signs of DR [154] and which result in the release of numerous cytokines, including, VEGF, IL-6, IL-1B, TNFa, and monocyte chemoattractant protein-1 (MCP-1) with several studies indicating the contribution of these to the microvascular permeability and occlusive complications as well as progressive neuronal apoptosis [64, 155]. It should be noted, however, that activated microglia may also demonstrate a neuro-supportive function, similar to Müller cells, producing anti-inflammatory and neurotrophic factors, (e.g. IGF-1, BDNF, and GDNF, among others [152, 156–158]). The detection of microglial activation ultimately may prove of value in early disease diagnosis, as modulation of microglial responses appears to provide the ability to alter disease progression.

Treatment of Diabetic Retinopathy

As discussed above, while the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study demonstrated that controlling blood glucose, as measured by HgbA1c and periodic blood glucose levels, reduced the

progression of developed complications such as DR, [159, 160], post-hoc analysis of the DCCT data has revealed that only 11% of the risk in retinopathy development could be attributed to hemoglobin A1c. Later studies showing significant, perhaps even greater impact of the glucose fluctuations [161], as well as the degree of insulin usage in type 2 DM with insulin resistance [162]. As discussed above, the systemic microvascular disease that causes the progressive, profound, microvascular occlusion and inflammatory injury is now recognized to exist in the prediabetic as well as the overt diabetic, especially among those demonstrating insulin resistance with hyper and hypoglycemic variability [163]. This accounts for a number of the drugs that were initially approved for the control of hyperglycemia, that are now recognized to have significant, but variable effects on individual end-organs. However, the clinical treatments, whether systemic or specifically directed to the retina, have been limited by the traditional evaluation methods of imaging and/or functional organ testing and only following stages of significant and often severe organ failure. The above cited microvascular and neuroparenchymal cellular pathologies represent a complex array of processes that are targets for earlier diagnosis and treatment. This chapter will be limited to the discussion of newer methods of retinal laser treatment upon the progressive neurovascular injury caused by diabetes as well as potential methods for initiation earlier in the course when microvascular injury and neuronal apoptosis are reversible. For a more comprehensive discussion of traditional hyperglycemia treatments as well as newer systemic treatments currently available or under clinical evaluation for treating the retina as well as brain neurovascular occlusive and inflammatory injury the reader is referred to these excellent review articles [87, 164–168].

New methods of imaging of the focal neuronal apoptosis and inflammation within the retina (via fluorescent staining of Bis(zinc-dipicolylamine), Zn-DPA) are in progress [169, 170] and appear to enable earlier detection of neuronal injury during the apoptosis process when reversible. This will then empower initiation of treatments before the death and severe, diffuse atrophy that is the current threshold. In addition, improvements in the scanning times of OCTangio devices have improved the evaluation of flow characteristics, and with improved sectoral microvascular lumen reconstruction will enable identification of the early focal abnormalities (perhaps along with analysis of retinal capillary white blood cell flow densities utilizing the non-invasive blue field, entoptic phenomenon [57, 125]). Whether these preclude or are associated with the focal neuronal apoptosis is for evaluation in the future as new methods now allow the functional testing to be overlaid onto the neuronal and microvascular occlusion lesion imaging. It is imperative, therefore, that diabetics and prediabetics be screened regularly, utilizing improved imaging as well as functional testing of resolved targets, not only at fixation [106, 164] but within the central visual field utilizing resolution targets under conditions of reduced contrast and luminance with fixation control [87] to define earlier, reversible disturbances.

Once discovered and tracked, however, the difficulty remains as to how to address the progressive neurovascular injury processes. It is axiomatic in medicine that the earlier an effective intervention can be applied, the better the outcomes [165]. Certainly it is easier to prevent the severe complications of disease, such as severe

vision loss from DR, than to attempt to restore normal form and function once it has been lost. Ethically, early, preventive treatment must be, not only effective, but extremely safe and maximally free of adverse treatment effects. This is because treatment may need to be continued for many years, during which time the impact of adverse effects are increasingly likely to occur. Practically, this is also because patients with early clinical disease are generally asymptomatic and functionally normal, although often modified by adaptation. Putting either at risk is unacceptable to patients who tend to place more value on their current state of being than upon a hypothetically better future that might only be attained through inconvenience and pain [171, 172]. As will be realized, such real considerations disqualify most therapeutic treatment options from consideration as preventive treatments for DR.

The History of Treatment of Diabetic Retinopathy: Continuous Wave Laser Retinal Photocoagulation

The apocryphal origins of retinal photocoagulation for the complications of diabetic retinopathy were the observations that eyes with large chorioretinal scars occurring in one eye, such as from congenital infections, appeared to be somewhat protected from DR progression and injury compared with their fellow eyes. Retinal photocoagulation, accomplished by xenon arc or laser, was recognized as an effective method of producing chorioretinal scarring, and on this basis, was applied to prevent the vision destructive complications [168, 173]. The mechanism for the laser effect was not known but presumed to be associated with reduction of the overall tissue ischemia, hypothesized to possibly also result in increased oxygen tension by thinning the retina and increasing diffusion of oxygen from the underlying choroid. Based on this observation, 500um, full thickness burns were placed in the periphery (Fig. 18.1), as far anterior as possible, preferably to the ora serrata, and within all areas posteriorly of absent capillary flow visualized on fluorescein angiography, but sparing the posterior retina so as to preserve central visual function, and with the burns placed approximately 0.5 disc diameters apart because of the postoperative eventual spread of the deep retinal and RPE scars, hopefully retaining some peripheral vision.

Pan-retinal scatter laser photocoagulation was demonstrated to reduce the incidence of severe vision loss due to complications of the epiretinal neovascularization from 16.3% to 6.4%, but was associated with some further decline in central acuity often by 2 or more ETDRS lines in nearly 50% of eyes [174]. Because the pan retinal laser was found to be superior to no treatment, it became widely adopted and employed for advanced stages of proliferative retinopathy to prevent vitreous hemorrhage and tractional complications. Secondary complications of the initiation or aggravation of macular edema that occurred due to inflammation resulting from thermal tissue destruction [175, 176] or from macular distortion that occurred because of the fibrosis and contracture of the neovascularization during involution that is now recognized to also be a result of the inflammation. Furthermore, by the time the

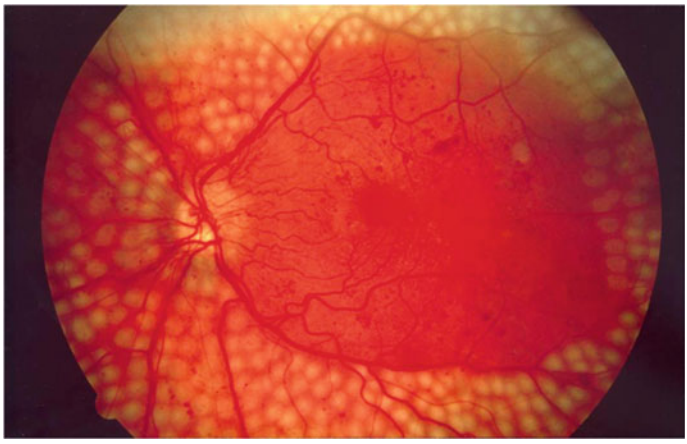

Fig. 18.1 Color fundus photograph of left fundus 2 weeks after the application of peripheral, panretinal laser photocoagulation with 500 um applications demonstrating nearly contiguous lesions applied peripheral to the disc and posterior vascular arcades [from: https://www.cairnseye.com/]

neovascularization was noted on examination or resulted in visual symptoms from a vitreous hemorrhage or traction distortion of the macular retina, the capillary nonperfusion had proceeded sufficiently posterior such that, with the burns destroying all layers of retina and underlying choroidal vasculature, the peripheral visual field was severely constricted, often to within 10–15 degrees of fixation, and with little alteration of the ongoing progressive macular OCT inner retinal microvascular loss and neuronal atrophy [177].

When macular edema was recognized as a common cause of vision loss, the application of focal laser photocoagulation, utilizing smaller, focal applications of full thickness burns was evaluated and, with the publication of the multiple reports from the Early Treatment Diabetic Study in 1987 [159], became the standard of care. Although the retinal edema, as measured by central retinal thickness or retinal volume, with or without cysts, was improved, improvement in central chart acuity was minimal. Furthermore, the parafoveal laser burns were associated with severe destruction of retinal photoreceptors and with progressive enlargement of the laser retinal scars inward and laterally [178], lead frequently to foveal involvement or to secondary choroidal neovascularization and subfoveal hemorrhage and fibrosis [179], However, the macular scarring was largely ignored, because of the use of chart acuity as the primary functional outcome. As discussed above, with macular disease, when charts are used to conduct any testing of central vision, the patient moves their eye searching for the best functioning area regardless of scotomas. When parafoveal full thickness burns are produced and result in significant paraxial visual field defects [179, 180], they result in non-trivial, adverse consequences, including, poor reading speed and ability, loss of night vision, loss of driving privileges, and disruption of circadian rhythms and normal sleep cycles, to name but a few [181–183]. As

destructive-sparing alternatives to photocoagulation became available (e.g. intravitreal injected anti-VEGF, Tie-2 compounds, and steroids), these drawbacks relegated laser application to lower tiers of treatment (initiated after intravitreal injections) or avoided all together [19, 184]. The frequency of the required intraocular injections, however, has restricted patient acceptance of these treatments, limiting the results and has forced the industry to turn to prolonged delivery ports, which require surgical implantation and have been associated with significant complications, including cataract, extrusion, and endophthalmitis [185], reducing the benefit/risk ratio. Such factors, therefore, preclude the consideration of either retinal photocoagulation or intravitreally injected drug therapy as early and / or preventive treatment of DR in its earliest stages of development when the injury is reversible and most amenable to treatment.

Current Retinal Laser Therapy of Diabetic Retinopathy

Current methods of laser treatment of the retina approach disease and treatment in a fundamentally different manner. Current laser treatment methods are the result of the discovery in 2000 that laser-induced retinal damage (LIRD), the single cause of all SAEs associated with conventional photocoagulation, was unnecessary for effective treatment [181, 186–189]. Instead, thermal laser photostimulation of the RPE, at levels sublethal to the retinal pigmented epithelium (RPE) and neurosensory retina (NSR), resulted in improved and normalized retinal function without adverse treatment effects [190, 191]. Furthermore, the effects of photothermal stimulation of the retina appeared to be agnostic to the cause of the underlying retinal dysfunction, thus allowing the treatment to normalize retinal function for a number of identified chronic progressive retinopathies (CPRs) [192, 193]. The action of the laser induced thermal change appeared to be a "non-specific trigger of disease-specific repair" through a physiologic, healing "reset" of the dysfunctional retina to normalize retinal function [191, 194].

If one were to attempt to prevent diabetic retinopathy using a targeted approach, the preceding review of the pathologic changes, which occur in the retina prior to the development of traditional clinical signs of retinopathy, makes clear that there are a great many potential treatment targets currently known, and almost certainly additional that remain unknown. Thus, targeted drug or biologic therapy to prevent DR in the face of the ongoing multi-dysfunction associated with systemic diabetes must confront the daunting challenges for any targeted therapy, rendering development of such a therapy—one that is both effective and without major adverse treatment effects—highly unlikely [195]. It should be noted as well that most of the potential targets reflect aspects of cellular dysfunction that then lead to further dysfunction, often in a vicious cycle. Rather than targeting the secondary effects of cell dysfunction as is attempted with current retinal biologics, current laser treatment addresses the cause of these effects, the DM-induced cellular dysfunction itself [194, 196].

All CPRs, including DR, result in progressive neuronal dysfunction and cell death, and while each may have different proximal causes, the particular stress placed on susceptible cells from these different diseases result in a common effect of excessive protein misfolding, aggregation, and resultant cellular dysfunction. A potential responsive healing process, known as the unfolded protein response (UPR) of the endoplasmic reticulum (ER) within the cell is responsible for proteostasis and maintenance of normal cell function [197–200]. Cell growth, gene mutations, environmental stressors (including DM), infection, reactive oxygen species (ROS), and aging all tax these cellular proteostasis mechanisms wherein the peroxisome proliferator activated receptor γ (PPARγ) plays a master gate-keeper roll both in the injury and repair [201]. If this dysfunction exceeds the capacity of the UPR to un-fold and disaggregate misfolded proteins, as well as the ERAD (endoplasmic reticulum-associated protein degradation process) the UPR will then initiate cellular apoptosis, with ultimately, cell and tissue failure [202].

Acting as "chaperones" that identify, transport, modulate, and aid the UPR function, "heat shock proteins" (HSP) particularly HSP 70, that are upregulated by photothermal stimulation and which bind immunoglobulin protein (BiP), are critical for cell homeostasis and proteostasis [203]. In neurodegenerative diseases, the gradual failure of the homeostatic capability of the UPR proceeds, eventually resulting in cell death [199]. Such gradual failure that is characteristic of CPRs appears to result because of poor stimulation of the protective HSP activation and the UPR with inadequate generation of HSP BiP [204]. Thus, in such chronic diseases the reparative system itself progressively fails [205–208]. Acute stressing of the UPR, modulated by HSP activation, however, improves UPR function with upregulation of protein repair and improved cell function and survival [200]. Sudden temperature elevations, as produced by the micropulsed laser treatment, appear the most effective and efficient activators of the HSP-initiated restoration of normal proteostasis, resulting in many effects that include improved mitochondrial function, energy production and utilization [197, 209, 210]. The laser photothermal application, furthermore upregulates the UPR to generate HSP's, which diffuse into the NSR to normalize cell function and thus inhibit the progressive multicellular apoptosis [194, 196, 199] through the protein refolding and processing in dysfunctional cells, but not in normal cells [211]. Thus, if both dysfunctional and normal RPE cells are directly exposed to MRT, the only effect will be normalization of the abnormal cell. This describes the "patho-selective" function of the laser induced effects [194]. Within in vitro, in vivo, and in human studies, micropulsed laser activation of the RPE results in a wide range of restorative effects that result in improved cell function, normalization of RPE cytokine expression and, in response, normalization of retinal Mueller cell function, producing increased markers of reparative acute reactions with decreased biomarkers of chronic inflammation, also resulting in reduced ROS, increased retinal NO, and local therapeutic immunomodulation [152, 153, 193, 212–218]. As discussed in detail within other chapters of this book, the laser applies 40 and100us pulses separated by off intervals (5% duty cycle) designed to preclude any possible RPE or retinal injury due to the accumulation of tissue heat, well above the Arrhenius integral for HSP activation but below that for thermal cell death [181, 190,

191, 219–221]. Furthermore, the use of longer laser wavelengths, such as 810 nm (near infra-red), improve safety further because of reduced absorption within the heterogeneously and irregularly pigmented RPE of humans [211, 219]. The clinical effect of this sublethal treatment to the retina, furthermore, is maximized by *en masse* recruitment of abnormal RPE through the confluent treatment of large areas of the RPE, primarily at present panmacular but with the early involvement worse in the peripheral retina and with demonstrated involvement in the causation of posterior progression, the treatments may be expanded to treat the peripheral retina as well.

Thus, by sublethal, photothermal activation of the salvific HSP response, laser treatment restores normalized cellular function both in the RPE and retina in a manifold of ways, without regard to the underlying clinical cause of the protein misfolding and dysfunction. It does this safely with repeated efficacy demonstrated in repeat treatments, fundamental requirements of any potentially useful early or preventive treatment for a CPR such as DR [182, 219]. In addition, it is axiomatic that for any treatment to be effective therapy, it should also be preventive, if provided sufficiently early. The paucity of preventive treatments in medicine is due the adverse effects that render many of the therapies unsuitable for that purpose. The micropulsed laser treatment, on the other hand, is both highly effective for treatment of DR and safe, without known adverse treatment effects. Furthermore, not only is there absolute absence of retinal injury, but in addition, the treatment is painless, increasing patient acceptance, a critical requirement for any early and /or preventive treatment as discussed above. Applying principles to the laser treatments discussed to preclude adverse treatment effects and maximize treatment efficacy; RCTs have shown laser to be comparable if not clinically superior to intravitreal anti-VEGF therapy, with a lower treatment burden [222] and longer duration of effect [192, 217, 223] (Figs. 18.2,18.3, and 18.4).

The question remains regarding whether the treatment should be applied in a contiguous fashion, not just pan-macular, but pan retinal for cases demonstrating earlier stages of retinopathy or for the later stages of retinopathy with progressed peripheral retinal as well as macular capillary non-perfusion and neuronal apoptosis but without DME or for the severe signs of peripheral ischemia preceding or with neovascularization. A small number of studies employing micropulsed laser have been reported wherein the laser has been applied in a contiguous fashion over the peripheral retina in addition to the macula [188, 224, 225]. The results have mirrored the results of treatment for DME, showing efficacy comparable to conventional photocoagulation (but without adverse treatment effects) and with visual results comparable to drug therapy (but with a longer duration of action). The acceptance of pan-retinal as well as pan-macular contiguous treatment is supported by the observations that peripheral DR lesions do increase the risk for progression and macular complications [226] implying that for all early, intermediate or advanced stages the treatment of micropulsed laser should be pan-retinal.

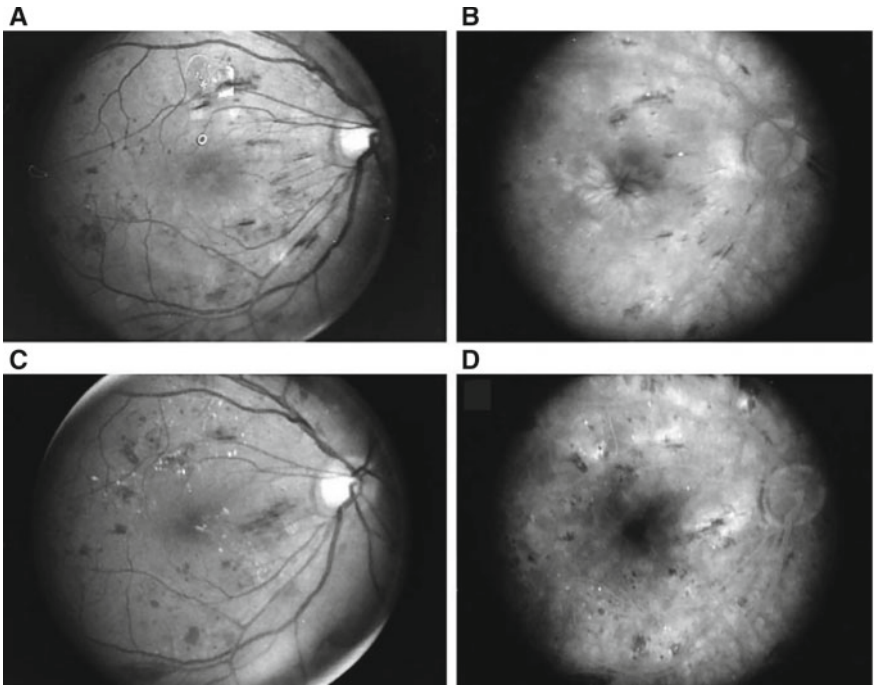

Fig. 18.2 **A** Preoperative red-free fundus photograph of patient with diffuse clinically significant diabetic macular edema and foveal cysts. (Note film development artefacts superior to fovea and at temporal edge of photograph). **B** Late phase preoperative intravenous fundus fluorescein angiogram of diffuse, clinically significant diabetic macular edema, with cystoid leakage pattern in fovea. **C** Red-free fundus photograph 8 months following 602 confluent grid applications of MRT throughout the macula extending to the edge of the fovea circumferentially.. Note marked reduction in macular edema without visible chorioretinal scarring or pigmentary disturbance. **D** Postoperative intravenous fundus fluorescein angiogram demonstrating marked reduction in diffuse, cystoid leakage, and without angiographically visible pigmentary disturbance or chorioretinal scarring [from: Luttrull, et al., 2005, ref. 187]

Conclusion

In all regards, as discussed above, the treatment of the neuro-vascular degeneration that occurs and progresses among individuals with diabetes as well as pre-diabetes to cause severe vision loss, even with the optimum glycemic control, remains unsatisfactory. This demands an urgency for defining treatment methods that prevent the devastating vision loss caused by this systemic disorder and the effects upon the retina. Certainly, such treatments must be entertained as early as possible in the course with repeated monitoring guidance and reapplication to achieve these goals.

The primary orientation here-to-fore, however, has been to focus interventions upon treating the late DR complications of macular edema and neovascularization with the continued monitoring via retinal imaging including fundus photographs,

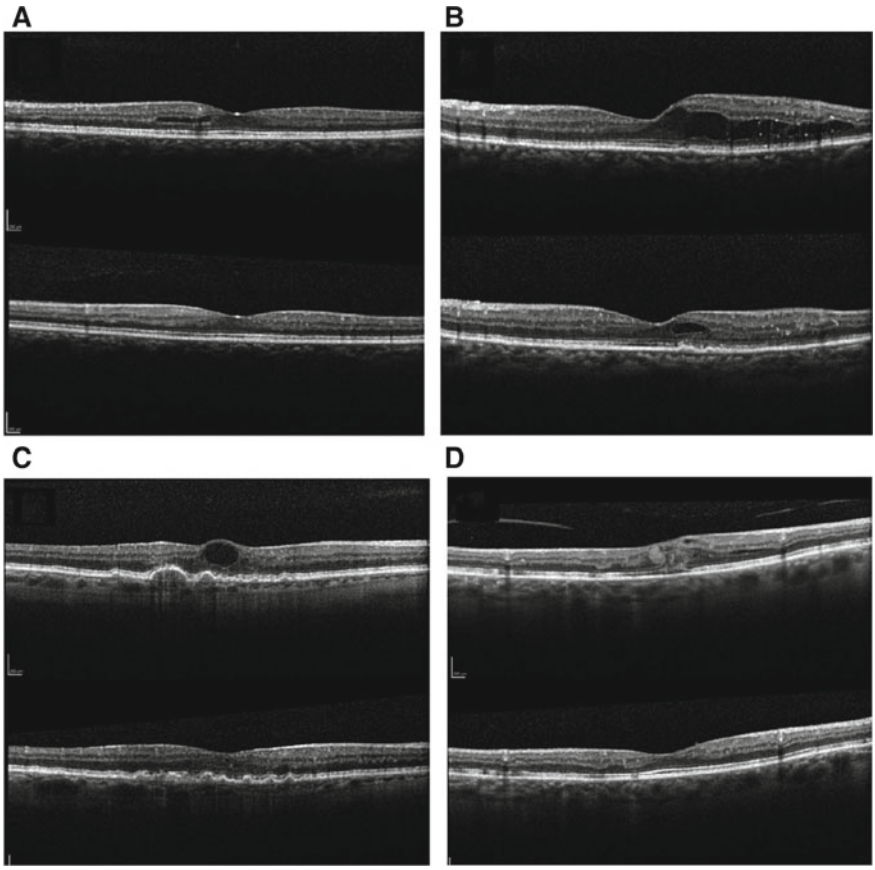

Fig. 18.3 Spectral-domain optical coherence tomograms (SD-OCT) of eyes with fovea-involving DME and chart BCVA's better than 20/40 treated with transfoveal MRT applied throughout macula. Despite mild macular thickening and good pre-treatment VAs, both macular thickening and VAs were significantly improved following treatment. In each pair, **A**–**D**, top of the frames represent preoperative SD-OCT and bottom of the frames represent postoperative SD-OCT). **A** Intrafoveal cysts without retinal thickening. **B** Intrafoveal thickening with minimal central foveal thickening. **C** Isolated central foveal cyst. **D** Diffuse macular thickening including the fovea [from: Luttrull, Sinclair, 2014, ref. 182]

IVFA and OCT and functional testing by chart acuity, and Humphrey visual fields performed under photopic conditions. As detailed above, these fail to detect the progression of the neurovascular injury until after significant, widespread microvascular occlusion and inflammatory injury cause neuronal apoptosis, death and atrophy. At these stages, the processes are poorly reversible with diabetes now becoming a major cause of mild, moderate and severe vision loss worldwide. What is absolutely required is the adoption of an attitude toward earlier intervention with methods that stop or preferentially reverse the neurovascular injury processes; however, at such

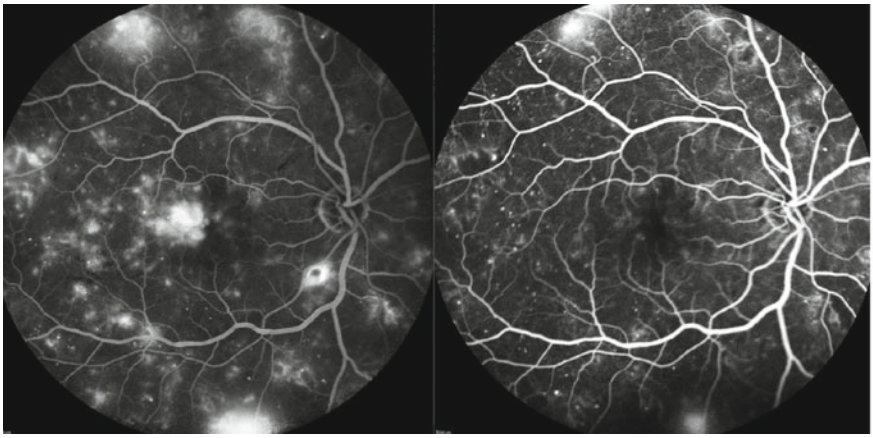

Fig. 18.4 Ten-minute post injection intravenous fundus fluorescein angiograms of eye with proliferative diabetic retinopathy before (left) and 3 years after (right) a single treatment session of panretinal MRT laser, with regression of neovascularization inferiorly, decreased fluorescein leakage and reversal of background retinopathy severity [from: Chhablani J, et al., 2018, ref. 222]

earlier stages such treatments must be non-invasive and easily tolerated by patients, with patient appreciated visual function outcomes.

The current evolution of laser therapy, involving sublethal micropulsed, contiguous applications, offers the ability to improve inflammation and visual function in eyes with diabetic retinopathy, with indications that the treatment is able to reverse, not just slow, disease progression and with maintenance of these improvements long-term (with guided retreatment as discussed). Because the laser treatment is without adverse treatment effects, and painless, it is the first treatment realistically appropriate for preventive use, at a time when the neurovascular progressive injury process is reversible and treatment is most effective [182], and with demonstration that the neurovascular protective effects are prolonged [187, 190, 191, 193, 211, 225–233]. Therefore, early treatment, especially prior to the development of classic DME or significant DR lesions, has been discussed above as it can effectively preclude vision loss in most eyes. Thus efficacy, durability, reliable safety and consequent repeatability of the laser therapy appear currently to make it the only viable, early and preventive intervention.

The question arises as to when to initiate intervention for this focal, progressive injury process. In principle, given the safety of the laser applications, we have proposed initiating treatment when testing of macular vision (not just central acuity) under mesopic or low contrast photopic conditions demonstrate loss, or when new methods of retinal imaging demonstrate early focal microvascular occlusion (via new constructs of OCTangio that improve quantitative analysis of focal lesions) or early neuronal apoptosis (e.g. via fluorescent staining of ZNDpA) [169, 170] or when far

peripheral retinal imaging in the infra-red wavelengths demonstrate the inflammatory process has progressed, thereby applying treatment when these processes are still potentially reversible.

The frequency of retreatment is dictated by the nature and severity of the disease process in the individual, with the more severe and rapidly progressive situations requiring more frequent retreatment, perhaps as often as every 3–4 months [182]. As a rule, however, the earlier the intervention is begun, the greater the long-term benefit. Compounding exponentially, the long-term benefits of even a slight slowing of a rapidly progressive disease may result in significantly prolonged retention of excellent visual function. Certainly, however, we must evaluate modalities for treatment of the more severe stages, at least to avoid the prevention of the severe blinding outcomes that currently manifest among so many individuals [233–238]. As discussed above, this most likely will require careful, multiphasic monitoring and multi-modal therapies, extending beyond those most often currently used [238].

Finally, the treatments must be associated in all cases with rehabilitation methods that understand the integrated visual field and the visual problems associated with real world task failure from focal defects in order to develop the assistive work-arounds together with adequate instruction and training to achieve patient engagement and task management.

References

1. Baranowska-Juran A, Matuszewski W, Bandurska-Stankiewicz E. Chronic microvascular complication in prediabetic states- an overview. J Clin Med. 2020;9:1–21. https://doi.org/10.3390/jcm9103289.
2. Centers for Disease Control and Prevention. National diabetes statistics report: Estimates of diabetes and its burden in the United States. Atlanta, GA: US Department of Health and Human Services; 2014.
3. Hugenschmidt C, Lovato J, Ambrosius W, et al. The cross-sectional and longitudinal associations of diabetic retinopathy with cognitive function and brain MRI findings: The action to control cardiovascular risk in diabetes (ACCORD) trial. Diabetes Care. 2014;37:3244–52. https://doi.org/10.2337/dc14-0502.
4. Joltikov, K, deCastro, V, Davila, J, et al. Multidimensional functional and structural evaluation reveals neuroretinal impariment in early diabetic retinopathy. Invest Ophthal vis Sci. 2017;58(6):Bio277–90. https://doi.org/10.1167/iovs.17-21863
5. Brannick B, Dagogo-Jack S. Prediabetes and cardiovascular disease: Pathophysiology and interventions for prevention and risk reduction. Endocrinol Metab Clin North Am. 2018;47(1):33–50. https://doi.org/10.1016/j.ecl.2017.10.001.
6. Marseglia A, Fratiglioni L, Kalpouzos GRW, Backman L, Xu W. Prediabetes and diabetes accelerate cognitive decline and predict microvascular lesions: a population-based cohort study. Alzheimer's & Dement: Transl Res & Clin Interv. 2019;15:25–33. https://doi.org/10.1016/j.jalz.2018.06.3060.
7. Liu B, Yu Y, Liu W, Deng T, Xiang D. Risk factors for non-arteritic anterior ischemic optic neuropathy: a large scale meta-analysis. Front Med. 2021;8(618353):1–14. https://doi.org/10.3389/fmed.2021.618353.
8. Sinclair, S, Schwartz, S. Diabetic retinopathy-An underdiagnosed and undertreated inflammatory, neuro-vascular complication of diabetes. In: Prime archives in endocrinology

(Vol. Open Access: https://videleaf.com/diabetic-retinopathy-an-underdiagnosed-and-undertreated-inflammatory-neuro-vascular-complication-of-diabetes/, pp. 1–42). Hyderabad, India: Vide Leaf; 2020.
9. Lee R, Wong T, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye & Vis (Lond). 2015;2:17. https://doi.org/10.1186/s40662-015-0026-2.
10. Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. Diabetes Care. 2017;40:412–8. https://doi.org/10.2337/dc16-2641.
11. Malek M, Khamseh M, Aghili R, Emami Z, Najafi L, Baradaran H. Medical management of diabetic retinopathy: an overview. Arch Iran Med. 2012;15(10):635–40 PMID: 23020540.
12. Longstreth W, Larsen E, Klein R, Wong T, Sharrett A, Lefkowitz D, Manolio T. Associations between findings on cranial magnetic resonance imaging and retinal photography in the elderly: the cardiovascular health study. Am J Epidemiology. 2006;165(1):78–84. https://doi.org/10.1093/aje/kwj350.
13. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35:556–64. https://doi.org/10.2337/dc11-1909.
14. Hanff T, Sharrett A, Mosley T, et al. Retinal microvascular abnormalities predict progression of brain microvascular disease: An atherosclerosis risk in communities magnetic resonance imaging study. Stroke. 2014;45:1012–7. https://doi.org/10.1161/STROKEAHA.113.004166.
15. Cheung CY, Tay WT, Ikram MK, et al. Retinal microvascular changes and risk of stroke: the Singapore Malay Eye Study. Stroke. 2013;44(9):2402–8. https://doi.org/10.1161/STROKEAHA.113.001738.
16. Jellinger K. Pathology and pathogenesis of vascular cognitive impairment- a critical update. Front Aging Neurosci. 2013;5:1–19. https://doi.org/10.3389/fnagi.2013.00017.
17. Hughes AD, Falaschetti E, Witt N, et al. Association of retinopathy and retinal microvascular abnormalities with stroke and cerebrovascular disease. Stroke. 2016;47:2862–4. https://doi.org/10.1161/STROKEAHA.116.014998.
18. Dumitrascu O, Demaerschalk B, Sanchez C, Almader-Douglas D, O'Carroll C, Aguilar M, Kumar G. Retinal microvascular abnormalities as surrogate markers of cerebrovascular ischemic disease: a meta-analysis. J Stroke and Cerebrovasc Dis. 2018;27(7):1960–68. https://doi.org/10.1016/j.jstrokecerebrovasdis2018.02.041
19. Mansour S, Browning D, Wong K, Flynn H Jr, Bhavsar A. The evolving treatment of diabetic retinopathy. Clin Ophthalmol. 2020;14:653–78. https://doi.org/10.2147/OPTH.S236637.
20. Fickweiler W, Wolfson E, Paniagua S, et al. The association of cognitive function and retinal neural and vascular structure in Type 1 diabetes. J Clin Endocrin Metab. 2021;106(4):1139–49. https://doi.org/10.1210/clinem/dgaa921.
21. Chai, Y, Zhang, YP, Qiao, YS, et al. Association between diabetic retinopathy, brain structural abnormalities and cognitive impairment for accumulated evidence in observational studies. Am J Ophthalmol. 2022:12124.https://doi.org/10.1016/j.ajo.2022.01.011
22. Agarwal A, Soliman M, Sepah Y, Do D, Nguyen Q. Diabetic retinopathy: variations in patient therapeutic outcomes and pharmacogenomics. Pharmacogenomics Pers Med. 2014;7:399–409. https://doi.org/10.2147/PGPM.S52821.
23. Patton N, Aslam T, Macgillivray T, Pattie A, Deary IJ, Dhillon B. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. J Anat. 2005;206(4):319–48. https://doi.org/10.1111/j.1469-7580.2005.00395.x.
24. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9(7):689–701. https://doi.org/10.1016/S1474-4422(10)70104-6.
25. Guzik TJ, Schramm A, Czesnikiewicz-Guzik M. Functional implications of reactive oxygen species (ROS) in human blood vessels. In: Laher I, editor. Systems biology of free radicals and antioxidants. Heidelberg, Springer, Berlin Heidelberg: Berlin; 2014. p. 1155–76.

26. Grunwald J, Riva C, Brucker A, Sinclair S, Petrig B. Altered retinal vascular response to 100% oxygen breathing in diabetes mellitus. Ophthalmology. 1984;91(12):1447–52. https://doi.org/10.1016/s0161-6420(84)34124-0.
27. Petzold, GC. Murthy, VN. Role of astrocytes in neurovascular coupling. Neuron. 2011;7(5):782–97.https://doi.org/10.1016/j.neuron.2011.08.009.
28. Schafer DP, Lehrman EK, Kautzman AG, et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron. 2012;74(4): 691–705https://doi.org/10.1016/j.neuron.2012.03.026.
29. Rashid K, Akhtar-Schaefer I, Langmann T. Microglia in retinal degeneration. Front Immunol. 2019;10(1975):1–19. https://doi.org/10.3389/fimmu.2019.01975.
30. Salmenson B, Reisman J, Sinclair S, Burge D. Macular capillary hemodynamic changes associated with Raynaud's phenomenon. Ophthalmology. 1992;99:914–9. https://doi.org/10.1016/s0161-6420(92)31874-3.
31. Drance S, Anderson DR, Schulzer M. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. Am J Ophthalmol. 2001;131:699–708. https://doi.org/10.1016/S0002-9394(01)00964-3.
32. Guo Y, Sun Y, Liu H, Cao K, Wang N. Systemic vascular dysregulation may be associated with lower peripapillary vessel density in non-glaucomatous healthy eyes: a prospective cross-sectional study. Front Med. 2021;8(678829):1–10. https://doi.org/10.3389/fmed.2021.678829.
33. Dorner G, Garhofer GBK, Polska E, Polak K, Riva C, Schmetterer L. Nitric oxide regulates retinal vascular tone in humans. Am J Physiol Heart Circ Physiol. 2003;285:H631–6. https://doi.org/10.1152/ajpheart.00111.2003.
34. Metea MR, Newman EA. Signaling within the neurovascular unit in the mammalian retina. Exp Physiol. 2007;92(4):635–40. https://doi.org/10.1113/expphysiol.2006.036376.
35. Kur J, Newman EA, Chan-Ling T. Cellular and physiological mechanisms underlying blood flow regulation in the retina and choroid in health and disease. Prog Retin Eye Res. 2012;31(5):377–406. https://doi.org/10.1016/j.preteyeres.2012.04.004.
36. Kisler K, Nelson AR, Rege SV, et al. Pericyte degeneration leads to neurovascular uncoupling and limits oxygen supply to brain. Nat Neurosci. 2017;20:406–16. https://doi.org/10.1038/nn.4489.
37. Yemisci M, Gursoy-Ozdemir Y, Vurul A, et al. Pericyte contraction induced by oxidative-nitrative stress impairs capillary reflow despite successful opening of an occluded cerebral artery. Nature Med. 2009;15(9):1031–7. https://doi.org/10.1038/nm.2022.
38. Ava S, Erdem S, Karahan M, Dursun M, Hazar L, Sen H, Keklikci U. Evaluation of the effect of obstructive sleep apnea syndrome on retinal microvascuarity by optical coherence tomography angiography. Photodiagn Photodyn Ther. 2022;38:1–5. https://doi.org/10.1016/j.pdpdt.2022.102761.
39. Karaca C, Karaca Z. Beyond hyperglycemia, evidence for retinal neurodegeneration in metabolic syndrome. Invest Ophthal vis Sci. 2018;59(3):1360–7. https://doi.org/10.1167/iovs.17-23376.
40. Grunwald J, Brucker A, Schwartz S, Braunstein S, Baker L, Petrig B, Riva C. Diabetic glycemic control and retinal blood flow. Diabetes Res and Clin Pract. 1990;39:602–7. https://doi.org/10.2337/diab.39.5.602.
41. Lott M, Slocomb J, Shivkumar V, et al. Impaired retinal vasodilator responses in prediabetes and type 2 diabetes. Acta Ophthalmol. 2013;91(6):e462-469. https://doi.org/10.1111/aos.12129.
42. Garhofer G, Zawinka C, Resch H, Kothy P, Schmetterer L, Dorner GT. Reduced response of retinal vessel diameters to flicker stimulation in patients with diabetes. Br J Ophthalmol. 2004;88(7):887–91. https://doi.org/10.1136/bjo.2003.033548.
43. Bek T, Hajari J, Jeppesen P. Interaction between flicker-induced vasodilatation and pressure autoregulation in early retinopathy of type 2 diabetes. Graefes Arch Clin Exp Ophthalmol. 2008;246(5):763–9. https://doi.org/10.1007/s00417-008-0766-y.

44. Singer M, Ashimatey B, Zhou X, Chu Z, Wang R, Kashani A. Impaired layer specific retinal vascular reactivity among diabetic subjects. PLOS One. 2020;15(9 e233871):1–11. https://doi.org/10.1371/journal.pone.0233871.
45. Umemura T, Kawamura T, Hotta N. Pathogenesis and neuroimaging of cerebral large and small vessel disease in type 2 diabetes: a possible link between cerebral and retinal microvascular abnormalities. J Diabetes Invest. 2017;8:134–48. https://doi.org/10.1111/jdi.12545.
46. Sorensen BM, Houben AJ, Berendschot TT, Schouten JS, Kroon AA, van der Kallen CJ, et al. Prediabetes and type 2 diabetes are associated with generalized microvascular dysfunction: the Maastricht study. Circulation. 2016;134(18):1339–52. https://doi.org/10.1161/CIRCULATIONAHA.116.023446.
47. Chiang JF, Sun MH, Chen KJ, et al. Association with obstructive sleep apnea and diabetic macular edema in patients with type 2 diabetes. Am J Ophthalmol. 2021;226:217–25. https://doi.org/10.1016/j.ajo.2021.01.022.
48. Cooper LS, Wong TY, Klein R, et al. Retinal microvascular abnormalities and MRI-defined subclinical cerebral infarction: the Atherosclerosis Risk in Communities Study. Stroke. 2006;37:82–6. https://doi.org/10.1161/01.STR.0000195134.04355.e5.
49. Wostyn P, De Groot V, Van Dam D, Audenaert K, Killer H, De Deyn P. The glymphatic hypothesis of glaucoma: a unifying concept incorporating vascular, biomechanical, and biochemical aspects of the disease. BioMed Res Int. 2017(ID 5123148):1–7. https://doi.org/10.1155/2017/5123148.
50. Suzen S, Buyukbingol E. Recent studies of aldose reductase enzyme inhibition for diabetic complications. Curr Med Chem. 2003;10(15):1329–52. https://doi.org/10.2174/0929867033457377.
51. Das Evcimen, N, King, GL. The role of protein kinase C activation and the vascular complications of diabetes. Pharmacol Res. 2007. 55(6), 498–510. https://doi.org/10.1016/j.phrs.2007.04.016.
52. Aiello LP, Vignati L, Sheetz MJ, et al, PKC-DRS and PKC-DRS2 Study Groups. Oral protein kinase c b inhibition using ruboxistaurin: efficacy, safety, and causes of vision loss among 813 patients (1,392 eyes) with diabetic retinopathy in the Protein Kinase Cb Inhibitor-Diabetic Retinopathy Study and the Protein Kinase C b Inhibitor-Diabetic Retinopathy Study 2. Retina. 2011;31(10):2084–94. https://doi.org/10.1097/IAE.0b013e3182111669.
53. Zong H, Ward M, Stitt AW. AGEs, RAGE, and diabetic retinopathy. Curr Diabetes Rep. 2011;11(4):244–52. https://doi.org/10.1007/s11892-011-0198-7.
54. Madsen-Bouterse, SA, Kowluru, RA. Oxidative stress and diabetic retinopathy: pathophysiological mechanisms and treatment perspectives. Rev Endocr Metab Disord. 2008;9(4):315–27. https://doi.org/10.1007/s11154-008-9090-4
55. Huru, J, Leiviska, I, Saarela, V, Liinamaa, M. Prediabetes influences the structure of the macula: Thinning of the macula in the Northern Finland Birth Cohort. Br J Ophthalmol. 2020;Epub,: 1–7. https://doi.org/10.1136/bjophthalmol-2020-317414.
56. Antonetti D, Klein R, Gardner T. Diabetic retinopathy. N Engl J Med. 2012;366(13):1227–39. https://doi.org/10.1056/NEJMra1005073.
57. Sonkin P, Kelly L, Sinclair S, Hatchell D. The effect of pentoxifylline on retinal capillary blood flow velocity and whole blood viscosity. American Journal Ophthalmology. 1993;115:775–80. https://doi.org/10.1016/s0002-9394(14)73647-5.
58. Van Hecke M, Dekker J, Nijpels G, et al. Inflammation and endothelial dysfunction are associated with retinopathy: The Hoorn Study. Diabetologia. 2005;48:1300–6. https://doi.org/10.1007/s00125-005-1799-y.
59. McLeod DS, Lefer DJ, Merges C, Lutty GA. Enhanced expression of intracellular adhesion molecule-1 and P-selectin in the diabetic human retina and choroid. Am J Pathol. 1995;147(3):642–53. PMID: 7545873.
60. Khoobehi B, Firn K, Thompson H, Reinoso M, Beach J. Retinal arterial and venous oxygen saturation is altered in diabetic patients. Invest Ophthal Visual Sci. 2013;54:7103–6. https://doi.org/10.1167/iovs.13-12723.

61. Wilkinson, CP, Ferris, FL 3rd, Klein, RE, et al. Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003;110(9):1677–82. https://doi.org/10.1016/S0161-6420(03)00475-5.
62. Zhang, X, Zeng, H, Bao, S, Wang, N, Gillies, M. Diabetic macular edema: New concepts in patho-physiology and treatment. Cell Biosci. 2014;1494:27. https://doi.org/10.1186/2045-3701-4-27.
63. Villarroel M, Ciudin A, Hernandez C, Simo R. Neurodegeneration: an early event of diabetic retinopathy. World J Diab. 2010;1(2):57–64. https://doi.org/10.4239/wjd.v1.i2.57.
64. Barber A, Gardner T, Abcouwer S. The significance of vascular and neural apoptosis to the pathology of diabetic retinopathy. Invest Ophthal Vis Sci. 2011;52(2):1156–63. https://doi.org/10.1167/iovs.10-6293.
65. Abu El-Asrar AM, Dralands L, Missotten L, et al. Expression of antiapoptotic and proapoptotic molecules in diabetic retinas. Eye (Lond). 2007;21(2):238–45. https://doi.org/10.1038/sj.eye.6702225.
66. Van Dijk HW, Verbraak FD, Stehouwer M, et al. Association of visual function and ganglion cell layer thickness in patients with diabetes mellitus type 1 and no or minimal diabetic retinopathy. Vision Res. 2011;51(2):224–8. https://doi.org/10.1016/j.visres.2010.08.024.
67. Van Dijk HW, Verbraak FD, Kok PHB, et al. Early neurodegeneration in the retina of type 2 diabetic patients. Invest Ophthalmol Vis Sci. 2012;53(6):2715–9. https://doi.org/10.1167/iovs.11-8997.
68. Vujosevic S, Midena E. Retinal layers changes in human preclinical and early clinical diabetic retinopathy support early retinal neuronal and Müller cell alterations. J Diabetes Res. 2013;2013: 905058. https://doi.org/10.1155/2013/905058.
69. Mizutani M, Gerhardinger C, Lorenzi M. Muller cell changes in human diabetic retinopathy. Diabetes. 1998;47(3):445–9. https://doi.org/10.2337/diabetes.47.3.445.
70. Van Dijk HW, Kok PHB, Garvin M, et al. Selective loss of inner retinal layer thickness in type 1 diabetic patients with minimal diabetic retinopathy. Invest Ophthalmol Vis Sci. 2009;50(7):3404–9. https://doi.org/10.1167/iovs.08-3143.
71. Chihara E, Matsuoka T, Ogura Y, Matsumura M. Retinal nerve fiber layer defect as an early manifestation of diabetic retinopathy. Ophthalmology. 1993;100(8):1147–51. https://doi.org/10.1016/s0161-6420(93)31513-7.
72. Lim H, Shin Y, Lee M, Park G, Jy K. Longitudinal changes in the peripapillary retinal nerve fiber layer thickness of patients with type 2 diabetes. JAMA Ophthalmol. 2019;137(10):1125–32.https://doi.org/10.1001/jamaophthalmol.2019.2537
73. Peng R, Zhu Z, Shen H, et al. Retinal nerve and vascular changes in prediabetes. Front Med. 2022;9: 777646. https://doi.org/10.3389/fmed.2022.777646.
74. Bringmann A, Iandiev I, Pannicke T, et al. Cellular signaling and factors involved in Müller cell gliosis: neuroprotective and detrimental effects. Prog Retin Eye Res. 2009;28(6):423–51. https://doi.org/10.1016/j.preteyeres.2009.07.001.
75. Zhong Y, Li J, Chen Y, Wang J, Ratan R, Zhang S. Activation of endoplasmic reticulum stress by hyperglycemia is essential for muller cell-derived inflammatory cytokine production in diabetes. Diabetes. 2012;61:492–504. https://doi.org/10.2337/db11-0315.
76. Bringmann A, Wiedemann P. Müller glial cells in retinal disease. Ophthalmologica. 2012;227:1–19. https://doi.org/10.1159/000328979.
77. Sofroniew MV. Molecular dissection of reactive astrogliosis and glial scar formation. Trends Neurosci. 2009;32:638–47. https://doi.org/10.1016/j.tins.2009.08.002.
78. Stitt AW, O'Neill CL, O'Doherty MT, Archer DB, Gardiner TA, Medina RJ. Vascular stem cells and ischaemic retinopathies. Prog Retin Eye Res. 2011;30:149–66. https://doi.org/10.1016/j.preteyeres.2011.02.001.
79. Franze K, Grosche J, Skatchkov SN, et al. Muller cells are living optical fibers in the vertebrate retina. Proc Natl Acad Sci U S A. 2007;104:8287–92. https://doi.org/10.1073/pnas.0611180104.

80. Reichenbach A, Bringmann A. New functions of Müller cells. Glia. 2013;61:651–78. https://doi.org/10.1002/glia.22477.
81. Lindenau W, Kuhrt H, Ulbricht E, Körner K, Bringmann A, Reichenbach A. Cone-to-Müller cell ratio in the mammalian retina: a survey of seven mammals with different lifestyle. Exp Eye Res. 2019;181:38–48. https://doi.org/10.1016/j.exer.2019.01.012.
82. Bresnick GH, Palta M. Predicting progression to severe proliferative diabetic retinopathy. Arch Ophthalmol. 1987;105(6):810–4. https://doi.org/10.1001/archopht.1987.01060060096041.
83. Lai Y, Chan WM, Lai R, Ngai J, Li H, Lam D. The clinical applications of multifocal electroretinography: a systematic review. Surv Ophthalmol. 2007;52(1):61–96. https://doi.org/10.1016/j.survophthal.2006.10.005.
84. Ng J, Bearse M, Schnck M, Barez S, Adams A. Local diabetic retinopathy prediction by multifocal ERG delays over 3 years. Invest Ophthal Vis Sci. 2008;49(4):1622–8. https://doi.org/10.1167/iovs.07-1157.
85. Adams A, Bearse M Jr. Retinal neuropathy precedes vasculopathy in diabetes: a function-based opportunity for early treatment intervention? Clin Exp Optom. 2012;95:256–65. https://doi.org/10.1111/j.1444-0938.2012.00733.x.
86. Simo R, Simo-Servat O, Bogdanov P, Hernandez C. Neurovascular unit: A new target for treating early stages of diabetic retinopathy. Pharmaceutics. 2021;13(8):1320, 1–39. https://doi.org/10.3390/pharmaceutics13081320.
87. Sinclair, SH, Miller, ST, Talekar, KS, Schwartz, SS. Diabetes mellitus associated neurovascular lesions in the retina and brain: a review. Frontiers Ophthalmol. 2022. Epub ahead of print.
88. American Academy of Ophthalmology. Diabetic retinopathy preferred practice pattern, ISSN 0161-6420/19, Elsevier, Inc. 2019. pp. 70–131. https://doi.org/10.1016/j.ophtha.2019.09.025.
89. Sinclair SH. Diabetic retinopathy: the unmet needs for screening and a review of potential solutions. Expert Rev Med Devices. 2006;3:301–13. https://doi.org/10.1586/17434440.3.3.301.
90. Bressler S, Qin H, Beck R, et al. Factors associated with changes in visual acuity and central subfield thickness at 1 year after treatment for diabetic macular edema with ranibizumab. Arch Ophthalmol. 2012;130(9):1153–61. https://doi.org/10.1001/archophthalmol.2012.1107.
91. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology. 2013;120:2013–22. https://doi.org/10.1016/j.ophtha.2013.02.034.
92. Bressler N, Odia I, Maguire M, et al. Association between change in visual acuity and change in central subfield thickness during treatment of diabetic macular edema in participants randomized to aflibercept, bevacizumab, or ranibzumab: a post hoc analysis of the protocol T randomized clinical trial. JAMA Ophthalmol. 2019;137(9):977–85. https://doi.org/10.1001/jamaophthalmol.2019.1963.
93. Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. New England J Med. 2015;372(13):1193–203. https://doi.org/10.1056/NEJMoa1414264.
94. Durbin M, An L, Shemonski N, et al. Quantification of retinal microvascular density in optical coherence tomographic angiography images in diabetic retinopathy. JAMA Ophthalmol. 2017;135(4):370–6. https://doi.org/10.1001/jamaophthalmol.2017.0080.
95. Aschauer J, Pollreisz A, Karst S, et al. Longitudinal analysis of microvascular perfusion and neurodegenerative changes in early type 2 diabetic retinal disease. Br J Ophthalmol. 2020;106:528–33. https://doi.org/10.1136/bjophthalmol-2020-317322.
96. Li X, Xie J, Zhang L et al. Identifying microvascular and neural parameters related to the severity of diabetic retinopathy using optical coherence tomography angiography. Invest Ophthal vis Sci. 2020;61(5:39):9. https://doi.org/10.1167/iovs.61.5.39.
97. Lim HB, Shin YI, Lee MW, et al. Ganglion cell - inner plexiform layer damage in diabetic patients: 3-year prospective, longitudinal. Observational Study Sci Rep. 2020;10(1):1470. https://doi.org/10.1038/s41598-020-58465-x.

98. Nesper P, Roberts P, Onishi A et al, I.O.V.S. Quantifying microvascular abnormalities with increasing severity of diabetic retinopathy using optical coherence tomography angiography. Invest Ophthal vis Sci. 2017;58: BIO307–315. https://doi.org/10.1167/iovs.17-21787.
99. Dimitrova G, Chihara E, Takahashi H, Amano H, Okazaki K. Quantitative retinal optical coherence tomography angiography in patients with diabetes without diabetic retinopathy. Invest Ophthalmol Vis Sci. 2017;58(1):190–6. https://doi.org/10.1167/iovs.16-20531.
100. Fawzi A. Consensus on optical coherence tomographic angiography nomenclature: do we need to develop and learn a new language. JAMA Ophthalmol. 2017;135(4):377–8. https://doi.org/10.1001/jamaophthalmol.2017.0149.
101. Burns S, Elsner A, Chui T, et al. In vivo adaptive optics microvascular imaging in diabetic patients without clinically severe diabetic retinopathy. Biomed Opt Express. 2014;5(3):14. https://doi.org/10.1364/BOE.5.000961.
102. Vujosevic S, Muraca A, Gatti V, et al. Peripapillary microvascular and neural changes in diabetes mellitus: an OCT-angiography study. Invest Ophthalmol Vis Sci. 2018;59(12):5074–81. https://doi.org/10.1167/iovs.18-24891.
103. Zeng Y, Cao D, Yu H, et al. Early retinal neurovascular impairment in patients with diabetes without clinically detectable retinopathy. Br J Ophthalmol. 2019;103(12):1747–52. https://doi.org/10.1136/bjophthalmol-2018-313582.
104. Ashraf M, Sampani I, Rageh A, Silva P, Aielllo L, Sun J. Interaction between the distribution of diabetic retinopathy lesions and the association of optical coherence tomography angiography scans with diabetic retinopathy severity. JAMA Ophthalmol. 2020;138(12):1291–7. https://doi.org/10.1001/jamaophthalmol.2020.4516.
105. Lee M, Lee W, Ryu C, et al. Peripapillary retinal nerve fiber layer and microvasculature in prolonged type 2 diabetes patients without clinical diabetic retinopathy. Invest Ophthal vis Sci. 2021;62(2):9. https://doi.org/10.1167/iovs.62.2.9.
106. Abràmoff MD, Fort PE, Han IC, et al. Approach for a clinically useful comprehensive classification of vascular and neural aspects of diabetic retinal disease. Invest Ophthalmol Vis Sci. 2018;59(1):519–27. https://doi.org/10.1167/iovs.17-21873.
107. Sun J, Aiello L, Abramoff M, et al. Editorial: Updating the staging system for diabetic retinal disease. Ophthalmology. 2020. EPub:1–4.https://doi.org/10.1016/j.ophtha.2020.10.008.
108. Schwartz S, Rachfal A, Corkey B. The time is now for new, lower diabetes diagnostic thresholds. Trends Endocrinol Metab. 2022;33(1):4–7. https://doi.org/10.1016/j.tem.2021.10.007.
109. Brannick B, Wynn A, Dagogo-Jack S. Prediabetes as a toxic environment for the initiation of microvascular and macrovascular complications. Experimental Biol and Med. 2016;241:1323–31. https://doi.org/10.1177/1535370216654227.
110. Rashidi A, Ghanbarian A, Azizi F. Are patients who have metabolic syndrome without diabetes at risk for developing chronic kidney disease? Evidence based on data from a large cohort screening population. Clin J Am Soc Nephrol. 2007;2(5):976–83. https://doi.org/10.2215/CJN.01020207.
111. Sun F, Tao Q, Zhan S. Metabolic syndrome and the development of chronic kidney disease among 118,924 non-diabetic Taiwanese in a retrospective cohort. Nephrology. 2010;15(1):84–92. https://doi.org/10.1111/j.1440-1797.2009.01150.x.
112. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977–86. https://doi.org/10.1056/NEJM199309303291401.
113. Diabetes Control and Complications Trial Research Group. Hypoglycemia in the diabetes control and complications trial. Diabetes. 1997;46(2):271–86. https://doi.org/10.1056/NEJM199309303291401.
114. Hirsch I, Brownlee M. Beyond hemoglobin A1c- the need for additional markers of risk for diabetic microvascular complications. JAMA. 2010;303(22):2291–2. https://doi.org/10.1001/jama.2010.785.

115. De Clerck E, Schouten J, Berendschot T, et al. Macular thinning in prediabetes or type 2 diabetes without diabetic retinopathy: the Maastricht Study. Acta Ophthalmol. 2018;96(2):174–82. https://doi.org/10.1111/aos.13570.
116. Bouvy WH, Kuijf HJ, Zwanenburg JJ, et al. Utrecht Vascular Cognitive Impairment Study group. Abnormalities of cerebral deep medullary veins on 7 tesla MRI in amnestic mild cognitive impairment and early Alzheimer's Disease: a pilot study. J Alzheimers Dis. 2017;57:705–10. https://doi.org/10.3233/JAD-160952.
117. Toth P, Tucsek Z, Sosnowska D, et al. Age-related autoregulatory dysfunction and cerebromicrovascular injury in mice with angiotensin II-induced hypertension. J Cereb Blood Flow Metab. 2013;33:1732–42. https://doi.org/10.1038/jcbfm.2013.143.
118. Toth P, Tucsek Z, Tarantini S, et al. IGF-1 deficiency impairs cerebral myogenic autoregulation in hypertensive mice. J Cereb Blood Flow Metab. 2014;34:1887–97. https://doi.org/10.1038/jcbfm.2014.156.
119. Chantelau E. Evidence that upregulation of serum IGF-1 concentration can trigger acceleration of diabetic retinopathy. Br J Ophthalmol. 1998;82(7):725–30. https://doi.org/10.1136/bjo.82.7.725.
120. Jorgensen D, Shaaban C, Wiley C, et al. A popultion neuroscience approach to the study of cerebral small vessel disease in midlife and late life: an invited review. Am J Physiol heart Circ Physiol. 2018;314:H1117-1136. https://doi.org/10.1152/ajpheart.00535.2017.
121. Nguyen J, Nishimura N, Fetcho RN, Iadecola C, Schaffer CB. Occlusion of cortical ascending venules causes blood flow decreases, reversals in flow direction, and vessel dilation in upstream capillaries. J Cereb Blood Flow Metab. 2011;31:2243–54. https://doi.org/10.1038/jcbfm.2011.95.
122. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414:813–20. https://doi.org/10.1038/414813a.
123. Brownlee M. The pathobiology of diabetic complications: A unifying mechanism. Diabetes. 2005;54(6):1615–25. https://doi.org/10.2337/diabetes.54.6.1615.
124. Iliaki E, Poulaki V, Mitsiades N, Mitsiades C, Miller J, Gragoudas E. Role of a4 integrin (CD49d) in the pathogenesis of diabetic retinopathy. Invest Ophthal Vis Sci. 2009;50(10):4898–904. https://doi.org/10.1167/iovs.08-2013.
125. Sonkin P, Kelly L, Sinclair S, Hatchell D. Pentoxifylline increases retinal capillary blood flow velocity in patients with diabetes. Arch Ophthalmol. 1993;111(12):1647–52. https://doi.org/10.1001/archopht.1993.01090120069024.
126. Joussen AM, Murata T, Tsujikawa A, Kirchhof B, Bursell SE, Adamis AP. Leukocyte-mediated endothelial cell injury and death in the diabetic retina. Am J Pathol. 2001;158(1):147–52. https://doi.org/10.1016/S0002-9440(10)63952-1.
127. Ejaz S, Chekarova I, Ejaz A, Sohail A, Lim CW. Importance of pericytes and mechanisms of pericyte loss during diabetes retinopathy. Diabetes Obes Metab. 2008;10(1):53–63. https://doi.org/10.1111/j.1463-1326.2007.00795.x.
128. Montagne A, Nikolakopoulou A, Zhao Z, et al. Pericyte degeneration causes white matter dysfunction in mouse CNS. Nat Med. 2018;24(3):326–37. https://doi.org/10.1038/nm.4482.
129. Kohama SG, Rosene DL, Sherman LS. Age-related changes in human and non-human primate white matter: from myelination disturbances to cognitive decline. Age (Dordr). 2012;34:1093–110. https://doi.org/10.1007/s11357-011-9357-7.
130. Luc K, Schramm-Luc A, Guzik TJ, Mikolajczyk TP. Oxidative stress and inflammatory markers in prediabetes and diabetes. J Physiol Pharmacol. 2019;70(6):809–824. https://doi.org/10.26402/jpp.2019.6.01.
131. Maschirow L, Khalaf K, Al-Aubaidy HA, Jelinek HF. Inflammation, coagulation, endothelial dysfunction and oxidative stress in prediabetes - biomarkers as a possible tool for early disease detection for rural screening. Clin Biochem. 2015;48(9):581–5. https://doi.org/10.1016/j.clinbiochem.2015.02.015.
132. Grossmann V, Schmitt VH, Zeller T, et al. Profile of the immune and inflammatory response in individuals with prediabetes and type 2 diabetes. Diabetes Care. 2015;38(7):1356–64. https://doi.org/10.2337/dc14-3008.

133. Spijkerman AMW, Gallet M-A, Tarnowal L, et al. Endothelial dysfunction and low-grade inflammation and the progression of retinopathy in Type 2 diabetes. Diabet Med. 2007;24:969–76. https://doi.org/10.1111/j.1464-5491.2007.02217.x.
134. Muni R, Kohly R, Lee E, et al. Prospective study of inflammatory biomarkers and risk of diabetic retinopathy in the diabetes control and complications trial. JAMA Ophthalmol. 2013;131(4):514–21.https://doi.org/10.1001/jamaophthalmol.2013.2299.
135. Vujosevic S, Simó R. Local and systemic inflammatory biomarkers of diabetic retinopathy: An integrative approach. Invest Ophthalmol Vis Sci. 2017;58:68–75. https://doi.org/10.1167/iovs.17-2176.
136. Skaper S, Facci L, Zusso M, Giusti P. An inflammation-centric view of neurological disease: Beyond the neuron. Front Cell Neurosci. 2018;12:72. https://doi.org/10.3389/fncel.2018.00072.
137. Minaker S, Mason R, Luna G, et al. Changes in aqueous and vitreous inflammatory cytokine levels in diabetic macular oedema: a systematic review and meta-analysis. Acta Ophthalmol. 2021;100(1):e53–70. https://doi.org/10.1111/aos.14891.
138. Rübsam A, Parikh S, Fort PE. Role of inflammation in diabetic retinopathy. Int J Mol Sci. 2018;19(4):942. https://doi.org/10.3390/ijms19040942.
139. Parsadaniantz S, Goazigo A, Sapienza A, Habas C, Baudouin C. Glaucoma: a degenerative optic neuropathy related to neuroinflammation? Cells. 2020;9(3):535, 1–14. https://doi.org/10.3390/cells9030535.
140. Ridet JL, Malhotra SK, Privat A, Gage FH. Reactive astrocytes: Cellular and molecular cues to biological function. Trends Neurosci. 1997;20(12):570–7. https://doi.org/10.1016/s0166-2236(97)01139-9.
141. Soni D, Sagar P, Takkar B. Diabetic retinal neurodegeneration as a form of diabetic retinopathy. Int Ophthalmol. 2021. EPub:1–26.https://doi.org/10.1007/s10792-021-01864-4.
142. Mysona BA, Shanab AY, Elshaer SL, El-Remessy AB. Nerve growth factor in diabetic retinopathy: beyond neurons. Expert Rev Ophthalmol. 2014;9(2):99–107. https://doi.org/10.1586/17469899.2014.903157.
143. Lieth, E, LaNoue, KF, Antonetti, DA, Ratz, M. Diabetes reduces glutamate oxidation and glutamine synthesis in the retina. The Penn State Retina Research Group. Exp Eye Res. 2000;70(6):723–30. https://doi.org/10.1006/exer.2000.0840.
144. Aoun P, Simpkins JW, Agarwal N. Role of PPAR-γ ligands in neuroprotection against glutamate-induced cytotoxicity in retinal ganglion cells. Invest Ophthalmol Vis Sci. 2003;44(7):2999–3004. https://doi.org/10.1167/iovs.02-1060.
145. Li Q, Puro DG. (2002) Diabetes-induced dysfunction of the glutamate transporter in retinal Muller cells. Invest Ophthalmol Vis Sci. 2002;43(9):3109–16 PMID: 12202536.
146. Lieth E, Barber AJ, Xu B, Dice C, Ratz MJ, Tanase D, Strother JM. Glial reactivity and impaired glutamate metabolism in short-term experimental diabetic retinopathy Penn State Retina Research Group. Diabetes. 1998;47(5):815–20. https://doi.org/10.2337/diabetes.47.5.815.
147. Harada C, Harada T, Quah HMA, et al. Potential role of glial cell line-derived neurotrophic factor receptors in Müller glial cells during light-induced retinal degeneration. Neuroscience. 2003;122(1):229–35. https://doi.org/10.1016/S0306-4522(03)00599-2.
148. Lynch MA. The multifaceted profile of activated microglia. Mol Neurobiol. 2009;40(2):139–56. https://doi.org/10.1007/s12035-009-8077-9.
149. Dong N, Xu B, Wang B et al. Study of 27 aqueous humor cytokines in patients with type 2 diabetes with or without retinopathy. Mol Vis. 2013;19:1734–46. PMC3733907.
150. Bringmann A, Pannicke T, Grosche J, et al. Müller cells in the healthy and diseased retina. Prog Retin Eye Res. 2006;25(4):397–424. https://doi.org/10.1016/j.preteyeres.2006.05.003.
151. Vujosevic S, Micera A, Bini S, Berton M, Esposito G, Midena E. Aqueous humor biomarkers of Müller cell activation in diabetic eyes. Invest Ophthalmol Vis Sci. 2015;56(6):3913–8. https://doi.org/10.1167/iovs.15-16554.
152. Midena E, Micera A, Frizziero L, Pilotto E, Esposito G, Bini S. Sub-threshold micropulse laser treatment reduces inflammatory biomarkers in aqueous humour of diabetic patients with macular edema. Sci Rep. 2019;9(1):10034. https://doi.org/10.1038/s41598-019-46515-y.

153. Midena E, Torresin T, Velotta E, Pilotto E, Parrozzani R, Frizziero L. OCT hyperreflective retinal foci in diabetic retinopathy: a semi-automatic detection comparative study. Front Immunol. 2021;12: 613051. https://doi.org/10.3389/fimmu.2021.613051.
154. Frizziero L, Calciati A, Midena G, Torresin T, Parrozzani R, Pilotto E, Midena E. Subthreshold micropulse laser modulates retinal neuroinflammatory biomarkers in diabetic macular edema. J Clin Med. 2021;10(14):3134. https://doi.org/10.3390/jcm10143134.
155. Yun JH. Interleukin-1β induces pericyte apoptosis via the NF-κB pathway in diabetic retinopathy. Biochem Biophys Res Commun. 2021;546:46–53. https://doi.org/10.1016/j.bbrc.2021.01.108.
156. Hauck SM, Kinkl N, Deeg CA, Swiatek-de Lange M, Schöffmann S, Ueffing M. GDNF family ligands trigger indirect neuroprotective signaling in retinal glial cells. Mol Cell Biol 2006;26:2746–57. https://doi.org/10.1128/MCB.26.7.2746-2757.2006.
157. Gonzalez H, Pacheco R. T-cell-mediated regulation of neuroinflammation involved in neurodegenerative diseases. J Neuroinflammation. 2014;11:201. https://doi.org/10.1186/s12974-014-0201-8.
158. Appel SH. CD4+ T cells mediate cytotoxicity in neurodegenerative diseases. J Clin Invest. 2009;119(1):13–5. https://doi.org/10.1172/JCI38096.
159. Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early treatment diabetic retinopathy study report number 2. Ophthalmology. 1987;94:761–74. https://doi.org/10.1016/s0161-6420(87)33527-4.
160. United Kingdom Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2. Lancet. 1998;352(9131):837–53 PMID: 9742976.
161. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial revisited. Diabetes. 2008;57(4):995–1001. https://doi.org/10.2337/db07-1618.
162. Esser N, Paquot N, Sheen AJ. Anti-inflammatory agents to treat or prevent type 2 diabetes, metabolic syndrome and cardiovascular disease. Expert Opin Investig Drugs. 2015;24(3):283–307. https://doi.org/10.1517/13543784.2015.974804.
163. Fort P, Losiewicz M, Reiter C et al. Differential roles of hyper glycemia and hypoinsulinemia in diabetes induced retinal cell death: Evidence for retinal insulin resistance. PLOS One. 2011;6(10):e26498, 1–12. https://doi.org/10.1371/journal.pone.0026498.
164. Chew EY, Ambrosius WT, Davis MD, et al. ACCORD Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010;363:233–44. https://doi.org/10.1056/NEJMoa1001288.
165. Chakravarthy H, Devanathan V. Molecular mechanisms mediating diabetic retinal neurodegeneration: potential research avenues and therapeutic targets. J Mol Neurosci. 2018;66(3):445–61. https://doi.org/10.1007/s12031-018-1188-x.
166. Teodoro JS, Nunes S, Rolo AP, Reis F, Palmeira CM. Therapeutic options targeting oxidative stress, mitochondrial dysfunction and inflammation to hinder the progression of vascular complications of diabetes. Front Physiol. 2019;9:1857. https://doi.org/10.3389/fphys.2018.01857.
167. Pillar S, Moisseiev E, Sokolovska J, Grzybowski A. Recent developments in diabetic retinal neurodegeneration: a literature review. J Diabetes Res. 2020;2020:1–13. https://doi.org/10.1155/2020/5728674.
168. Chalke S, Kale P. Combinational approaches targeting neurodegeneration, oxidative stress, and inflammation in the treatment of diabetic retinopathy. Curr Drug Targets. 2021;22:1–15. https://doi.org/10.2174/1389450122666210319113136.
169. Kwong JM, Hoang C, Torrevillas RM, et al. Bis(zinc-dipicolylamine), Zn-DPA, a new marker for tracking apoptotic retinal ganglion cells. Invest Ophthal Vis Sci. 2014;55(8):4913–21. https://doi.org/10.1167/iovs.13-13346.
170. Mazzoni F, Muller C, DeAssis J, Leevy W, Finnemann S. Non-invasive in vivo fluorescence imaging of apoptotic retinal photoreceptors. Nat Sci Rep. 2019;9(1):1590. https://doi.org/10.1038/s41598-018-38363-z.

171. Rofagha S. Minimizing risks to patients by improving presentation of clinical trial results in geographic atrophy trials. Ophthalmology Retina. 2022;6(5):337–8. https://doi.org/10.1016/j.oret.2021.12.018.
172. Akl EA, Briel M, You JJ, et al. Potential impact on estimated treatment effects of information lost to follow-up in randomized controlled trials (LOST-IT): Systematic review. BMJ. 2012;344: e2809. https://doi.org/10.1136/bmj.e2809.
173. Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. Ophthalmology. 1981;88:583–600. https://doi.org/10.1016/S0161-6420(81)34978-1.
174. Fong DS, Aiello L, Gardner, TW, King, GL, Blankenship, G, Cavallerano, JD, Ferris, FL. 3rd, Klein, R, American Diabetes Association. Diabetic retinopathy. Diabetes Care. 2003; Jan;26 Suppl 1:S99-S102. https://doi.org/10.2337/diacare.26.2007.s99.
175. Ferris FL, Podgor, MJ, Davis, MD. Macular edema in Diabetic Retinopathy Study patients. Diabetic retinopathy study report number 12. Ophthalmology. 1987;94(7):754–60. https://doi.org/10.1016/s0161-6420(87)33526-2.
176. Nonaka A, Kiryu J, Tsujikawa A, et al. Inflammatory response after scatter laser photocoagulation in nonphotocoagulated retina. Invest Ophthalmol Vis Sci. 2002;43(4):1204–9 PMID: 11923267.
177. Huang T, Li X, Xie J, et al. Long-term retinal neurovascular and choroidal changes after panretinal photocoagulation in diabetic retinopathy. Frontiers Med. 2021;8:1–11. https://doi.org/10.3389/fmed.2021.752538.
178. Schatz H, Madeira D, McDonald HR, Johnson RN. Progressive enlargement of laser scars following grid laser photocoagulation for diffuse diabetic macular edema. Arch Ophthalmol. 1991;109(11):1549–51. https://doi.org/10.1001/archopht.1991.01080110085041.
179. Hudson C, Flanagan JG, Turner GS, Chen HC, Young LB, McLeod D. Influence of laser photocoagulation for clinically significant diabetic macular edema (DMO) on short wavelength and conventional automated perimetry. Diabetologia. 1998;41(11):1283–92. https://doi.org/10.1007/s001250051066.
180. Striph GG, Hart WM Jr., Olk RJ. Modified grid laser photo- coagulation for diabetic macular edema. The effect on the central visual field. Ophthalmology. 1988;95(12):1673–9. https://doi.org/10.1016/s0161-6420(88)32957-x.
181. Luttrull J, Spink C. Serial optical coherence tomography of subthreshold diode laser micropulse photocoagulation for diabetic macular edema. Ophthalmic Surg Lasers Imaging. 2006;37(5):370–7. https://doi.org/10.3928/15428877-20060901-03.
182. Luttrull J, Sinclair S. Safety of transfoveal subthreshold diode micropulse laser for fovea-involving diabetic macular edema in eyes with good visual acuity. Retina. 2014;34(10):2010–20. https://doi.org/10.1097/IAE.0000000000000177.
183. Bughi S, Shaw S, Bessman A. Laser damage to retinal ganglion cells. The effect on circadian rhythm. J Diabetes Complications. 2006;20(3):184–7. https://doi.org/10.1016/j.jdiacomp.2005.06.006.
184. Glassman A, Baker C, Beaulieu W, et al. DRCR Retina Network. (2020). Assessment of the DRCR Retina Network approach to management with initial observation for eyes with center-involved diabetic macular edema and good visual acuity: A secondary analysis of a randomized clinical trial. JAMA Ophthalmol, 138(4):341–9https://doi.org/10.1001/jamaophthalmol.2019.6035.
185. Campochiaro P, Marcus D, Awh C, et al. The port delivery system with ranibizumab for neovascular age-related macular degeneration results from the randomized phase 2 Ladder clinical trial. Ophthalmology. 2019;126(8):1141–54. https://doi.org/10.1016/j.ophtha.2019.03.036.
186. Vujosevic S, Bottega E, Casciano M, Pilotto E, Convento E, Midena E. Microperimetry and fundus autofluorescence in diabetic macular edema: Subthreshold micropulse diode laser versus modified early treatment diabetic retinopathy study laser photocoagulation. Retina. 2010;30(6):908–16. https://doi.org/10.1097/IAE.0b013e3181c96986.

187. Luttrull JK, Musch DC, Mainster MA. Subthreshold diode micropulse photocoagulation for the treatment of clinically significant diabetic macular oedema. Br J Ophthalmol. 2005;89(1):74–80. https://doi.org/10.1136/bjo.2004.051540.
188. Luttrull J, Spink C. Reply letter to D. Kuman et al re Pan-retinal subthreshold laser for proliferative diabetic retinopathy. Eye. 2009;23(11):2123. https://doi.org/10.1038/eye.2008.416.
189. Figueira J, Khan J, Nunes S, et al. Prospective randomized controlled trial comparing subthreshold micropulse diode laser photo-coagulation and conventional green laser for clinically significant diabetic macular oedema. Br J Ophthalmol. 2009;93(10):1341–4. https://doi.org/10.1136/bjo.2008.146712.
190. Luttrull J, Dorin G. Subthreshold diode micropulse laser photocoagulation (SDM) as invisible retinal phototherapy for diabetic macular edema: a review. Curr Diabetes Rev. 2012;8(4):274–84. https://doi.org/10.2174/157339912800840523.
191. Luttrull JK, Sramek C, Palanker D, Spink C, Musch D. Long-term safety, high-resolution imaging, and tissue temperature modeling of subvisible diode micropulse photocoagulation for retinovascular macular edema. Retina. 2011;32(2):375–86. https://doi.org/10.1097/IAE.0b013e3182206f6c.
192. Lavinsky D, Cardillo JA, Melo LA Jr, Dare AR, Farah ME, Belfort R. Randomized clinical trial evaluating mETDRS versus normal or high-density micropulse photocoagulation for diabetic macular edema. Invest Ophthalmol Vis Sci. 2011;52(7):4314–23. https://doi.org/10.1167/iovs.10-6828.
193. Luttrull JK, Kent D. Modern retinal laser for neuroprotection in open-angle glaucoma. In: Samples JF, Ahmed I, editors. New Concepts in Glaucoma Surgery Series (pp. 1–20). Amsterdam, the Netherlands: Kugler; 2019
194. Luttrull, JK, Margolis, BWL. Functionally guided retinal protective therapy as prophylaxis for age-related and inherited retinal degenerations. A pilot study. Invest Ophthalmol Vis Sci. 2016;7(1):265–75. https://doi.org/10.1167/iovs.15-18163.
195. Hall J, Matos S, Gold S, Severino LS. The paradox of sustainable innovation: The 'Eroom' effect (Moore's law backwards). J Clean Prod. 2018;172: 3487–3497. https://doi.org/10.1016/j.jclepro.2017.07.162. ISSN 0959-6526.
196. Luttrull JK, Chang DB, Margolis BWL, Dorin G, Luttrull DK. Laser re-sensitization of medically unresponsive neovascular age-related macular degeneration: efficacy and implications. Retina. 2015;35(6):1184–94. https://doi.org/10.1097/IAE.0000000000000458.
197. Schröder M, Kaufman RJ. The mammalian unfolded protein response. Annu Rev Biochem. 2005;74:739–89. https://doi.org/10.1146/annurev.biochem.73.011303.074134.
198. Wu MY, Yiang GT, Lai TT, Li CJ. The oxidative stress and mitochondrial dysfunction during the pathogenesis of diabetic retinopathy. Oxid Med Cell Longev. 2018;2018:3420187. https://doi.org/10.1155/2018/3420187.
199. Terrab L, Wipf P. Hsp70 and the Unfolded Protein Response as a Challenging Drug Target and an Inspiration for Probe Molecule Development. ACS Med Chem Lett. 2020;11(3):232–6. https://doi.org/10.1021/acsmedchemlett.9b00583.
200. Melo EP, Konno T, Farace I, Awadelkareem MA, Skov LR, Teodoro F, Sancho TP, Paton AW, Paton JC, Fares M, Paulo PMR, Zhang X, Avezov E. Stress-induced protein disaggregation in the endoplasmic reticulum catalysed by BiP. Nat Commun. 2022;13(1):2501. https://doi.org/10.1038/s41467-022-30238-2.
201. Cai W, Yang T, Liu H, Han L, Zhang K, Hu X, Chen J. Peroxisome proliferator-activated receptor γ (PPARγ): A master gatekeeper in CNS injury and repair. Prog Neurobiol. 2018;163–164:27–58. https://doi.org/10.1016/j.pneurobio.2017.10.002.
202. Meusser B, Hirsch C, Jarosch E, Sommer T. ERAD: the long road to destruction. Nat Cell Biol. 2005;8:766–72. https://doi.org/10.1038/ncb0805-766.
203. Richter K, Haslbeck M, Buchner J. The heat shock response: life on the verge of death. Mol Cell. 2010;40(2):253–66. https://doi.org/10.1016/j.molcel.2010.10.006.
204. Vitale M, Bakunts A, Orsi A, et al. Inadequate BiP availability defines endoplasmic reticulum stress. ELife. 2019;8: e41168. https://doi.org/10.7554/eLife.41168.

205. Lu RC, Tan MS, Wang H, Xie AM, Yu JT, Tan L. Heat shock protein 70 in Alzheimer' disease. Biomed Res Int. 2014;2014: 435203. https://doi.org/10.1155/2014/435203.
206. Srivastava K, Narang R, Bhatia J, Saluga D. Expression of heat shock protein 70 gene and its correlation with essential hypertension. PLoS ONE. 2016;11(3): e0151060. https://doi.org/10.1371/journal.pone.0151060.
207. Stetler RA, Gan Y, Zhang W, Liou AK, Gao Y, Cao G, Chen J. Heat shock proteins: cellular and molecular mechanisms in the central nervous system. Progress Neurobiol. 2010;92(2):184–211. https://doi.org/10.1016/j.pneurobio.2010.05.002.
208. Burton DGA, Faragher RGA. Obesity and type-2 diabetes as inducers of premature cellular senescence and ageing. Biogerontology. 2018;19(6):447–59. https://doi.org/10.1007/s10522-018-9763-7.
209. Baldwin RL. Review: Energetics of Protein Folding. J Mol Biol. 2007;371(2):283–301. https://doi.org/10.1016/j.jmb.2007.05.078.
210. Beckham JT. The role of heat shock protein 70 in laser irradiation and thermal preconditioning. PhD dissertation, Vanderbilt University Press. 2008.
211. Chang D, Luttrull J. Comparison of subthreshold 577 and 810nm micropulse laser effects on heat-shock protein activation kinetics: Implications for treatment efficacy and safety. Trans Vis Sci Technol. 2020;9(5):23. https://doi.org/10.1167/tvst.9.5.23.
212. Hattenbach LO, Beck KF, Pfeilschifter J, Koch F, Ohrloff C, Schake W. Pigment epithelium-derived factor is up regulated in photocoagulated human retinal pigment epithelial cells. Ophthalmic Res. 2005;37(6):341–6. https://doi.org/10.1159/000088263.
213. Glass C, Saijo K, Winner B, Marchetto M, Gage F. Mechanisms underlying inflammation in neurodegeneration. Cell. 2010;140(6):918–34. https://doi.org/10.1016/j.cell.2010.02.016.
214. Sramek C, Mackanos M, Spitler R, Leung LS, Nomoto H, Contag CH, Palanker D. Non-damaging retinal phototherapy: dynamic range of heat shock protein expression. Invest Ophthalmol Vis Sci. 2011;52(3):1780–7. https://doi.org/10.1167/iovs.10-5917.
215. Kern T, Barber A. Retinal ganglion cells in diabetes. J Physiol. 2008;586(18):4401–8. https://doi.org/10.1113/jphysiol.2008.156695.
216. De Cillà S, Vezzola D, Farruggio S, et al. The subthreshold micropulse laser treatment of the retina restores the oxidant/antioxidant balance and counteracts programmed forms of cell death in the mice eyes. Acta Ophthalmol. 2019;97(4):559–67. https://doi.org/10.1111/aos.13995.
217. Frizziero L, Calciati A, Torresin T, Midena G, Parrozzani R, Pilotto E, Midena E. Diabetic macular edema treated with 577-nm subthreshold micropulse laser: a real-life. Long-Term Study J Pers Med. 2021;11(5):405. https://doi.org/10.3390/jpm11050405.
218. Gao X, Xing D. Molecular mechanisms of cell proliferation induced by low power laser irradiation. J Biomed Sci. 2009;16(1):4. https://doi.org/10.1186/1423-0127-16-4.
219. Khetarpal S, Kaw U, Dover JS, Arndt KA. Laser advances in the treatment of burn and traumatic scars. Semin Cutan Med Surg. 2017;36(4):185–91. https://doi.org/10.12788/j.sder.2017.030.
220. Keunen, J, Battaglia-Parodi, M, Vujosevic, S, Luttrull, J. International retinal laser society guidelines for subthreshold laser treatment. Transl Vis Sci Technol. 2020;9(9):15. https://doi.org/10.1167/tvst.9.9.15.
221. Dorin G. Subthreshold and micropulse diode laser photocoagulation. Semin Ophthalmol. 2003;18(3):147–53. https://doi.org/10.1076/soph.18.3.147.29812.
222. Chhablani J, Roh YJ, Jobling AI, et al. Restorative retinal laser therapy: present state and future directions. Surv Ophthalmol. 2018;63(3):307–28. https://doi.org/10.1016/j.survophthal.2017.09.008.
223. Glassman AR, Wells JA 3RD, Josic K, et al, for the Diabetic Retinopathy Clinical Research Network. Five-Year Outcomes After Initial Aflibercept, Bevacizumab, or Ranibizumab Treatment for Diabetic Macular Edema (Protocol T Extension Study). Ophthalmology. 2020;127(9):1201–10. https://doi.org/10.1016/j.ophtha.2020.03.021.
224. Amoaku WM, Ghanchi F, Bailey C, et al. Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group. Eye (Lond). 2020;34(Suppl 1):1–51. https://doi.org/10.1038/s41433-020-0961-6.

225. Luttrull JK. Laser is the first-choice treatment for diabetic retinopathy. Amsterdam Retina Debate. 2017. Annual meeting of the European Society of Retina Specialists (Euretina); Sept 8, Barcelona, Spain.
226. Laursen ML, Moeller F, Sander B, Sjoelie AK. Subthreshold diode micropulse laser treatment in diabetic macular edema. Br J Ophthalmol. 2004;88(9):1173–9. https://doi.org/10.1136/bjo.2003.040949.
227. Brader HS, Young LH. Subthreshold diode micropulse laser: A review. Semin Ophthalmol. 2016;31(1–2):30–9. https://doi.org/10.3109/08820538.2015.1114837.
228. Chen DY, Chen YM, Hsieh TY, Hsieh CW, Lin CC, Lan JL. Significant effects of biologic therapy on lipid profiles and insulin resistance in patients with rheumatoid arthritis. Arthritis Res Ther. 2015;17(1):52. https://doi.org/10.1186/s13075-015-0559-8.
229. Scholz P, Altay L, Fauser S. A Review of subthreshold micropulse laser for treatment of macular disorders. Adv Ther. 2017;34(7):1528–55. https://doi.org/10.1007/s12325-017-0559-y.
230. Sivaprasad S, Sandhu R, Tandon A, Sayed-Ahmed K, McHugh DA. Subthreshold micropulse diode laser photocoagulation for clinically significant diabetic macular oedema: a three-year follow up. Clin Exp Ophthalmol. 2007;35(7):640–4. https://doi.org/10.1111/j.1442-9071.2007.01566.x.
231. Sivaprasad S, Dorin G. Subthreshold diode laser micropulse photocoagulation for the treatment of diabetic macular edema. Expert Rev Med Devices. 2012;9(2):189–97. https://doi.org/10.1586/erd.12.1.
232. Jorge EC, Jorge EN, Botelho M, Farat JG, Virgili G, El Dib R. Monotherapy laser photocoagulation for diabetic macular oedema. Cochrane Database Syst Rev. 2018;10(10):CD010859. https://doi.org/10.1002/14651858.CD010859.pub2.
233. Luttrull JK, Musch D, Spink C. Subthreshold diode micropulse panretinal photocoagulation for proliferative diabetic retinopathy. Eye (Lond). 2008;22(5):607–12. https://doi.org/10.1038/sj.eye.6702725.
234. Patel D, Patel SN, Chaudhary V, Garg SJ. Complications of intravitreal injections: 2022. Curr Opin Ophthalmol. 2022;33(3):137–46. https://doi.org/10.1097/ICU.0000000000000850.
235. Vujosevic S, Gatti V, Muraca A, et al. Optical coherence tomography angiography changes after subthreshold micropulse yellow laser in diabetic macular edema. Retina. 2020;40(2):312–21. https://doi.org/10.1097/IAE.0000000000002383.
236. Vujosevic S, Toma C, Villani E, et al. Subthreshold micropulse laser in diabetic macular edema: 1-Year improvement in OCT/OCT-Angiography biomarkers. Transl Vis Sci Technol. 2020;9(10):31. https://doi.org/10.1167/tvst.9.10.31.
237. Jhingan M, Goud A, Peguda HK, Khodani M, Luttrull JK, Chhablani J. Subthreshold microsecond laser for proliferative diabetic retinopathy: a randomized pilot study. Clin Ophthalmol. 2018;15(12):141–5. https://doi.org/10.2147/OPTH.S143206.
238. Marcus D, Silva P, Liu D, & et al. DRCR Retina Network. Association of predominantly peripheral lesions on ultra-widefield imaging and the risk of diabetic retinopathy worsening over time. JAMA Ophthalmol. 2022. Epub ahead of print.

Chapter 19
The Future for Retinal Laser Treatment. Is There One?

Jeffrey K. Luttrull

Prediction: Retina laser treatment should become the most important and widely used treatment in ophthalmology for the treatment and prevention of virtually all causes of irreversible visual loss.

That is, it *should* become. But will it? The ancient world had the Oracle of Delphi [1]. The closest thing we have had to predict the future in the modern world is The Spectator magazine. The Spectator is a weekly British magazine that has been published continuously since 1828 [2]. Over the years, The Spectator has offered a regular vignette posting predictions 10, 25, 50 years into the future, from prior editions of the magazine. The long publishing history of the Spectator has allowed readers to read and assess those past predictions for accuracy. As it happens, The Spectator's predictions about the future are virtually never accurate.

This is not because the prognosticators of The Spectator are stupid or foolish. Anything but. The problem with predicting the future is two-fold: First, our only frame of reference is the past. This causes us to imagine the future only in terms of what we know now, or can imagine, based on our experience and current understanding. Thus, the future we tend to imagine is a better now. We expect current trends to continue, debts to be paid, and justice to finally be done. But, in general, our expectations are based on experience, not prescience. The Spectator is no different.

The second reason the future cannot be predicted is that disruptive events occur that are unanticipated by our experience, current thinking, or current technology. It is these unanticipated disruptive changes that will change the future far more profoundly than the incrementalism that dominates our thinking and limits imaginations [3, 4]. We can't predict the future because the things that will define it do not exist and have likely not even occurred to anyone yet. This is easily confirmed by looking at the things that define our lives today. Who saw google or Tesla coming in 2000? Who even knew how important they would become when they appeared? Few, if any.

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A. Grzybowski et al. (eds.), *Retina Lasers in Ophthalmology*,
https://doi.org/10.1007/978-3-031-25779-7_19

My bold prediction for the idea future of medicine also comes from experience, albeit a virtual one. I think Star Trek had it right with Bones' "Tricorder". The Tricorder was small hand-held device that he simply waved at a sick or injured person. The device both diagnosed and treated them, just like that. Why Bones had to be a doctor to do this was never clear to me (concerning note to the AMA). But that's where we're headed. Maybe an implanted chip instead of a thing we need to hold in our hand…? It's coming, for sure.

Absent prescience, focus on near-term incrementalism is a safer bet. As we are primarily concerned with the future of retinal laser treatment, it is safe to bet that retinal laser will become more effective, safer, faster, easier, more pleasant, and more useful. The bigger question is whether anyone will care? Will laser be replaced by something we cannot currently envisage? Almost certainly. Nothing lasts forever. But, when, how, and by what, is unclear. Because the best we can do is project incrementally, in the following we will examine the general attributes of currently available laser modes to better understand what they do, and what room for improvement there might be in the future.

Candidate directions for the future of retinal laser therapy: how do they compare? We ask reason to point the way.

Mechanism of Retinal Laser

As discussed in more detail in "Neuroprotection", all therapeutic retinal laser effects are mediated by RPE cells that are affected by the laser but not killed. Thus, the response to laser damaging to the retina is characterized by the same biologic effects arising from laser treatment sublethal to the retina, with additional effects resulting from tissue destruction, death, debridement, remodeling, and repair [5–7]. The effects arising only from laser-induced tissue damage are nontherapeutic and clinically detrimental, as they include principally inflammation, loss of function, and local fibrosis. Thus, the therapeutic effects of laser modes of inherently destructive laser modes such as conventional photocoagulation (CPC) (including the PASCAL), SRT, and 2RT are indirect, with all direct effects being adverse. In contrast, the therapeutic effects of MPL sublethal to the RPE are direct, arising from the area directly exposed to the laser beam, and thus entirely therapeutic and without adverse treatment effects [7–10]. The implications of this difference are difficult to overstate. The results of the Early Treatment of Diabetic Retinopathy Study (EDTRS) presaged this understanding, finding that increased treatment intensity increased adverse treatment effects, while increased density increased therapeutic effectiveness [11]. A fundamental difference between ETDRS CPC and laser treatment entirely sublethal to the retina, such as SDM MPL, is that increasing density of CPC to improve clinical effectiveness also reduces visual function. The less retina, the less disease. However, like amputation instead of antibiotics, this approach is at odds with clinical goals of sight preservation and vision improvement. For laser sublethal to the RPE, increasing

treatment density and area increases the therapeutic effect by maximizing the restorative effects of treatment and improving, rather eliminating retinal and visual function [10]. These principles are reflected in some basic clinical observations: that there are no outcome differences associated with laser wavelength, as retinal destruction by any means is retinal destruction; that the detrimental effects of less damaging laser treatment modalities are differences of degree, and not kind; and that the visual benefits of destructive laser modes are reduced according to the degree of LIRD produced by that particular mode of treatment [7–13].

The fundamental differences in the effects of current laser modes, CPC, SRT, 2RT and MPL are, as suggested above, evident in their effects on retinal and visual function. These then determine how, when, where, for what, and how often each can be used therapeutically, and how well they achieve clinical goals. These inherent properties also determine the potential for each laser mode going into the future.

Arguably the most important advance needing to be made in ophthalmology is prevention of the major causes of irreversible visual loss. These are, in order of significance, AMD, DR, open angle glaucoma (OAG), and inherited retinal degenerations (IRDs). Some might argue that acquired myopia belongs in that list [14]. It is axiomatic that to slow, stop, or reverse disease progression and reduce the risks of visual loss, any effective treatment must first improve retinal function [15, 16]. Then, such a treatment would either have to be a permanent cure, or if temporarily effective, be renewable without limit to allow the benefits of treatment to be maintained.

There are many studies on the biologic responses to retinal laser treatment that are covered in the chapter on "Neuroprotection" and are relevant to this discussion. However, in this section we will focus on the key end-effects of laser treatment—retinal and visual function—rather than how and why we got there. For the purposes of examining the end-results of retinal laser on retinal function, electrophysiology is a widely available and highly sensitive measure of the retinal physiology that has been used to study the response to various current laser modes. This information should be helpful in suggesting which laser modes may be best suited best to the future job of preventing vison loss.

By definition, CPC reduces overall retinal function by destroying the retinal directly where, and near, it is applied. How much the result of testing such as electroretinography (ERG) is affected by the inherently destructive retina laser modes, including CPC, depends primarily on treatment density and retinal area covered. Thus, heavy panretinal photocoagulation (PRP) markedly reduces retinal function by full field electroretinography (ERG), while only a few focal spots of CPC in anywhere in the retina may have little effect on the ERG, despite complete loss of retinal function at the application spots. While there is some recovery after resolution of the acute inflammation and healing that follows CPC, the loss of visual function is permanent and may progress over time due to progressive retinal atrophy resulting from enlargement of the CPC scars [17, 18]. Regarding short-pulse CW laser (PASCAL), a study 104 eyes of 52 patients to undergo panretinal laser for PDR was reported, randomizing patients between conventional panretinal photocoagulation (PRP) and PASCAL peripheral retinal laser. After treatment there was no significant difference in VA between the groups. Full field electroretinography (ERG) and flicker

ERG were significantly reduced both groups, with a significantly greater reduction in the PRP group compared to the PASCAL group [19]. In another study, retinal function was assessed in eyes randomized between ranibizumab alone, and PASCAL or conventional CPC peripheral retinal treatment with or without ranibizumab, for proliferative diabetic retinopathy (PDR). At 48 months full-field ERG responses were diminished in all eyes, even in drug-only eyes. However, this reduction in the drug alone eyes was mild compared to the laser-treated eyes. In this study, there was no difference in reduced retinal function by ERG between the eyes treated with CPC and the PASCAL [20]. The PASCAL is designed to photocoagulate the outer retina and photoreceptors, reducing damage to the RPE and overlying neurosensory retina [10]. Thus, it is not surprising that panretinal PASCAL treatment reduces the ERG response, but may preserve retinal function better than CPC [21]. However, the Manchester study showed that PASCAL treatment of sufficient density can reduce retinal function as effectively as conventional suprathreshold photocoagulation [20]. A search of the literature failed to produce studies examining changes in retinal function by electrophysiology in humans following SRT and 2RT.

Regarding MPL, Venkatesh et all reported 46 eyes of 33 patients randomized between 532 nm focal laser and 810 nm "SDM" for DME. These were evaluated with multifocal ERG before and after treatment. With an average follow up of 6 months 18/23 532 nm and 4/23 SDM eyes showed ERG worsening after treatment. Contrast sensitivity, VA and DME reduction were the same between the groups [22]. Jhingan and associates compared CPC PRP and MPL PRP for severe NPDR and low-risk PDR in 20 eyes of 10 patients. At 9 months post treatment, the conventional PRP eyes had worse visual fields, contrast sensitivity, and ERG compared to the MPL eyes, but the difference was not significant [23].

In 2016, 158 eyes of 108 patients with AMD, and 10 eyes of 8 patients with IRDs (rod-cone degeneration (four eyes), cone-rod degeneration (three eyes), and Stargardt's disease (three eyes)) were evaluated before, and 1 month after. panmacular SDM MPL by pattern electroretinography (PERG). Overall VAs were stable, while the PERG responses were improved in both AMD ($p = 0.0001$) and the IRD groups ($p = 0.002$). In the AMD eyes, additional testing of contrast acuity ($p = 0.006$) and microperimetry ($p = 0.046$) were also improved [15].

In a subsequent study, 26 eyes of 15 pts with retinitis pigmentosa were reported, aged 16–69 (avg. 47) years. Each underwent panmacular SDM MPL. Before, and approximately one month after treatment, each eye was tested by PERG and mesopic visual function testing. All PERG indices improved after treatment, with significant improvements in two signal latency measures (the MagD (μV)/Mag (μV) ratio ($P < 0.0001$), and the MagD (μV) amplitude ($P = 0.0003$). All mesopic visual function indices were also significantly improved, ($p = 0.02$ to $p = 0.002$), as was average logMAR VA (improving from avg. 0.6 to 0.4) ($p = 0.02$) [16].

That same year, 2018, 88 eyes of 48 consecutive patients with open angle glaucoma (OAG) were reported [24]. All had glaucomatous optic neuropathy and visual field loss prior to panmacular SDM MPL treatment. Pretreatment, IOPs ranged 6–23 mmHg (average: 13) on 0–3 (average: 1.6) medications. 33 eyes had had prior glaucoma surgery. Snellen visual acuities (VA) ranged 20/15 to count fingers (median

20/60). All were tested by PERG, visually evoked response (VER) and mesopic visual function testing (MVFT) before and approximately one month following SDM MPL treatment. Prior to treatment, both VEPs and MVFTs of all eyes were abnormal. Following SDM, Snellen VA was improved ($p = 0.005$). IOPs were unchanged. VER P1 amplitudes ($p = 0.001$), PERG amplitudes ($p = 0.05$), mesopic VA ($p < 0.0001$) and mesopic automated perimetry ($p < 0.0001$) were all significantly improved [24].

Not surprising, visual function tends to parallel retinal function, and thus the effects of the various laser modes on retinal function. CPC for macular disease rarely improves VA, except indirectly, such as treatment relatively distant from the fovea to reduce subretinal fluid from CSR or CNV [25–27]. In most applications for MPC, however, the hope is a reduced rate and risk of visual loss, rather than visual improvement.

The visual results of the PASCAL, SRT and 2RT tend to reflect stabilization of visual acuity in most applications. This includes trial for treatment of idiopathic macular telangiectasis, central serous chorioretinopathy (CSR), DME, and PDR for the PASCAL; DME, AMD and CSR for SRT; and DME and AMD for 2RT. For all short-pulse laser modes, treatment of CSR was generally effective, with improved VA. Visual results in DME tended to be stable or slightly improved, but not worsened. Treatment of eyes with intermediate AMD with 2RT reduced drusen, but to no significant effect. However, treatment of advanced dry AMD, characterized by reticular pseudodrusen and/or geographic atrophy, was significantly worsened by both SRT and 2RT (nanosecond laser). [28–42]. In all applications of SRT and 2RT, inherently destructive to the RPE and often adjacent structures as well, showed clinically visible laser lesions following treatment. In one study of 577 nm PASCAL for CSR, a titration algorithm ("endpoint management") was used to try to avoid RPE damage. According to the authors, this technique was successful in avoiding detectable laser lesions by FFA, OCT, and fundus autofluorescence photography (FAF). In these eyes, VA was significantly improved [29].

As noted previously, the effects of MPL can span the entire range from suprathreshold CPC (inherently destructive to the retina) to SDM (which is reliably sublethal to the RPE) in all eyes, depending upon the laser parameters employed [7–10, 43]. For the purposes of this discussion, we will focus on SDM as the most different treatment modality when compared to CPC and short-pulse lasers that are inherently damaging to the retina. We continue to place the PASCAL in this group, even though treatment without retinal damage has been reported in one paper of 12 eyes. This is because, despite a titration algorithm, the narrow therapeutic range of CW lasers, of just 0.010 W in breadth in the case of the PASCAL, is simply too small a target to consistently "hit" reliably in a large number of eyes and laser spots, due to the marked susceptibility of such a narrow safety window to eye-specific factors, such as media opacity, fundus pigmentation, and regional differences in retina fundus pigmentation and retinal thickness [7–10, 29–32, 43, 31]. There is a substantive difference between treatment than can be retina-sparing, and treatment that is consistently and reliably retina-sparing [10, 30, 32, 43, 31].

In general, the visual results of SDM MPL reflect visual improvement in most applications. These include DME, PDR, dry and wet AMD, CSR, IRDs including

retinitis pigmentosa, OAG, BRVO, and post-membrane peeling maculopathy [24, 27, 30, 44–63]. In particular, where head-to-head comparison of visual results of CPC and SDM MPL are reported (all for DME), the visual results of MPL are always superior to CPC [27, 46, 61–64]. A single trial comparing short-pulse CW laser (PASCAL) to MPL, found MPL visual results better [34]. It is interesting to note that, in DME, VA often improves out of proportion to the decrease in macular thickening, a marked contrast to CPC [61–64]. In some studies of DME employing the SDM high-density treatment strategy, the visual results of MPL rival intravitreal drug therapy [27, 65].

While retinal and visual function are objective measures, "safety" has been an historically fluid concept. The definition of safe laser treatment has reflected our understanding of treatment, and the available modes of treatment. In the CPC era, the many and significant adverse treatment effects of CPC, sufficiently well known that no list is required here, were considered acceptable because, compared to no treatment for such things and DME, PDR, and extrafoveal CNV, CPC was significantly better than no treatment at all. Since LIRD was presumed to be necessary for a therapeutic effect, efforts to improve safety centered primarily around reducing the severity of the inherent adverse effects, by reducing the intensity of suprathreshold CPC, and breaking treatment, such as CPC PRP, into partial treatments spread over time to reduce treatment-associated inflammation and pain [66]. As CPC intensity gradually declined, "subthreshold" therapy increased in popularity [7, 10]. New approaches to limiting LIRD to reduce the severity of the inherent adverse effects of LIRD, such as the PASCAL, SRT, and 2RT were developed. However, because LIRD was still the goal of treatment as it was universally believed to be necessary for therapeutically effectiveness, the inherent risks and adverse effects of retinal laser persisted [10]. However, a new definition of laser safety gradually emerged, placing into disfavor the dense white suprathreshold full-thickness burns of the ETDRS and MPSG [11–13, 66, 67].

It has been clear for nearly 2 decades that LIRD is in fact unnecessary, and even detrimental, to achieving optimal therapeutic effectiveness [51–53]. Responsible for all adverse effects of retinal laser treatment and unnecessary, the new standard for treatment safety is complete avoidance of LIRD with treatment that is sublethal to the RPE, and reliably so. Taken to its logical conclusion, this means that safe retinal laser treatment is now defined as treatment that is reliably safe in the fovea, and without any adverse treatment effects [30].

If we sum up the properties of current retinal laser modalities in an attempt to predict an incremental future and thus technical progress, we find:

- The most important future application of retinal laser is prevention of visual loss from the major chronic progressive retinopathies.
- To do this, treatment must improve retinal function. Available evidence indicates MPL is the best candidate in this regard.
- Preventive treatment works best given early. This means prior to symptomatic vision loss and often clinical findings of disease. To treat and retreat asymptomatic patients at low current risk of vision loss, treatment must be extraordinarily safe.

This means *reliably* safe (sublethal to the RPE) in the fovea, whether treated intentionally or inadvertently. Current evidence suggests MPL is the best candidate in this regard.

- Preventive treatment must therefore preserve or improve vision function and visual acuity, and not for any reason worsen visual acuity. Only MPL has demonstrated this ability in all tested applications, including those without macular edema or fluid.
- To maintain treatment effects over a lifetime of disease, treatment must be repeatable and renewable over a lifetime. Retinal damaging treatment modalities are not suited to such treatment as they quickly become visually threatening due to the accumulation of LIRD. MPL, employing the SDM paradigm reliably sublethal to the RPE, has been demonstrated to be infinitely repeatable with renewable therapeutic effects. Thus, current evidence suggests MPL is the best candidate in this regard.
- To maximize treatment safety, preventive laser parameters and treatment should be uniform in all eyes, with minimal reliance on surgeon judgement. Because reliably safe retinal laser treatment is possible, the only remaining risk of treatment is surgeon misjudgment or error. Therefore, treatment should not be influenced by patient- or eye-specific factors that would require adjustment of laser parameters on a per eye basis. Current evidence indicates that MPL is the only treatment modality with a demonstrated facility in this regard.
- The fact that LIRD is unnecessary and responsible for all adverse effects arising from retinal laser treatment redefines it, from a prerequisite of treatment to serious adverse treatment effect (SAE), or the most serious complication of laser treatment. Possible, or even frequent, avoidance of LIRD is unacceptable when reliably consistent LIRD avoidance is available. It is this level of safety that makes all else noted above possible. Thus, basic medical ethics require use of only treatments that are reliably sublethal to the retina. Current evidence indicates MPL as the best candidate in this regard.

The above conclusions suggest that MPL is the best candidate for the future of retinal laser treatment. It also raises two critical objections to continued use of retina-damaging laser modalities, all conceived and developed at a time when such damage was universally believed to be necessary for effective treatment; a practical objection, and an ethical objection.

From a practical point of view, retinal laser treatment has been shown to improve retinal and visual function in a wide variety of disparate chronic progressive retinopathies, united in their fundamental commonality of representing neurodegenerations. Some of these include IRDs and OAG. Little imagination is needed to see that superimposition of LIRD in these settings can only be detrimental to retinal and visual function. Further, any degree of LIRD markedly limits both application, such as to the fovea, and maintenance treatment over the lifetime of the patient if necessary. A further advantage of treatment sublethal to the RPE is that laser can be applied to the entire retina to address a panretinopathy, such as diabetic retinopathy or retinitis pigmentosa, to maximize therapeutic effects, in much the same way that

intravitreal drug therapy treats the entire retina. Such "total retinal treatment" is forbidden to retinal damaging laser modes, due to the inevitable loss of retinal and visual function that would ensue.

The ethical objection to retina-damaging laser modes is likewise compelling. Past and even current acceptance of the adverse treatment effects inherent to retina-damaging treatment modes (even those described as "non-damaging" despite being photodisruptive to the RPE and outer retina) is a holdover from the CPC era when LIRD was thought to be necessary, and when there were no other, particularly no retina-sparing, treatment options available. Thus, the numerous and often severe adverse effects of CPC were considered acceptable when the benefits of treatment were compared to no treatment at all. Such decades long universally-held attitudes die slowly and persist even to this day, in spite of the advent of effective retina-sparing treatment alternatives.

Without invoking Hippocrates, a brief consideration of retina damaging vs. retina sparing treatment can be instructive. It is axiomatic in medicine that riskier, more invasive treatments should be considered over safer, less invasive treatments only if the added risks and complexity offer enough added benefit to justify the added risks and adverse effects [68]. Therefore, it is appropriate to ask if retina-damaging treatments are superior to sublethal treatments, and if so, are they sufficiently superior to justify the risks and inherent adverse treatment effects?

As described above, rather than superior, and certainly sufficiently superior to justify the risks and inherent adverse effects of treatment, the therapeutic effects of retinal-damaging laser treatments are instead consistently inferior to retina-sparing treatments by virtually all measures, the inferiority of damaging treatments is generally proportional to the severity of treatment associated LIRD. However, the differences are of degree, not kind.

Also axiomatic in medicine is that intervention should begin with the safest, simplest, least expensive, and least invasive treatment likely to be effective [69]. Thus, the inherent adverse effects of CPC have relegated it to rescue therapy behind drug therapy for most indications [70]. SDM MPL, absent any known adverse effects and thus without the adverse effects and risks of intravitreal drug therapy, however, is favorably positioned both practically and ethically as the first-choice treatment for many conditions also amenable to drug therapy [71].

Thus, from both a practical and ethical point of view, retinal laser treatment has a potentially important role to play in the goal of prevention of vision loss from the most important causes of irreversible vision loss, but only if it is reliably sublethal and absolutely non-damaging to the RPE and neurosensory retina.

This is "Modern Retinal Laser Therapy" (MRT) [32, 72, 73]. In short, MRT eschews LIRD in favor of low-intensity treatment reliably sublethal to the RPE. MRT eschews focal, local, and low-density grid treatment required by CPC and other damaging modes of treatment in favor of high-density treatment of large areas of dysfunctional retina, not with the desire to eliminate it, but with the intent to improve and normalize its function and maximize the clinical effects of treatment by maximal recruitment of dysfunctional retina to the therapeutic cause. Current data, although limited, suggests that MRT has the greatest potential of any currently

known treatment modality, laser, drug, or other, to prevent vision loss in the future by virtue of its safety, durability, effectiveness, low cost, and breadth of indications [74–76].

To do this, more studies are required. This represents the single greatest obstacle to realizing the potential of MRT, because such studies are expensive and thus require sponsorship and support of parties expecting to benefit financially from the study outcomes. Currently, for this reason, the pharmaceutical industry dominates clinical data generation. Despite its potential benefits to society and healthcare, retinal laser treatment lacks such influential benefactors. This will need to change [77–79].

All current retinal laser platforms are designed to do treatment damaging to the retina, whether it be conventional CPC or more selective destruction of the outer retina (PASCAL), or RPE (SRT and 2RT). This is because they were all conceived of decades ago when the presumption of necessary LIRD was accepted universally. With time and progress in our understanding of the mechanism of action of retinal laser, some of these systems have been repurposed to perform less or non-damaging treatment by adding MPL capability. However, the design and use of all current systems remains dictated by their original intent and maintained capability of performing treatment intentionally destructive to the retina.

An additional incremental change in design was the introduction of application of pre-programmed patterned laser applications by the PASCAL. This facility has now been adopted by all currently retinal laser manufactures. A further incremental improvement in a number of retinal laser platforms is the added option of increasing the density of grid treatments by moving the spots closer together to reduce untreated retina and increase treatment density. Again, this is achieved by repurposing the underlying CPC laser delivery platform. The purported advantage of using such pattern applications is to improve treatment speed. However, as discussed elsewhere, once one considers the programming and treatment design time, the time savings seems to be minimal, if not taking longer to perform, than simple treatment aided by the standard laser repeat mode [80].

It has been well established that LIRD is contraindicated as neither directly nor independently contributing therapeutic effectiveness. Further, we now have MPL laser parameters that have proven to be safe in effective I all eyes, without regard for eye-specific variations in media opacity, retinal thickness, or pigmentation. Thus, titration of laser parameters, necessary for damaging laser modes such as CPC and SRT, is not only unnecessary, but increases the risk of LIRD and jeopardizes treatment safety if it leads to departure from known safe parameters [9, 10, 30–32]. Thus, the only risk of MRT is surgeon error, either by accidental or intentional use of parameters destructive to the retina. Because all current laser platforms are fundamentally designed to do damaging treatment, generally CPC, this risk remains an inherent property of all. (Figs. 19.1 and 19.2).

Thus, retinal laser technology has not caught up with our current understanding and approach to retinal laser treatment, best exemplified by SDM MLT MRT. Because MRT applies treatment safely, geographically, and in high density, there is no need for precise targeting. The capacity to perform retina-damaging treatment can now be eliminated from laser platforms—at least those dedicated to treating macular

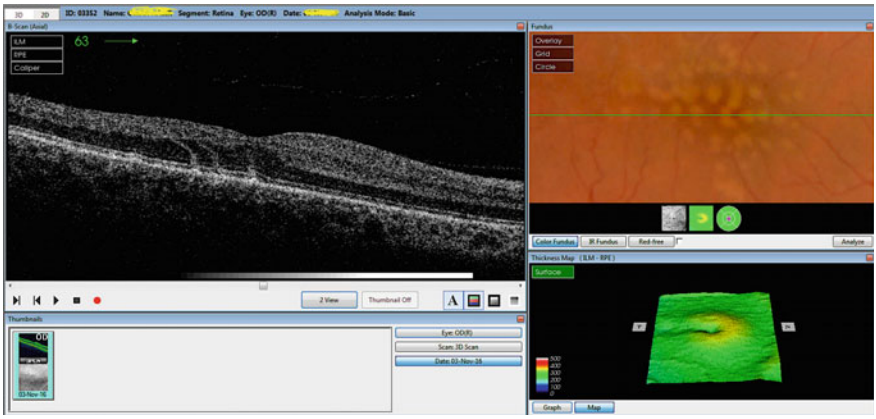

Fig. 19.1 Fundus photograph and OCT of an eye three days following 577 nm MPL (5% duty cycle) for a branch retinal vein occlusion. A titration algorithm was employed in an attempt to adjust treatment to be subthreshold and sublethal to the RPE. After treatment the patient reported visual loss and multiple central scotomata. Note multiple threshold and suprathreshold retinal burns in a low-density grid pattern. From: *Chang DB, Luttrull JK. Comparison of subthreshold 577 nm and 810 nm micropulse laser effects on heat-shock protein activation kinetics: Implications for treatment efficacy and safety. Transl Vis Sci Tecnol. 2020 Apr 28;9(5):23. doi: 10.1167/tvst.9.5.23. eCollection 2020 Apr.*

disease and chronic progressive retinopathies (CPC will still be required for retinal cautery/retinopexy of retinal breaks)—also eliminating associated risks of treatment. Finally, substantial work has been done to understand how to optimize laser parameters for both safety and efficacy (Chang DB, Luttrull JK, unpublished data). All of these considerations suggest ample room for improvement in the safety and efficacy of retinal laser treatment, if MRT concepts are applied, via automation. Stay tuned for further developments.

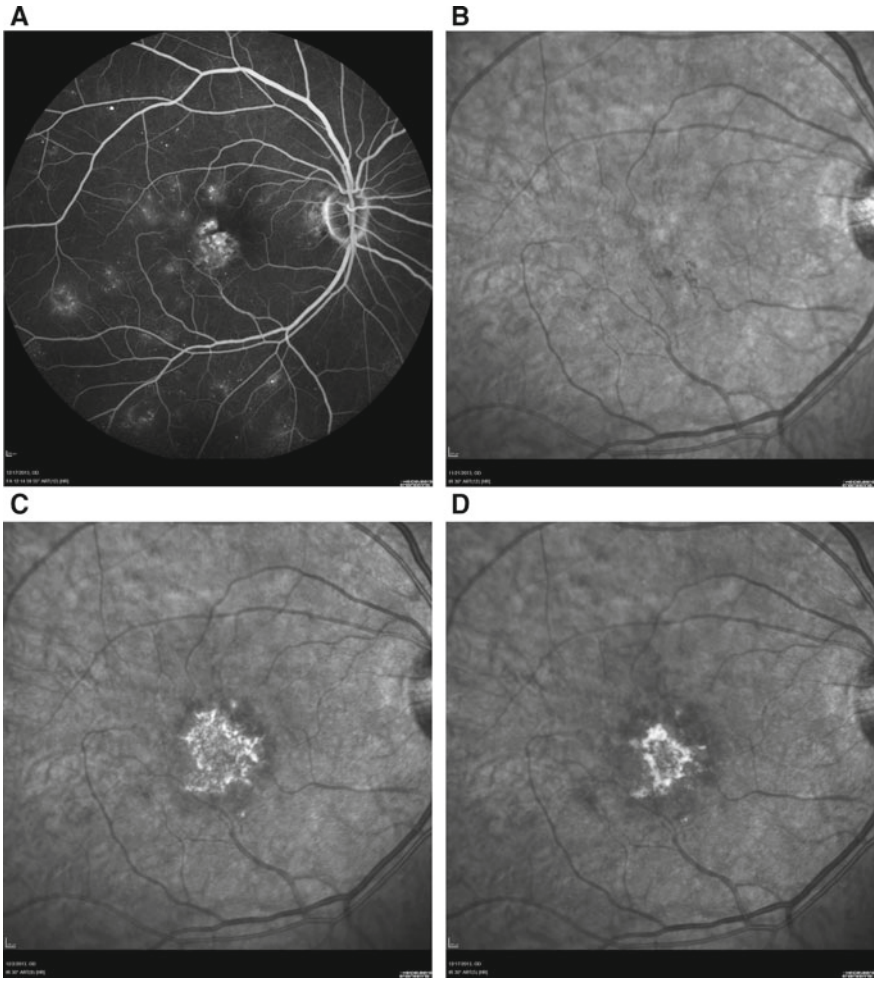

Fig. 19.2 **A** Intravenous fundus fluorescein angiogram of 56 year-old Asian woman with proliferative diabetic retinopathy and center-involving macular edema. **B** Infrared autofluorescence fundus photography (FAF) on prior to treatment. **C** FAF one week following 810 nm panmacular SDM MPL for center-involving DME. The patient reported that 3 days following treatment her vision worsened and a central scotoma appeared. Note the macular laser burns. Visual acuity before treatment 20/50; one week post treatment 20/400. **D** FAF two weeks later, three weeks following treatment. Note shrinkage of laser lesion. VA 20/200. The cause of the macular laser damage appeared to most likely be due to inadvertent use of a 15% duty cycle rather than the intended 5% duty cycle

References

1. Fairbanks A. Herodotus and the oracle of delphi. Class J. 1906;1(2):37–48.
2. The Spectator magazine. Press Holdings, London. ISSN: 0038-6952.
3. Reza FM (1994) [1961]. An introduction to information theory. Dover Publications, Inc., New York. ISBN: 0-486-68210-2.

4. Christiansen C. The innovator's dilemma. 1st ed. Boston, USA: Harvard Business Review Press; May 1, 1997. ISBN-10: 0875845851; ISBN-13: 978-0875845852.
5. Richert E, Papenkort J, von der Burchard C, Klettner A, Arnold P, Lucius R, Brinkmann R, Framme C, Roider J, Tode J. Selective retina therapy and thermal stimulation of the retina: different regenerative properties—implications for AMD therapy. BMC Ophthalmol. 2021;21(1):412. https://doi.org/10.1186/s12886-021-02188-8. PMID: 34847865; PMCID: PMC8630886.
6. Tackenberg MA, Tucker BA, Swift JS, Jiang C, Redenti S, Greenberg KP, Flannery JG, Reichenbach A, Young MJ. Müller cell activation, proliferation and migration following laser injury. Mol Vis. 2009;15:1886–96. PMID: 19768129; PMCID: PMC2746266.
7. Luttrull JK, Dorin G. Subthreshold diode micropulse photocoagulation as invisible retinal phototherapy for diabetic macular edema A review. Curr Diabetes Rev. 2012;8:274–84.
8. Luttrull JK, Sramek C, Palanker D, Spink CJ, Musch DC. Long-term safety, high-resolution imaging, and tissue temperature modeling of subvisible diode micropulse photocoagulation for retinovascular macular edema. Retina. 2012;32(2):375–86.
9. Chang DB, Luttrell JK. Comparison of subthreshold 577nm and 810nm micropulse laser effects on heat-shock protein activation kinetics: Implications for treatment efficacy and safety. Transl Vis Sci Tecnol. 2020 Apr 28;9(5):23. Doi: 10.1167/tvst.9.5.23. eCollection 2020 Apr
10. Chhablani J, Roh YJ, Jobling AI, Fletcher EL, Lek JJ, Bansal P, Guymer R, Luttrull JK. Restorative retinal laser therapy: present state and future directions. Surv Ophthalmol. 2018;63(3):307–28.
11. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol. 1985;103(12):1796–806. PMID: 2866759.
12. Atmaca LS, Ozmert E, Gündüz K. Comparisons of photocoagulation treatment in exudative age-related macular degeneration with the blue-green argon, green argon and red krypton laser wavelengths. Ophthalmologica. 1993;207(1):46–54. https://doi.org/10.1159/000310405. PMID: 7506402.
13. Evaluation of argon green vs krypton red laser for photocoagulation of subfoveal choroidal neovascularization in the macular photocoagulation study. Macular Photocoagulation Study (MPS) Group. Arch Ophthalmol. 1994;112(9):1176–84. https://doi.org/10.1001/archopht.1994.01090210060017. PMID: 7522004.
14. GBD 2019 Blindness and Vision Impairment Collaborators; Vision Loss Expert Group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. Lancet Glob Health. 2021;9(2):e144–60. https://doi.org/10.1016/S2214-109X(20)30489-7. Epub 2020 Dec 1. Erratum in: Lancet Glob Health. 2021 Apr;9(4):e408. PMID: 33275949; PMCID: PMC7820391.
15. Luttrull JK, Margolis BWL. Functionally guided retinal protective therapy as prophylaxis for age-related and inherited retinal degenerations. A pilot study. Invest Ophthalmol Vis Sci. 2016;57(1):265–75. https://doi.org/10.1167/iovs.15-18163.
16. Luttrull JK. Improved retinal and visual function following subthreshold diode micropulse laser (SDM) for retinitis pigmentosa. Eye (London) Feb 2018 PAP open access. https://doi.org/10.1038/s41433-018-0017-3.
17. Messias A, Ramos Filho JA, Messias K, Almeida FP, Costa RA, Scott IU, Gekeler F, Jorge R. Electroretinographic findings associated with panretinal photocoagulation (PRP) versus PRP plus intravitreal ranibizumab treatment for high-risk proliferative diabetic retinopathy. Doc Ophthalmol. 2012;124(3):225–36. https://doi.org/10.1007/s10633-012-9322-5. Epub 2012 Mar 29. PMID: 22457045
18. Morgan CM, Schatz H. Atrophic creep of the retinal pigment epithelium after focal macular photocoagulation. Ophthalmology. 1989;96:96e103.
19. Ye H, Yu M, Lu L, Jin C, Luo G. Electroretinogram evaluation for the treatment of proliferative diabetic retinopathy by short-pulse pattern scanning laser panretinal photocoagulation. Lasers Med Sci. 2018 Jul;33(5):1095–102. https://doi.org/10.1007/s10103-018-2474-0. Epub 2018 Mar 15. Erratum in: Lasers Med Sci. 2018 Apr 28; PMID: 29542045.

20. Messias K, Barroso RM, Jorge R, Messias A. Retinal function in eyes with proliferative diabetic retinopathy treated with intravitreal ranibizumab and multispot laser panretinal photocoagulation. Doc Ophthalmol. 2018;137(2):121–9. https://doi.org/10.1007/s10633-018-9655-9. Epub 2018 Sep 12. PMID: 30209775.
21. Kriechbaum K, Bolz M, Deak GG, Prager S, Scholda C, Schmidt-Erfurth U. High-resolution imaging of the human retina in vivo after scatter photocoagulation treatment using a semiautomated laser system. Ophthalmology. 2010;117(3):545–51. https://doi.org/10.1016/j.ophtha.2009.07.031. Epub 2010 Jan 19. PMID: 20031226.
22. Venkatesh P, Ramanjulu R, Azad R, Vohra R, Garg S. Subthreshold micropulse diode laser and double frequency neodymium: YAG laser in treatment of diabetic macular edema: a prospective, randomized study using multifocal electroretinography. Photomed Laser Surg. 2011;29(11):727–33. https://doi.org/10.1089/pho.2010.2830. Epub 2011 May 25. PMID: 21612513.
23. Jhingan M, Goud A, Peguda HK, Khodani M, Luttrull JK, Chhablani J. Subthreshold microsecond laser for proliferative diabe tic retinopathy: a randomized pilot study. Clin Ophthalmol. 2018;12:141–5. https://doi.org/10.2147/OPTH.S143206. PMID: 29391774; PMCID: PMC5774491.
24. Luttrull JK, Samples JR, Kent D, Lum BJ: Panmacular subthreshold diode micropulse laser (SDM) as neuroprotective therapy in primary open-angle glaucoma. Glaucoma Research 2018–2020, pp. 281–294 Edited by: John R. Samples and Paul A. Knepper © 2018 Kugler Publications, Amsterdam, The Netherlands.
25. Diabetic Retinopathy Clinical Research Network (2009). The course of response to focal/grid photocoagulation for diabetic macular edema. Retina (Philadelphia, Pa.), 29(10):1436–43. https://doi.org/10.1097/IAE.0b013e3181bcef6b.
26. Bressler SB, Almukhtar T, Aiello LP, Bressler NM, Ferris FL, 3rd, Glassman AR, Greven CM. Diabetic retinopathy clinical research Network. Green or yellow laser treatment for diabetic macular edema: exploratory assessment within the Diabetic Retinopathy Clinical Research Network. Retina (Philadelphia, Pa.) 33(10):2080–8. https://doi.org/10.1097/IAE.0b013e318295f744.
27. Lavinsky D, Cardillo JA, Melo LA Jr, Dare A, Farah ME, Belfort R Jr. Randomized clinical trial evaluating mETDRS versus normal or high-density micropulse photocoagulation for diabetic macular edema. Invest Ophthalmol Vis Sci. 2011;52(7):4314–23. https://doi.org/10.1167/iovs.10-6828. PMID: 21345996.
28. Lavinsky D, Silva MOD, Chaves AE, Schneider WFM, Lavinsky F, Palanker D. Functional and structural effects of nondamaging retinal laser therapy for macular telangiectasia type 2: a randomized sham-controlled clinical trial. Retina. 2021;41(3):487–94. https://doi.org/10.1097/IAE.0000000000002882. PMID: 33370517.
29. Lavinsky D, Palanker D. Nondamaging photothermal therapy for the retina: initial clinical experience with chronic central serous retinopathy. Retina. 2015;35(2):213–22. https://doi.org/10.1097/IAE.0000000000000340. PMID: 25158944.
30. Luttrull JK, Sinclair SD. Safety of transfoveal subthreshold diode micropulse laser for intrafoveal diabetic macular edema in eyes with good visual acuity. Retina. 2014;34(10):2010–20.
31. Lavinsky D, Sramek C, Wang J, Huie P, Dalal R, Mandel Y, Palanker D. Subvisible retinal laser therapy: titration algorithm and tissue response. Retina. 2014;34(1):87–97. https://doi.org/10.1097/IAE.0b013e3182993edc. PMID: 23873164.
32. Keunen JEE, Battaglia-Parodi M, Vujosevic S, Luttrull JK. International Retinal Laser Society Guidelines for Subthreshold Laser Treatment. Transl Vis Sci Technol. 2020;9(9):15. https://doi.org/10.1167/tvst.9.9.15. eCollection 2020 Aug.PMID: 32879771.
33. Roisman L, Magalhães FP, Lavinsky D, Moraes N, Hirai FE, Cardillo JA, Farah ME. Micropulse diode laser treatment for chronic central serous chorioretinopathy: a randomized pilot trial. Ophthalmic Surg Lasers Imaging Retina. 2013;44(5):465–70. https://doi.org/10.3928/23258160-20130909-08. PMID: 24044709.

34. Al-Barki A, Al-Hijji L, High R, Schatz P, Do D, Nguyen QD, Luttrull JK, Kozak I. Comparison of short-pulse subthreshold (532 nm) and infrared micropulse (810 nm) macular laser for diabetic macular edema. Sci Rep. 2021;11(1):14. https://doi.org/10.1038/s41598-020-79699-9. PMID: 33420100; PMCID: PMC7794500.
35. Jain A, Collen J, Kaines A, Hubschman JP, Schwartz S. Short-duration focal pattern grid macular photocoagulation for diabetic macular edema: four-month outcomes. Retina. 2010;30(10):1622–6. https://doi.org/10.1097/IAE.0b013e3181e095d8. PMID: 21060272.
36. Yasui A, Yamamoto M, Hirayama K, Shiraki K, Theisen-Kunde D, Brinkmann R, Miura Y, Kohno T. Retinal sensitivity after selective retina therapy (SRT) on patients with central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol. 2017;255(2):243–54. https://doi.org/10.1007/s00417-016-3441-8. Epub 2016 Aug 6. PMID: 27497611.
37. Roider J, Liew SH, Klatt C, Elsner H, Poerksen E, Hillenkamp J, Brinkmann R, Birngruber R. Selective retina therapy (SRT) for clinically significant diabetic macular edema. Graefes Arch Clin Exp Ophthalmol. 2010;248(9):1263–72. https://doi.org/10.1007/s00417-010-1356-3. PMID: 20393742.
38. Park YG, Kim JR, Kang S, Seifert E, Theisen-Kunde D, Brinkmann R, Roh YJ. Safety and efficacy of selective retina therapy (SRT) for the treatment of diabetic macular edema in Korean patients. Graefes Arch Clin Exp Ophthalmol. 2016;254(9):1703–13. https://doi.org/10.1007/s00417-015-3262-1. Epub 2016 Jan 23. PMID: 26803489. No signif change VA or CFT.
39. Pelosini L, Hamilton R, Mohamed M, Hamilton AM, Marshall J. Retina rejuvenation therapy for diabetic macular edema: a pilot study. Retina. 2013;33(3):548–58. https://doi.org/10.1097/IAE.0b013e3182670fea. PMID: 23023529.
40. Prahs P, Walter A, Regler R, Theisen-Kunde D, Birngruber R, Brinkmann R, Framme C. Selective retina therapy (SRT) in patients with geographic atrophy due to age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2010;248(5):651–8. https://doi.org/10.1007/s00417-009-1208-1. Epub 2009 Dec 22. PMID: 20024687
41. Guymer RH, Wu Z, Hodgson LAB, Caruso E, Brassington KH, Tindill N, Aung KZ, McGuinness MB, Fletcher EL, Chen FK, Chakravarthy U, Arnold JJ, Heriot WJ, Durkin SR, Lek JJ, Harper CA, Wickremasinghe SS, Sandhu SS, Baglin EK, Sharangan P, Braat S, Luu CD; Laser Intervention in Early Stages of Age-Related Macular Degeneration Study Group. Subthreshold Nanosecond Laser Intervention in Age-Related Macular Degeneration: The LEAD Randomized Controlled Clinical Trial. Ophthalmology. 2019 Jun;126(6):829–38. https://doi.org/10.1016/j.ophtha.2018.09.015. Epub 2018 Sep 20. PMID: 30244144.
42. Wu Z, Luu CD, Hodgson LAB, Caruso E, Brassington KH, Tindill N, Aung KZ, Harper CA, Wickremasinghe SS, Sandhu SS, McGuinness MB, Chen FK, Chakravarthy U, Arnold JJ, Heriot WJ, Durkin SR, Wintergerst MWM, Gorgi Zadeh S, Schultz T, Finger RP, Cohn AC, Baglin EK, Sharangan P, Guymer RH; LEAD Study Group. Secondary and Exploratory Outcomes of the Subthreshold Nanosecond Laser Intervention Randomized Trial in Age-Related Macular Degeneration: A LEAD Study Report. Ophthalmol Retina. 2019 Dec;3(12):1026–1034. https://doi.org/10.1016/j.oret.2019.07.008. Epub 2019 Jul 22. PMID: 31582304.
43. Dorin G. Subthreshold and micropulse diode laser photocoagulation. Semin Ophthalmol. 2003;18(3):147–53. https://doi.org/10.1076/soph.18.3.147.29812. PMID: 15513476.
44. Frizziero L, Calciati A, Torresin T, Midena G, Parrozzani R, Pilotto E, Midena E. Diabetic Macular Edema Treated with 577-nm Subthreshold Micropulse Laser: A Real-Life, Long-Term Study. J Pers Med. 2021;11(5):405. https://doi.org/10.3390/jpm11050405. PMID: 34067994; PMCID: PMC8152245

45. Parodi MB, Spasse S, Iacono P, Di Stephano G, Canziani T, Ravalico G. Subthreshold grid laser treatment of macular edema secondary to branch retinal vein occlusion with micropulse infrared (810 nano meter) diode laser. Ophthalmology. 2006;113(12):2237e42.
46. Vujosevic S, Bottega E, Casciano M, Pilotto E, Convento E, Midena E. Microperimetry and fundus autofluorescence in diabetic macular edema: subthreshold micropulse diode laser versus modified early treatment diabetic retinopathy study laser photocoagulation. Retina. 2010;30(6):908–16. https://doi.org/10.1097/IAE.0b013e3181c96986. PMID: 20168272.
47. Vujosevic S, Martini F, Longhin E, Convento E, Cavarzeran F, Midena E. Subthreshold micropulse yellow laser versus subthreshold micropulse infrared laser in center-involving diabetic macular edema: morphologic and functional safety. Retina. 2015;35(8):1594–603. https://doi.org/10.1097/IAE.0000000000000521. PMID: 25719988.
48. Luttrull JK, Chang DB, Margolis BWL, Dorin G, Luttrull DK. Laser re-sensitization of medically unresponsive neovascular age-related macular degeneration: efficacy and implications. Retina. 2015;35(6):1184–94.
49. Luttrull JK. Low-intensity/high-density subthreshold diode micropulse laser (SDM) for central serous chorioretinopathy. Retina. 2016;36(9):1658–63.
50. Luttrull JK, Sinclair SH, Elmann S, Glaser BM. Low incidence of choroidal neovascularization following subthreshold diode micropulse laser (SDM) for high-risk AMD. PLoS ONE. 2018;13(8): e0202097. https://doi.org/10.1371/journal.pone.0202097.
51. Luttrull JK, Musch MC, Mainster MA. Subthreshold diode micropulse photocoagulation for the treatment of clinically significant diabetic macular edema. Br J Ophthalmol. 2005;89(1):74–80.
52. Luttrull JK, Spink CJ: Serial optical coherence tomography of subthreshold diode laser micropulse photocoagulation for diabetic macular edema. Ophthalmic Surg, Lasers Imaging. 2006;37:370–7.
53. Luttrull JK, Spink CJ, Musch DA. Subthreshold diode micropulse panretinal photocoagulation for proliferative diabetic retinopathy. Eye. 2008;22(5):607–12.
54. Luttrull JK. Subthreshold diode micropulse laser (SDM) for persistent macular thickening and limited visual acuity after epiretinal membrane peeling. Clin Ophthalmol. 2020;14:1177–88.
55. Luttrull JK, Sinclair SH, Elmann S, Chang DB, Kent D. Slowed progression of age-related geographic atrophy following subthreshold laser. Clin Ophthalmol. 2020;14:2983–2993.
56. Luttrull JK, Gray G. Prevention of neovascular AMD: Real world efficacy of program of panmacular laser for vision protection. Researchgate.net (2021). https://www.researchgate.net/publication/349952308_Prevention_of_neovascular_AMD_Real_world_efficacy_of_program_of_panmacular_laser_for_vision_protection.
57. Jorge EC, Jorge EN, Botelho M, Farat JG, Virgili G, El Dib R. Monotherapy laser photocoagulation for diabetic macular oedema. Cochrane Database Syst Rev. 2018;10(10):CD010859. https://doi.org/10.1002/14651858.CD010859.pub2.
58. Gawęcki M, Jaszczuk-Maciejewska A, Jurska-Jaśko A, Grzybowski A. Functional and morphological outcome in patients with chronic central serous chorioretinopathy treated by subthreshold micropulse laser. Graefes Arch Clin Exp Ophthalmol. 2017;255(12):2299–306.
59. Gawęcki M, Jaszczuk-Maciejewska A, Jusrka-Jaśko A, Kneba M, Grzybowski A. Transfoveal micropulse laser treatment of central serous chorioretinopathy within six months of disease onset. J Clin Med. 2019. https://doi.org/10.3390/jcm8091398.
60. Malik KJ, Sampat KM, Mansouri A, Mansouri A, Steiner JN, Glaser BM. Low-intensity/high density subthreshold micropulse diode laser for chronic central serous chorioretinopathy. Retina. 2015;35:532–6.
61. Brader HS, Young LH. Subthreshold diode micropulse laser: a review. Semin Ophthalmol. 2016;31(1–2):30–9. https://doi.org/10.3109/08820538.2015.1114837. PMID: 26959127.
62. Scholz P, Altay L, Fauser S. A review of subthreshold micropulse laser for treatment of macular disorders. Adv Ther. 2017 Jul;34(7):1528–55. https://doi.org/10.1007/s12325-017-0559-y. Epub 2017 May 24. PMID: 28540655; PMCID: PMC5504253.

63. Sivaprasad S, Dorin G. Subthreshold diode laser micropulse photocoagulation for the treatment of diabetic macular edema. Expert Rev Med Devices. 2012;9(2):189–97. https://doi.org/10.1586/erd.12.1. PMID: 22404779.
64. Chen G, Tzekov R, Li W, Jiang F, Mao S, Tong Y. Subthreshold micropulse diode laser versus conventional laser photocoagulation for diabetic macular edema: a meta-analysis of randomized controlled trials. Retina. 2016;36(11):2059–65. https://doi.org/10.1097/IAE.0000000000001053. PMID: 27096529.
65. Frizziero L, Calciati A, Torresin T, Midena G, Parrozzani R, Pilotto E, Midena E. Diabetic macular edema treated with 577-nm subthreshold micropulse laser: a real-life, long-term study. J Pers Med. 2021;11(5):405. https://doi.org/10.3390/jpm11050405.PMID:34067994;PMCID:PMC8152245.
66. Mainster MA. Decreasing retinal photocoagulation damage: principles and techniques. Semin Ophthalmol. 1999; 14:200e9.
67. Akduman L, Olk RJ. Subthreshold (invisible) modified grid diode laser photocoagulation in diffuse diabetic macular edema (DDME). Ophthalmic Surg Lasers. 1999;30(9):706–14. PMID: 10574491.
68. Edelstein L. The Hippocratic oath: text, translation and interpretation. 1943. p. 56. ISBN 978-0-8018-0184-6.
69. Varkey B. Principles of clinical ethics and their application to practice. Med Princ Pract. 2021;30:17–28. https://doi.org/10.1159/000509119.
70. Glassman AR, Wells JA 3RD, Josic K, Maguire MG, Antoszyk AN, Baker C, Beaulieu WT, Elman MJ, Jampol LM, Sun JK, for the diabetic retinopathy clinical research network. Five-year outcomes after initial aflibercept, bevacizumab, or ranibizumab treatment for diabetic macular edema (protocol t extension study). Ophthalmol. 2020;127(9):1201–10.
71. Luttrull JK. Laser is the first-choice treatment for diabetic retinopathy. Amsterdam Retina Debate. Annual meeting of the European Society of Retina Specialists (Euretina) 2017; Sept 8, Barcelona, Spain.
72. Kozak I, Luttrull JK. Modern retinal laser therapy. Saudi J Ophthalmol 2015;29(2):137–46.
73. Dennett D. Darwin's dangerous idea and the meanings of life. New York, New York; Simon and Shuster; 1995. ISBN 978-0-684-80290-9.
74. Halawa OA, Lin JB, Miller JW, Vavvas DG. A review of completed and ongoing complement inhibitor trials for geographic atrophy secondary to age-related macular degeneration. J Clin Med. 2021;10(12):2580. https://doi.org/10.3390/jcm10122580.
75. Hall J, Matos S, Gold S, Severino LS. The paradox of sustainable innovation: The 'Eroom' effect (Moore's law backwards). J Clean Prod. 2018;172:3487–97. https://doi.org/10.1016/j.jclepro.2017.07.162.ISSN0959-6526.
76. Lin A, Giuliano CJ, Palladino A, John KM, Abramowicz C, Yuan ML, Sausville EL, Lukow DA, Chait AR, Galluzzo ZC, Tucker C, Sheltzer JM. Off-target toxicity is a common mechanism of cancer drugs undergoing clinical trials. Sci Transl Med. 2019;11(509):eaaw8412. https://doi.org/10.1126/scitranslmed.aaw8412.
77. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2017;(2). Art. No.: MR000033. https://doi.org/10.1002/14651858.MR000033.pub3.
78. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. Cochrane Database Syst Rev. 2014;(4). Art. No.: MR000034. https://doi.org/10.1002/14651858.MR000034.pub2.
79. Dal Bó E. Regulatory capture: a review. Oxf Rev Econ Policy. 2006;22(2):203–25. https://doi.org/10.1093/oxrep/grj013.
80. Chhablani J, Luttrull JK. Retina debate: Is navigated laser the answer for DME? Retinal Physician. 2020:22–5.