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DIABETIC RETINOPATHY: MEDICAL AND SURGICAL THERAPIES (PK KAISER, SECTION EDITOR)

New Laser Technologies for Diabetic Retinopathy

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Abstract Diabetic retinopathy is a leading cause of severe visual impairment for adults worldwide. Vision loss from systemic diabetes usually occurs secondary to macular edema or from de novo proliferation from the retinal vasculature. The Diabetic Retinopathy Study (DRS) established that panretinal photocoagulation (PRP) reduces the risk of severe vision loss from proliferative disease by >50 % and, thus, PRP has become the gold standard in the treatment of proliferative disease. The Early Treatment of DRS expanded the use of laser photocoagulation to clinically significant macular edema. Advances in laser technology have led to the development of semi-automated lasers, including pattern scanning laser (PASCAL®, Topcon) and fully automated lasers, such as the navigating lasers (NAVILAS®, OD/OS), that aim to deliver faster, safer, more accurate, and less painful treatment of diabetic eye disease and other retinal conditions. Sublethal phototherapy with subthreshold diode micropulsed laser treatment for macular edema has led to a paradigm shift in our understanding of retinal photocoagulation by demonstrating similar efficacy with less collateral damage. Here, we review the current data on laser treatment of diabetic retinopathy with an emphasis on understanding the new laser photocoagulation technologies for treatment of proliferative diabetic retinopathy and clinically significant diabetic macular edema.

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Introduction

Diabetic retinopathy is a microvascular complication of systemic diabetes and is a leading cause of vision loss in adults worldwide [1, 2]. Screening and treatment of diabetic eye disease is the most common reason for vitreoretinal specialist referral [3]. The prevalence of retinopathy among diabetics in the USA was 28.5 % in 2008 [1]. The American Diabetes Association [4] recommends annual ophthalmic examinations with more frequent follow-up of high-risk patients. Management of diabetic retinopathy aims to prevent progression and treat established disease.

Prevention of vision loss is the most important step in management of patients with systemic diabetes and is accomplished through optimizing treatment of systemic conditions, addressing modifiable risk factors, and regular ophthalmic screening [5]. Studies have found poor glycemic control to be a risk factor for severe diabetic retinopathy and, thus, access to diabetes dietary counseling and regular medical care is critical [6, 7]. Systemic conditions such as hypertension, dyslipidemia, nephropathy, pregnancy, and anemia are also risk factors for vision loss [7–10]. Ensuring patients are regularly followed by primary care physicians, have access to resources for optimal management of their medical conditions, and are counseled on modifiable risk factors such as smoking, can significantly reduce the progression and severity of diabetic eye disease [11–15].

Despite prevention efforts, patients often progress to more severe forms of diabetic retinopathy warranting

intervention including clinically significant macular edema (CSME) and proliferative diabetic retinopathy (PDR). Two landmark trials established the vision-saving potential of laser photocoagulation for patients with advanced diabetic retinopathy: (1) The Diabetic Retinopathy Study (DRS) [16, 17], in which panretinal photocoagulation (PRP) demonstrated significant vision-saving potential for high risk PDR, and (2) Early Treatment of DRS (ETDRS), in which focal/grid laser photocoagulation showed significant vision benefit in patients with CSME [18••]. These trials and subsequent studies established laser photocoagulation as one of the most efficacious first-line treatment for PDR and CSME. Recently, pharmacologic therapy with vascular endothelial growth factor (VEGF) inhibitors has demonstrated even greater vision benefit for CSME and will likely supplant macular laser photocoagulation as a front-line therapy.

Advances in laser technology have led to the development of semi-automated lasers, including pattern scanning laser (PASCAL®, Topcon) and navigating lasers (NAVILAS®, OD/OS), that aim to refine the delivery of laser photocoagulation in a faster, safer, more accurate, and less painful way while minimizing adverse side effects. Sublethal phototherapy with subthreshold diode micropulsed (SDM) laser treatment for macular edema has led to a paradigm shift in our understanding of retinal photocoagulation by demonstrating similar efficacy with less collateral damage. Here, we will briefly discuss the treatment of diabetic retinopathy, and the traditional laser delivery models for PDR and CSME, and then review the newest automated lasers, including PASCAL® and NAVILAS®, and SDM laser therapy. The purpose of this review is to update ophthalmologists on the newest laser therapies for treatment of diabetic retinopathy.

Treatment of Diabetic Retinopathy

Diabetic retinopathy usually manifests after years of systemic diabetes, but histological studies of the retina and its support cells reveal that microscopic changes are present well before clinical detection is possible [19–21]. Regular vigilant screening and evaluation of changes over time are the foundation of diabetic eye care. The first sign of any diabetic retinopathy is usually microaneurysms. Table 1 describes a simplified diabetic retinopathy classification scheme used in this review that is adapted from the ETDRS and the Wisconsin Epidemiological Study of Diabetic Retinopathy [6, 22, 23]. This is similar to the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Severity Scales published by the Global Diabetic Retinopathy Project Group [24]. In general, diabetic retinopathy is classified as non-PDR (NPDR) or PDR, both of

Table 1 Classification of diabetic retinopathy

Classifications	Definitions
Non-proliferative diabetic retinopathy	
Mild	At least one microaneurysm
	AND
	Did not meet more severe criteria
Moderate	Microaneurysms/hemorrhage greater than standard image 2A[a]
	OR
	Cotton wool spots, intraretinal microvascular abnormalities (IRMA), venous beading
Severe (*high-risk*)	Microaneurysms and/or hemorrhage greater than standard image 2A[a] in all four quadrants
	OR
	IRMA greater than standard photograph 8A[a]
	OR
	Venous beading in more than two quadrants
Very severe (*high-risk*)	Two or more of the severe criteria
Clinically significant macular edema	Thickening of retina <500 μm from macula center
	OR
	Hard exudates and thickened retina <500 μm from center of macula
	OR
	Zone or retinal thickening at least one disk area in size less than one disk away from macula center
Proliferative diabetic retinopathy	
Early	Presence of new vessels
	AND
	Did not meet high-risk or severe criteria
High-risk	New vessels on or within one disc diameter of the optic disc (>standard photograph 10A[a])
	OR
	Vitreous or preretinal hemorrhage with new vessels
Severe	Hemorrhage obscuring posterior pole
	OR
	Macular detachment

A variety of severity and classification schema for diabetic retinopathy have been proposed. For the purpose of this review, the above classification scheme represents a simple severity scale for evaluating new laser technology and other treatments for diabetic eye disease at varying levels of severity adapted from the ETDRS and the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) [6, 22, 23]. These are similar to the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Severity Scales published by the Global Diabetic Retinopathy Project Group [24]. It is important to note that studies use different precise definitions for classifying diabetic retinopathy, and any interpretations made from their conclusions should be applied only to the disease severity as defined by the study

[a] Standard images refer to the references fundus photos in the Early Treatment of Diabetic Retinopathy Study (ETDRS) [18••, 84, 85]

which can also have CSME that alters the recommended treatment. This review will not focus on the presentation, evaluation, classification, or diagnosis of different stages of diabetic eye disease, but will instead briefly summarize the current recommendations for treatment to set the stage for understanding the applications of new laser technologies.

Non-proliferative Diabetic Retinopathy

Vision loss from diabetic retinopathy is primarily via development of CSME or progression to proliferative disease. Mild and moderate NPDR without CSME should be carefully observed with regular follow-up, but no therapy is currently recommended. The ETDRS demonstrated vision benefit of early PRP for patients with severe and very severe NPDR without CSME [18••, 25]. The ETDRS also showed that eyes with CSME involving or threatening the center of vision are at high-risk of vision loss [26••]. Treatment of CMSE is a rapidly evolving field in ophthalmology with an ever-expanding role of intravitreal VEGF-inhibitors (ranibizumab, Genentech/bevacizumab, Genentech/aflibercept, Regeneron) in the context of known long-term benefits of focal laser photocoagulation. We will not discuss these interesting developments here, but simply summarize the current state of knowledge on the treatment of CSME with NPDR.

Prophylactic laser treatment of macular edema that is not clinically significant is generally not recommended. When CSME does develop, the physician can administer intravitreal injections of VEGF-inhibitors, perform focal/grid laser photocoagulation, or both [27–29, 30•, 31–34]. Intravitreal corticosteroids and vitreous surgery are alternative therapies when the two first-line treatments fail. In the ETDRS, when focal laser photocoagulation was performed on eyes with CSME, the risk of moderate visual loss was decreased by 50 % and many clinicians continue to treat in this manner [26••]. Recently, intravitreal 0.3 mg ranibizumab (Lucentis, Genentech) was approved for the treatment of diabetic macular edema and trials have demonstrated short-term superior efficacy to focal/grid laser photocoagulation alone. The most effective treatment to date for CSME has been ranibizumab injections plus deferred focal laser therapy with a mean +2.9 more letters gained when compared to injection with prompt focal/laser therapy at 3-year follow-up [35••]. Intravitreal corticosteroids have also demonstrated short-term benefit, but come with the added risks of exacerbating glaucoma and cataracts. In the presence of vitreomacular traction or failure of first-line treatments, vitreous surgery can be considered.

Proliferative Diabetic Retinopathy

The metabolic derangements in glucose are not well tolerated in the delicate retinal architecture and can cause reduced perfusion and local retinal ischemia. In response, angiogenic factors such as VEGF are released to increase the blood supply to the ischemic retina, but the chaotic growth of these new vessels does more harm than good; the de novo vessels directly impede vision, undergo fibrosis with membrane formation, and ultimately create traction of the posterior vitreous leading to hemorrhage and/or traction retinal detachment. PDR is an advanced stage of diabetic eye disease that can rapidly result in severe, irreversible vision loss [36]. Risk factors for PDR include duration of diabetes (25 % with type I disease and 16 % with type II progress to PDR at 15 years), poor glycemic control, and type I diabetes [6, 37, 38].

The DRS showed that prompt PRP reduces vision loss in patients with high-risk PDR [39]. In cases where PDR is inadequately treated with PRP, then vitrectomy followed by laser ablation is recommended. Both the DRS and ETDRS showed that full scatter photocoagulation could exacerbate macular edema leading to moderate visual loss when done immediately [18••, 39]. When PRP is planned in eyes with CSME, then focal photocoagulation should be performed first followed with delayed PRP.

Manual Lasers for Diabetic Retinopathy

LASER is an acronym for light amplification by stimulated emission of radiation. The ability to use light from various sources, originally the sun, to photocoagulate the retina has been known for centuries. Over the last few decades, ophthalmologists have embraced the precision, speed, and ease of laser technology for the treatment of many disorders including diabetic retinopathy. By refining the spectrum of light, selecting specific wavelengths, varying pulse duration and, recently, adding automated components, a myriad of laser technologies are available to the practicing clinician.

Originally, the ETDRS involved argon laser applied directly to microaneurysms and areas of retinal thickening. Other historical lasers include the ruby (694 nm), argon (488,514 nm), and krypton (647 nm) lasers. These older lasers were effective for reducing vision loss, but came with many undesirable consequences such as pain, large areas of "thermal blooming", i.e. collateral photocoagulation of nearby tissues through heat diffusion in horizontal and vertical directions [40], and fibrosis of the disrupted retinal pigmented epithelium or other serious complications in rare cases [41]. Over time, laser technology has been refined to apply smaller, less intense, and less frequent burns. The most common lasers used today are the frequency-doubled Nd:YAG (532 nm, green light) and the yellow semiconductor laser (577 nm).

Focal/Grid Photocoagulation for Clinical Significant Macular Edema

The Diabetic Retinopathy Clinical Research network (DRCR.net) [42] have summarized general guidelines for manual focal/grid laser administration. They recommend the direct treatment of all leaking microaneurysms in areas of retina thickening with a targeted 50-μm direct spot treatment for 0.05–0.10 s. Microaneurysm color change is not required, but a slight change with a gray-white burn may facilitate confirmation of accurate administration. For grid treatment, the physician should target all areas with edema that are not associated with microaneurysm with the same range as focal for superior, nasal, and interior quadrants of the macula and a slightly enlarged potential parameter in the temporal region (500–3,500 μm). The target burn size and duration are the same as for focal, with ideally a light gray visible burn scar, separated from the other scar by two burn widths. The DRCR.net protocol is used for any yellow or green laser with lenses that increase or decrease the burn size by less than 10 % [42].

Panretinal Photocoagulation

PRP is the indicated for high-risk PDR, rubeosis with or without neovascular glaucoma, PDR not involving the disc with capillary non-perfusion, and widespread retinal ischemia. The DRS and other studies have found PRP to reduce the cumulative risk of severe vision loss by more than 50 % at 6 years [16, 17, 43, 44]. Regression of neovascularization occurs in 30–55 % of eyes after PRP [16, 39]. Typical treatment includes 600–1,600 burns on the retina, 500 μm in size, in a confluent grid pattern for neovascularization not involving the optic disc.

Complications and adverse side effects can be significant drawbacks to PRP because they occur with relatively high frequency. Most patients suffer from some impairment of dark adaptation, visual field loss, and pain. Pain during laser treatment is highly variable and depends on characteristics of both the laser and the patient. Importantly, adherence to recommended PRP schedules depends on the patients' willingness to return. Often times, patients will require retrobulbar or peribulbar anesthesia to complete treatment. Other less common, but more serious, reported complications of PRP include corneal abrasions, mydriasis due to damage of nerves, macular edema, choroidal detachment or hemorrhage, exudative retinal detachment, subretinal neovascularization, vitreous hemorrhage from regression of neovascular tissue, lens opacities, and vascular occlusions.

New Laser Technologies for Diabetic Retinopathy

Following Moore's law, the introduction of lasers to ophthalmology resulted in a proliferation of increasingly sophisticated delivery systems. The newest lasers on the block are those using automated delivery technologies to increase accuracy of retinal ablation, decrease pain by optimizing pulse intensity and duration, and reducing the number of treatment sessions required. These include the pattern scanning photocoagulator (PASCAL®) and navigated laser (NAVILAS®). Sublethal retinal phototherapy with the SDM laser for diabetic macular edema has challenged the underlying paradigm of retinal laser photocoagulation treatment by demonstrating that retinal damage is not necessary for the treatment of macular edema and other retinovascular disorders. Here, we will review the current literature on these new laser therapies.

PAttern-SCAnning Laser (PASCAL®)

In 2005, the first semi-automated laser therapy for retinal diseases was introduced—the PASCAL® pattern-scanning photocoagulator (OptiMedica; Topcon Medical Laser Systems, Santa Clara, CA, USA) [45••]. PASCAL® can rapidly deliver various patterns of 532-nm laser pulses (56 spots in 0.6 s) with the depression of a foot pedal that can be controlled by the physician (Fig. 1). The laser settings are manipulated with a touch screen graphic user interface that allows flexibility based on clinical judgment and conditions being treated (Fig. 1a). Predetermined photocoagulation patterns include arcs with concentric rows, circles for small holes, square arrays for PDR, and standard single-spot photocoagulation (Fig. 1b).

PASCAL® aims to address the shortcomings of manual laser therapy: pain, thermal blooming from heat diffusion, inadvertent photocoagulation of adjacent tissues, the inconvenience of multiple sessions, and the time required to perform treatment. The indications for retinal photocoagulation with PASCAL® are the same as those for traditional slit-lamp photocoagulation. The laser delivers the entire treatment in one sitting by using shorter exposure duration than conventional photocoagulation (10–20 vs. 100–200 ms). The shorter exposure duration is the primary driver of the benefits of PASCAL® because it reduces heat diffusion in the retina resulting in limited thermal blooming and, thus, the patient experiences less pain [46, 47]. Studies report that patients prefer single session PRP with to traditional multi-session single-spot argon laser treatments and that PASCAL® laser produces less anxiety, fewer headaches, and is well tolerated with topical anesthesia alone [48–50].

The Manchester Pascal Study randomized 40 eyes with PDR and compared conventional single-spot multi-session

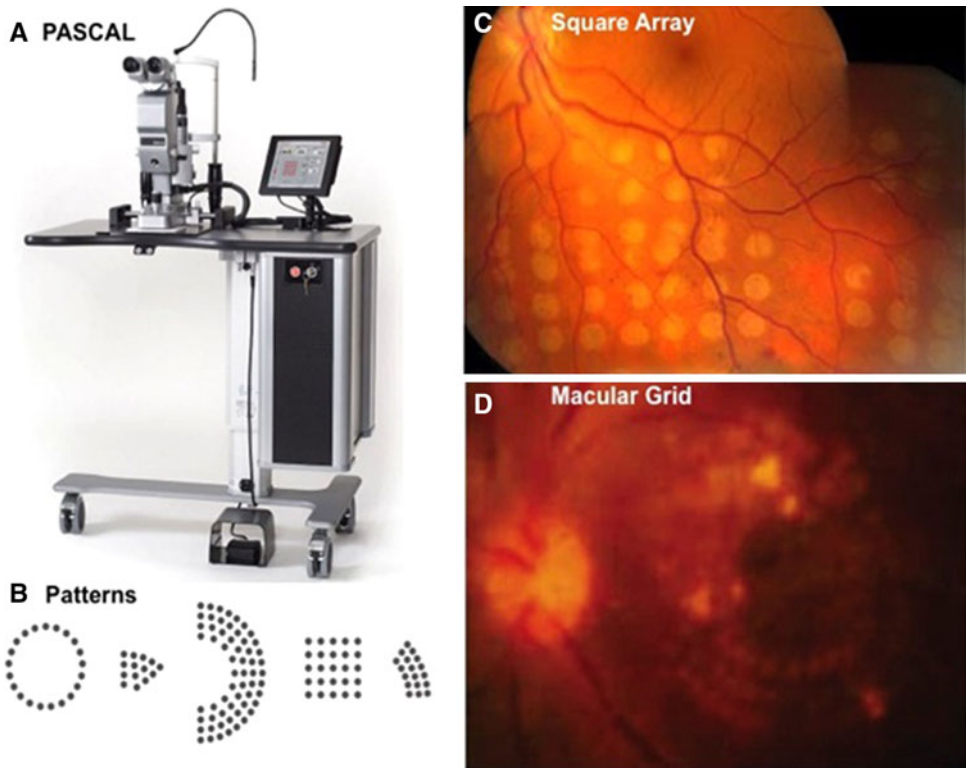

Fig. 1 Pattern-scanning laser PASCAL®. **a** The slim line PASCAL® photocoagulator set-up demonstrating the slit-lamp-based pattern scanning laser system with touchscreen graphic user interface. Depression of the foot pedal delivers laser therapy that can be halted with release of the pedal. **b** The laser comes with predetermined patterns that can be adjusted by the user and include the circular, arc, modified grid, square array, and triple arc in addition to the conventional single spot. **c** Panretinal photocoagulation (PRP) for proliferative diabetic retinopathy with a 3 × 3 *square array* that can also be set to 2 × 2, 4 × 4, and 5 × 5. **d** Comparing conventional with pattern laser treatment with a macular grid for clinically significant diabetic macular edema. The extrafoveal burns on the superonasal hemisphere are conventional single spot treatment while the burns on the lower, inferotemporal extrafoveal region were performed with PASCAL®. All photos were reproduced with permission from the makers of the pattern-scanning photocoagulator: Topcon Medical Laser Systems (Santa Clara, CA, USA)

PRP to single-session PASCAL® treatment. The main outcomes were OCT measures, visual acuity, regression of neovascularization, and quality measures. The study found PASCAL® is safe, has similar or reduced rates of adverse events, decreases the total macular thickness at 4 weeks, results in equivalent visual acuity and regression of neovascularization when compared with argon laser, and that it significantly reduces patient pain resulting in increased patient satisfaction [49, 51, 52, 53•]. Other studies have corroborated these findings when treating PDR and have also published similar safety and outcome results when PASCAL® was used in treating high-risk NPDR and diabetic macular edema [46, 54–57]. Other groups have also reported equivalent patient vision and outcomes for diabetic retinopathy treatment when compared with argon laser with most studies reporting fewer adverse events [46–54, 57–60]. Taken together, these results suggest that PASCAL® offers an optimized alternative to traditional manual laser therapy for the treatment of diabetic retinopathy as well as other retinal disorders. Data from properly powered longitudinal studies will be necessary to understand the efficacy and effectiveness of this new technology for retinal therapy in the long run.

NAVIgated LASer (NAVILAS®)

In 2009, the first retinal navigation device was approved by the FDA for the treatment of retinal disorders—the NAVILAS® laser system (OD–OS Retina Navigation, Germany). The technology incorporates wide-field fundus viewing and eye tracking and integrates multiple imaging modalities, such as OCT and fluorescein angiogram (FA), to improve the ease and accuracy of retinal photocoagulation. NAVILAS® can be used for a variety of retinal disorders with three primary settings: focal, multimodal, and PRP, with an automated 532-nm laser of variable intensity, fluence, and duration.

The NAVILAS® laser system was developed to improve the accuracy of laser photocoagulation delivery. By combining a diagnostic camera system with the therapeutic

laser, the physician is able to image, plan, and treat a patient with one device. The device offers four real-time retinal imaging modalities: (1) true-color mydriatic FA, (2) non-mydriatic FA, (3) infrared, and (4) red-free. With these features, the physician can image, plan, and treat in one rapidly adapting platform. As the patient fixates, the images can be used to create a treatment plan with highlighted markers of target areas overlying real-time images to assist and document precise delivery of photocoagulation. The eye tracking software ensures that automated photocoagulation only proceeds when the patients' eye is in position, with an automatic disarm when the eye loses fixation. Thus, the physician can rapidly and accurately delivery laser treatment with automated patterns, but the device has safeguards to prevent inadvertent photocoagulation. The pulse duration can be manipulated from 10 to over 100 ms based on physician preferences and indication. During the process, the physician can also record the treatment for documentation and teaching.

Published studies using NAVILAS® are limited likely due to the relatively recent release. The two largest studies with NAVILAS® were performed by Kozak et al. [61, 62•], in which series of patients with diabetic retinopathy and diabetic macular edema underwent NAVILAS® therapy. They concluded that NAVILAS® was safe and had better accuracy of retinal photocoagulation when compared with a retrospective review of argon laser therapy. Patients treated had significant improvements in visual acuity and significantly decreased OCT measures of thickness, and reported less pain when compared with traditional argon PRP [61, 62•]. Two other pilot studies have found similar results in terms of safety, outcomes in diabetic macular edema, and reduction of pain [63, 64]. There are no published studies evaluating navigated laser photocoagulation in the long run, and there are no head-to-head trials of the two automated lasers.

SMD Laser

Over the last four decades, CSME has been managed with focal/grid photocoagulation based on demonstrated vision benefits in the ETDRS [26••]. Like other lasers for the retina, the long-held paradigm in administration of focal photocoagulation has been that iatrogenic retinal damage is necessary and acceptable given the significant visual acuity benefits in CSME. Over time, the lasers have become less intense, more accurate, and more precise in their ablation to the extent that the original notion of necessary retinal damage was questioned with the first near-infrared 810-nm diode laser that was micropulsed, rather than administered continuously, for treatment of CSME [65, 66•]. This new technology uses a longer wavelength (lower energy) and is administered in micropulses that reduces the thermal damage on the retinal to nearly undetectable levels. The introduction of this technology with early reports of equivalent efficacy gave rise to the concept of invisible retinal phototherapy.

Initial case intervention studies comparing SDM laser to traditional focal argon laser in the ETDRS demonstrated promising results—reporting similar efficacy and effectiveness for treatment of macular edema using invisible, or sublethal, retinal phototherapy [65, 67–71]. Since its introduction in the mid-1990s, four clinical trials have compared SDM laser to traditional argon laser for CSME, with outcome measures including the final best corrected visual acuity, relevant OCT measures including retinal thickness, safety, and multifocal electroretinography (mfERG) recordings, to assess remaining retinal functionality after treatment [68, 72•, 73, 74]. These studies have all reported that SDM is equally efficacious for the treatment of diabetic macular edema when compared to traditional Nd:YAG laser [70, 71]. Venkatesh et al. [74] assessed differences in final retinal function with mfERG and found that SDM results in significantly increased remaining retinal function, and these results have been replicated in other studies [75] SDM has also demonstrated good long-term safety profiles [76]. Reviews of this SDM technology for retinal phototherapy have found it to be a clinically effective and nearly harmless treatment for diabetic macular edema as well as other disorders [77, 78].

The discovery that macular edema and proliferative retinopathy can be treated without concomitant retinal damage has fundamentally changed our understanding of retinal disease. The exact mechanism of sublethal therapy for retinal photocoagulation remains to be unraveled, but offers a new arena of investigation for treatment of diabetic eye disease and other retinal disorders that could improve patient outcomes and further reduce adverse effects. In patients with CSME, SDM laser photocoagulation offers similar treatment efficacy with regard to final visual acuity outcomes with minimal retinal damage. Further, because of the invisible retinal phototherapy and ability to repeat the treatment, the SDM laser is particularly appealing for treatment near the fovea. However, the invisible phototherapy also makes monitoring of serial treatments difficult due to lack of reliable dosimetry making the treatment difficult to standardize across centers. Ohkoshi et al. [79] recently reported that scanning laser ophthalmoscopy in retro-mode could be used to detect sites of SDM application for treatment tracking. This may offer some relief to the issue of tracking treatments, but needs more research supporting its use as a monitoring modality. The primary limitation of wide SDM adoption is the emergence of primary pharmacologic therapy with intravitreal injections that may entirely replace focal laser therapy as first-line treatment for CSME.

Conclusions

One in ten Americans has systemic diabetes, and the Center for Disease Control and Prevention predicts that over the coming decades the number will rapidly increase to between one in five and one in three by 2050, based on current trends [80, 81]. This reflects shortcomings in the diagnosis, follow-up, screening, and limitations in current treatment of systemic diabetes. Although the metabolic derangement has direct effects on the neurons and support cells of the retina, the retinal vascular changes dominate the clinical manifestations of the ocular disease and are directly implicated in macular edema and neovascularization that represent the principal causes of vision loss. The ocular complications arising from PDR remain a leading cause of severe, irreversible visual impairment in developing countries [82]. Properly controlling a patients' glucose, blood pressure, and lipids is critical for not only preventing development of retinopathy but also maximizing the efficacy of treatment [83].

Over the past 50 years, we have made leaps and bounds in the treatment of diabetic eye disease. Advances in automated laser technology systems have resulted in faster, safer, more accurate, and less painful treatment when compared to manual single-spot lasers. SDM laser therapy now has multiple level one studies supporting the efficacy of sublethal therapy for the treatment of macular edema and has altered our fundamental understanding of retinal photocoagulation. Advances in pharmacologic therapy using anti-VEGF agents have yielded unprecedented vision outcomes for diabetic macular edema. These new pharmacologic therapies have revolutionized the field of ophthalmology and offer significant reductions in vision loss when compared to laser alone, but the long-term outcome with these treatments is still being unraveled. Further, intravitreal injections are an unpleasant experience for patients and are often anxiety-provoking—how will the long-term delivery of VEGF antagonists develop and how will these be incorporated with the established efficacy of laser treatments? The research does not keep up with the innovation in either of these fields, and we are left to contemplate what the optimal treatment strategy for an individual patient sitting in the examination room will be with an arsenal of new treatments, but limited data, on their use.

The establishment of standard treatment algorithms incorporating these evolving pharmacologic and laser technologies is difficult but necessary to determine an evidence-based integration of treatments, including the dose (for injections), schedule, and frequency. Overall, the rapid evolution of therapy for diabetic retinopathy offers hope to the millions suffering from vision loss. The new lasers discussed in this review will likely be adopted as the new standard because of their many benefits, and two of them are already widely used in the USA, including our home clinic at Stanford. Long-term, well-designed, longitudinal trial data are needed to answer the many questions about the newest laser therapies before we can give a final verdict on for their use in the treatment of diabetic retinopathy.

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- • Of importance
- •• Of major importance

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