SUPPLEMENT TO
NOVEMBER 2009
REVIEW OF OPTOMETRY
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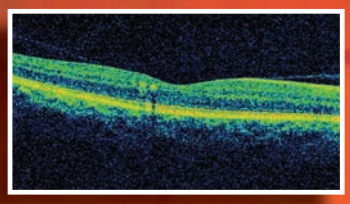

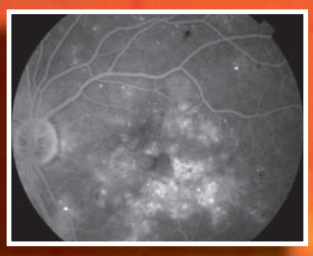

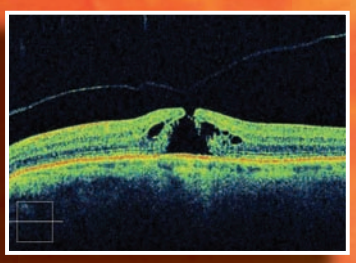

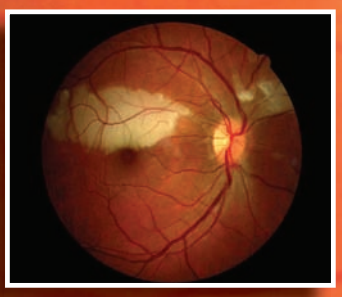

The Sixth Annual Guide to

RETINAL DISEASE

PEER • REVIEWED • PRA • ARTICLE

Take on AMD by Preparing Your Practice and Your Patients

By Sheryl Blankenship, O.D.

THE PSYCHOLOGICAL EFFECTS OF VISION LOSS can be devastating and life altering. Severe vision loss not only affects the patient, but his or her family and caretakers.

Age-related macular degeneration is one of the leading causes of blindness in patients 65 years of age and older. If AMD is not detected in its early stages, the effects are often irreversible. Patients with AMD have a much harder time performing everyday activities, such as shopping, housework, making phone calls and cooking, than their peers without vision impairment.[1]

As optometrists, we have both the power and the responsibility to help our patients prevent and manage AMD. There is no cure for dry AMD, so it can often seem like a tedious waiting game to determine if a patient will develop choroidal neovascularization (CNV), indicating a conversion to wet AMD. During this period, continuous monitoring provides you the best chance to document conversion and implement treatment in a timely fashion.

Until recently, however, many testing options, such as Amsler grid, mainly relied on at-home patient monitoring. Clearly, at-home monitoring raises issues of compliance and performance accuracy. To preserve our patients' sight, we must educate them on the risk factors for AMD as well as provide them with the most up-to-date monitoring and treatment options for this debilitating condition.

Help Patients Help Themselves

Effective communication with your patient is one of the most important factors to consider in the management of any condition. With regard to AMD, patient communication can be beneficial well before a diagnosis is confirmed. The identification of risk factors is an integral part of this process.

While some risk factors for AMD, such as age, race, gender or family history, cannot be controlled, others, such as smoking and obesity, can be eliminated. It can be helpful to discuss the visual consequences of AMD early on even if your patients have several risk factors that they cannot control. If, however, your patients demonstrate several modifiable risk factors for AMD, education on preventative health measures is absolutely critical. Common preventative measures for AMD include:[2]

- Taking AREDS-approved supplements to boost the body's defense against AMD.
- Eating a diet rich in leafy greens and fish.
- Maintaining a healthy weight.
- Maintaining normal blood pressure.
- Not smoking.
- Exercising regularly.
- Wearing sunglasses to protect against ultraviolet light.

Nutritional Supplements

Proper nutrition and dietary supplementation can help your patients prevent and limit the progression of AMD. Data from the Age-Related Eye Disease Study suggested that participants with intermediate or advanced AMD in one eye reduced their chances of disease progression by approximately 25% with a daily high-dose supplement of vitamin C, vitamin E, beta-carotene and zinc.[3] More importantly, participants who took a daily supplement reduced their risk of vision loss by approximately 19%. These data underscore the vital role that good nutrition can play in preserving vision.

Research shows that more than half of the elderly population currently uses one or more dietary supplements.[4] So, the addition of an AREDS-recommended supplement often is a simple step for many patients. There are many options available, including PreserVision Eye Vitamins (Bausch & Lomb), Ocuvite Eye Vitamin and Mineral Supplements (Bausch & Lomb) and I-Caps Eye Vitamins (Alcon).

AREDS 2 researchers currently are examining the effects of lutein and zeaxanthin on AMD development and progression. Both lutein and zeaxanthin are components of macular pigment and might offer protection against AMD.[5] Because macular pigment is provided to the body exclusively through dietary intake, it is especially important that patients make every effort to consume these essential nutrients. One study found that even diseased maculae can accumulate lutein and zeaxanthin, suggesting that it is never too late for patients to incorporate these substances––either by consuming more spinach and broccoli or by taking a supplement.[6]

Be sure to thoroughly examine your patients' medical histories and be aware of any additional medications and/or supplements that they may be taking. Advise your patients that certain supplements can cause adverse reactions when taken in conjunction with various medications.[7]

Amsler Grid Monitoring

Unfortunately, preventative measures cannot guarantee that your patients will not develop AMD. Even patients who strictly follow preventative protocols may present with dry AMD. And when this happens, monitoring for conversion to wet AMD is the next step in preserving their sight.

Currently, nearly eight million Americans have early AMD. During the next five years, 1.3 million of those individuals will progress to wet AMD.[3] When you diagnose patients with dry AMD, expedient implementation of a monitoring program is your best chance of identifying CNV at its earliest appearance.

The Amsler grid is often used for monitoring AMD patients because it is cost effective and can be performed almost anywhere. However, relying solely upon the Amsler grid for CNV detection is not enough to ensure that your patients' sight will be saved.

For example, the Amsler grid has low sensitivity and cannot always compensate for the brain's inherent ability to correct for visual impairment.[8] The brain "knows" what the Amsler grid should look like and may complete any missing information the affected eye did not capture, yielding a false negative result. So, the brain's natural correction ability can actually mask early stages of vision loss. In fact, significant vision loss often occurs well before changes are seen on Amsler grid.

Use Technology to Save Vision

Instructing dry AMD patients to monitor their sight at home helps increase the chances of saving their vision. But, your expectations for reliable self-testing results must be realistic. Because of the limitations of the Amsler grid (which demonstrates just 29% sensitivity), you must take it upon yourself to provide the most effective in-office testing available.[9]

• *Foresee PHP.* At our practice, we use preferential hyperacuity perimitry (Foresee PHP, Sightpath Medical/Reichert) to monitor AMD development and progression. Foresee PHP employs the visual phenomenon of hyperacuity—the patient's ability to detect small differences in the relative location of visual stimuli. The short test presents the patient with dot-deviation signals that include a misalignment, or artificial distortion, that he or she must identify.

As AMD progresses, drusen may cause retinal pigment epithelium elevation.[10] This elevation subsequently creates pathological changes that can make straight lines appear distorted.

The Foresee PHP presents patients with a series of dotted lines. Each line has a distortion that the patient must identify. (This line is also known as the "artificial distortion.") If his or her condition is advancing, the patient will often identify a pathological distortion that is not actually present, rather than the artificial distortion. The hyperacuity test demonstrates 82% sensitivity as well as 88% specificity.[11]

Foresee PHP compares the patient's test results with results from an AMD normative database, which provides a comprehensive analysis. In many cases, the test is able to identify CNV in patients that are asymptomatic. A 2008 study indicated that 66% of the participants found to have CNV by Foresee PHP were unaware of any functional changes in their vision.[12] We ask our patients to take the test quarterly, or more often if they demonstrate a high risk for conversion to wet AMD.

• *Optical coherence tomography.* In addition to Foresee PHP, our practice uses OCT. We have found that use of both technologies is ideal to not only monitor AMD, but also diagnosis CNV. While the Foresee PHP is a functional test that monitors a patient's hyperacuity, the OCT provides an image of the retina that measures retinal thickness and reveals the presence of fluid.

The OCT depicts a cross section of the retina that allows the clinician to see its individual layers. Utilizing the OCT's ability to measure changes in retinal thickness can help pinpoint the location of a pathology and identify drusen that are growing in the retinal pigment epithelium. OCT's imaging capabilities can also confirm the presence of retinal bleeding caused by wet AMD.

Preparing For the Future

Considering that the number of AMD cases will rise exponentially during the next 20 years, it is imperative that you help your patients take control of their visual health. Proper education is the first step in helping your patients not only eliminate modifiable risk factors for AMD, but also take preventative measures to preserve their sight.

However, patient education alone is not enough. In addition, you must arm your practices with the most advanced technology available to ensure that you are doing everything possible for your patients. By implementing technology into your practice, you will have the best chance to save your AMD patients' sight and prevent the devastating effects of irreversible vision loss. ■

Dr. Blankenship is in private practice in Baker City, Ore. She has a specific interest in glaucoma, macular degeneration and ophthalmic disease.

Technology Helps Save Sight

• *History.* A 72-year-old white female presented with drusen that appeared indicative of dry AMD. The patient's ocular history was significant for drusen. Her medical history included osteoarthritis, hypertension, and viral meningitis with encephalitis and peptic ulcer disease. Her current medications included hydrochlorothiazide, amitriptyline, Prilosec (omeprazole, AstraZeneca Pharmaceuticals), Lexapro (escitalopram oxalate, Forest Pharmaceuticals) Benicar (olmesartan medoxomil, Sankyo Pharmaceuticals), PreserVision Eye Vitamins (Bausch & Lomb) and fish oil.

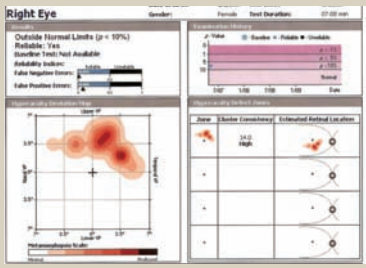

Figure 1.

• *Diagnostic Data.* Her best-corrected visual acuity was 20/25 O.D. and 20/20 O.S. Except for the presence of soft drusen, her retinal examination was unremarkable. The patient demonstrated healthy optic nerves and immature cataracts. Her intraocular pressure measured 16mm Hg O.U. Considering the significant drusen, we advised her to begin an at-home monitoring program on Amsler grid, and instructed her to contact us immediately if she noticed any change in vision.

• *Discussion.* Not long after our patient's initial visit, we incorporated the Foresee PHP into our office. I asked her to return and serve as one of our test patients for training on the device. At this visit, her PHP examination revealed suspected CNV in the macular field of her right eye (*figure 1*), so we scheduled her for an OCT evaluation the next day. The OCT confirmed the results seen on PHP. We referred her to a retina specialist for treatment before she had identified any visual changes. She received two injections of Avastin (bevacizumab, Genentech/Roche) during a two-month period. Following both injections, her vision stabilized at 20/50 O.D. Because of the increased likelihood for conversion in the fellow eye, we began monitoring her in three-month intervals on Foresee PHP. Nearly a year and a half after we identified CNV in her right eye, the PHP showed comparable abnormalities in her left eye (*figure 2*). We confirmed the presence of CNV in her left eye on OCT and promptly referred her to a retinal specialist. Again, the retinal specialist treated her with an Avastin injection. Thankfully, this time she received treatment before any vision loss occurred.

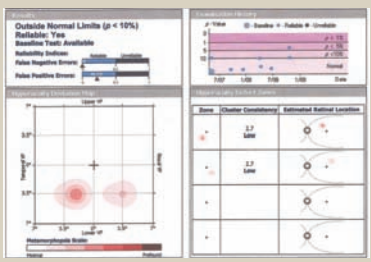
Figure 2.

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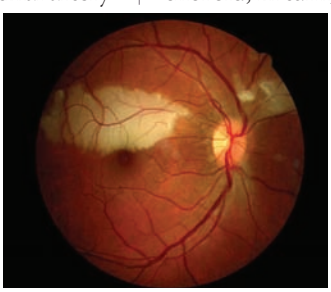
An Overview of Retinal Artery Occlusion

By Andrew S. Gurwood, O.D., F.A.A.O., Diplomate, and Marc D. Myers, O.D., F.A.A.O.

RETINAL ARTERY OCCLUSION is an ophthalmic emergency that can potentially result in blindness.[1,2] Depending on the location of the blockage, retinal artery occlusions are categorized as branch, central or ophthalmic.[3] They are not the result of a single disease, but the manifestation of a combination of chronic systemic abnormalities.[2,3] And as such, retinal artery occlusions have no definitive epidemiology.

The causative factors of retinal artery occlusion can be understood by studying associated systemic diseases and behaviors, including heart disease, cardiovascular disease, subacute bacterial endocarditis, tumors, leukemia, corticosteroid injection, polyarteritis nodosa, syphilis, blunt trauma, radiation exposure, optic nerve drusen, amniotic fluid embolism, smoking, obesity and cocaine abuse.[3,4] Also, the majority of patients who suffer a retinal artery occlusion are age 50 and older.[3]



Fundus photograph of a branch retinal artery occlusion.

Because we are considered primary care providers, our position in the healthcare stratum enables us to offer advice to our patients that might help prevent these events as well as identify or assess associated systemic disorders. Here, we discuss the symptoms and pathophysiology of retinal artery occlusion as well as several management strategies.

Anatomical Considerations

The anatomical construct of the neurosensory retina can be described as a photoreceptor (rod or cone) and two neurons (horizontal, bipolar or amicrine cell, as well as a ganglion cell).[5,6] Visible photons that enter the eye stimulate the photoreceptors by way of reflection off of the retinal pigment epithelium (RPE).

Through biochemical processes, the charged photoreceptors convert the electromagnetic energy into a streaming electric signal that can be propagated through internal biologic wiring (the visual pathway).[7-10] This ongoing chain of events becomes neurally converted into the images we observe. The signals are simultaneously relayed into the cerebral cortex for further interpretation, providing the sense of sight.

The neurosensory retina is supported by the vitreous humor and has 10 distinguishable components that are traditionally divided between the inner and outer layers.[5,6] The outer layers (closest to the sclera) are nourished by the choreocapillaris of the choroid. The choroid, in turn, receives its blood supply from the long and short posterior ciliary arteries.[5,11,12] The inner layers (closest to the vitreous humor) are nourished by the retinal arteriolar and supportive intraretinal capillary network.[5,11,12]

The continuous and complex nature of retinal metabolism mandates a consistent flow of energy and oxygen. Any interruption to the vital vascular supply can cause irreparable damage.[5,11,12]

Signs and Symptoms of Retinal Artery Occlusion

Patients who experience retinal artery occlusion present with a chief complaint of sudden, painless, vision loss.[1-4] In many instances, vision loss is noticed upon waking. However, when either a branch retinal artery is involved or a cilioretinal artery that preserves central vision is present, patients may complain of experiencing shadows or describe what appears to be an obstruction in their visual field. Some patients may report previous episodes of transient visual loss.[3,4,13] Concurrent pain is more indicative of an underlying ocular ischemic syndrome (carotid circulation) than a local retinal artery occlusion.[14]

• *Amaurosis fugax.* In Greek, the word "amaurosis" translates to darkness.[15] And in Latin, the word "fugax" translates to fleeting. In an ophthalmic context, the term amaurosis fugax (AF) is used to describe an event of monocular vision loss that persists for a few seconds to several minutes.[15-18]

Typically, AF presents as a sudden, painless loss of vision, without visible evidence of headache, an embolic event or hemodynamic insufficiency.[15-23] Episodes of AF frequently leave some permanent remnant, such as a relative scotoma or distortion.[15-23] Additionally, AF may forecast impending retinal hemorrhages, cotton wool spots, central retinal vein occlusion, anterior ischemic optic neuropathy, retinal artery occlusion, ophthalmic artery occlusion and cerebrovascular accident (CVA).[20,24] Finally, AF usually can be suggestive of beginning, impending or worsening vascular disease.[21] As such, its epidemiology is non-specific and associated with various systemic illnesses that induce it, including heart disease, carotid artery disease, and athero or arterial sclerosis, as well as a history of smoking, hyperlipidemia and advanced age (greater than or equal to 64 years).[15-26]

• *Transient ischemic attack of the eye.* Transient ischemic attack (TIA) of the eye is characterized by either monocular or binocular vision loss that persists from minutes to hours. Its process typically includes neurologic symptoms and may induce other noticeable visual phenomena, such as entoptic phenomena or scintillating scotoma (these events may not affect acuity).[17]

• *Transient visual obscuration.* Transient visual obscuration (TVO) resides on the continuum of AF and TIA, but is characterized by visual blur or dysfunction rather than visual loss. In cases of TIA, scotomas may be altitudinal, sectoral or homonymous.[17] Monocular sectoral episodes indict the carotid/ocular circulation.[17] Binocular homonymous events signify a retrochiasmal effect and often indicate a posterior or vertebral circulatory issue. Like AF, TIA and TVO are signs of beginning, impending or worsening vascular disease.[15-25]

Both TIA and TVO are on a continuum with AF; however, they are considered their own entity not only because of the length of time the respective event lasts, but also because they can impact more than one neurologic area. While AF is strictly a local ocular event, TIA represents the beginning of a territorial insult. As the name implies, TIA

temporarily affects a sector of neurologic tissue.[15-25] When the effects of an episode of TIA remain permanent, the event is considered a cerebrovascular accident or stroke.

All retinal artery occlusions do not present in the same way. Differing development alters the funduscopic appearance. When blood flow is impeded, retinal function is compromised immediately—though initially, the retina may appear unaffected.[1-4,13]

However, as the ischemia evolves, retinal arteries may become visibly narrowed, demonstrating segmented interrupted flow known as "boxcarring." Over time, the retina may appear pale and edematous.[1-4,13]

As capillary blood flow becomes stagnant from poor push or perfusion, nerve fiber layer hemorrhages may present in the parapapillary area.[3] The classic macular "cherry red spot" seen in conventional cases of central retinal artery occlusions occurs because of the nature of photoreceptors and foveolar architecture.[3] Here, choroidal circulation is highlighted by the surrounding retinal pallor, which permits it to stand out.[1-4,13,14,27-30]

Though retinal edema may resolve within six to 10 weeks after acute injury, complete function rarely returns.[1-4] The formation of retinal neovascularization and iris neovascularization (rubeosis) is rare, because the affected tissues are infracted rather than ischemic; however, this complication is possible secondary to vascular endothelial growth factor (VEGF) release.[1-3,31] Neovascular glaucoma and hemolytic glaucoma from hyphema secondary to ruptured iris neovascularization are also a possibility anytime rubeosis forms.

Pathophysiology of Retinal Artery Occlusion

• *Embolic obstruction.* While the etiology of retinal artery obstruction is primarily embolic, the events are not always visible.[2] Bright, white, glistening, refractile emboli represent trapped cholesterol particles known as Hollenhorst plaques.[3-5] Solid, white, non-refractile plugs are typically calcific in nature and can be traced to the valves of the heart. Long, white, intravascular obstructions made up of platelets and fibrin are known as platelet-fibrinogen plaques.[3,4,13]

The literature suggests embolic disease's etiology is related to malfunctioning clotting factors in the blood caused by antiphospholipid disease, factor VIII abnormality, and protein S and C alteration.[27-29] Amniotic fluid embolism has also been recorded as an unusual, but plausible, source of retinal emboli.[30]

Emboli released from any of the aforesaid sources can travel through the vascular system and become lodged inside a retinal vessel. Once lodged, a partial or complete obstruction may form that restricts blood flow and oxygen transmission to distal tissues.[2,4] When the oxygen-sensitive retinal elements lose their source of nourishment, they quickly begin to fail and demonstrate symptoms of variable visual phenomena or complete, painless vision loss.[1-4,13,14,27] Clearly, retinal tissue is extremely sensitive to oxidative stress.[32] So, the inner layers of the retina succumb to ischemia with intracellular edema and necrosis within minutes of an event.[3]

When partial or complete retinal arterial occlusion occurs, tissue ischemia ensues. This process induces the release of cytokines, chemoattractants and angiogenesis factors, which initiate the process of inflammation and new blood vessel growth in both the anterior and posterior segments.[31] Fibroproliferative neovascularization of the iris has the potential to cause angle neovascularization and subsequent obliteration of the aqueous drainage access, which pulls the iris into apposition with Schwalbe's ring.[31] The process is often referred to as "zippering," and produces a secondary neovascular angle closure.[31] Interestingly, neovascular complications from retinal artery occlusion are infrequent when compared to other causes of retinal vascular disease, such as retinal vein occlusion and diabetes, because the retinal tissues typically die rather than starve.[2,33]

Generally, retinal emboli are found in elderly male patients with a history of smoking, hypertension, diabetes, elevated total and low-density lipoprotein cholesterol, and self-reported angina.[34-37] Fibrin-platelet aggregate emboli and calcific emboli are also commonly associated with retinal vascular occlusion.[38-40] Significantly less common are emboli consisting of air, aseptic emboli (pus-containing bacteria) or foreign body emboli (such as talc).[38-40]

• *Vascular involvement.* Clearly, hypertension is a major risk factor for the development of microvasculopathy.[41] It increases the risk for retinal vascular events, such as retinal vein occlusion, retinal artery occlusion and ischemic optic neuropathy.[41] Sickle cell disease also has been noted as an etiology of retinal artery occlusion.[42] While most cases of retinal artery obstruction are the result of underlying cardiac, carotid, vascular, hemodynamic and/or autoimmune diseases, there are rare instances where retinal artery occlusions have occurred in healthy individuals who exhibit no attributable systemic etiology.[27,43]

An early, critical event in the process of atherogenesis is the focal accumulation of lipid-laden foam cells that are derived from macrophages, smooth muscle cells, and other vascular cells.[44-47] As lipid-laden foam cells increase in number, they merge to form fatty streaks. Alone, fatty streaks typically pose no health risk.[44-47] But, when foam cell activity continues for several years, fatty streaks may further develop into a fibrous plaque (atherosclerotic lesion).[44-47]

• *Fibrous plaques.* Fibrous plaque formation may lead to thinning of the smooth muscle within the arterial wall, weakening it and increasing the possibility of plaque rupture.[44-47] A connective tissue cap is formed on the surface of the plaque. This cap is subject to sheering forces exerted by laminar blood flow. The consistency of the connective tissue cap may vary; and thinner caps have a greater likelihood of rupturing, which can cause localized platelet aggregation and possible thrombus formation.[44-47] Interestingly, nearly 70% of thrombi are clinically silent while the

Important Clinical Questions

Here are some important clinical questions to ask patients who present complaining of sudden, painless vision loss:

- What activities immediately preceded vision loss?
- Was it in one eye or both?
- Was vision completely lost during the episode?
- Was vision blacked-out or blurry?
- How long did vision loss persist?
- When vision returned, did it come back suddenly or gradually?
- Did the episode leave any permanent vision loss?
- Has this happened before, and if so, how many times?
- If the episodes are new, what is the frequency and has the frequency changed at all?
- Did you experience a headache after the episode?
- Are you a migraine headache sufferer?

atherosclerotic lesion heals and undergoes reendothelialization.[44-47] When thrombi migrate, they are referred to as "thromboemboli." Like fibrous plaques, thromboemboli threaten the flow of blood and oxygen throughout the body and often are responsible for ischemic stroke, myocardial infarction or respiratory distress.[44-47]

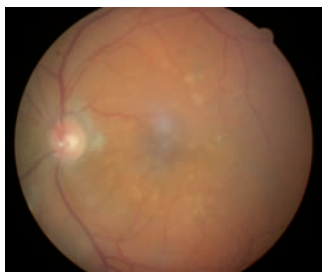
Ruptured fibrous plaques may also send unstable fragments through the blood stream.[44-47] These emboli often travel through vessels without consequence; however, larger fragments can become lodged in distal vessels, obstruct the passage of blood and oxygen, and result in ischemia.[44-47] Ruptured fibrous plaques often travel to the retinal vascular system and result in occlusion.[34-37]

• *Giant cell arteritis.* Giant cell arteritis (GCA) is a systemic vasculitis that predominantly affects the medium-sized extracranial arteries of the carotid circulation.[48] In the eye, GCA may lead to arteritic ischemic optic neuropathy, which precipitates blindness. In the body, however, GCA may lead to stroke or death.[49] Although primarily a disease of older individuals (more than 70 years of age), GCA should not be overlooked in patients more than 40 years of age who experience the tell-tale visual, ocular or systemic symptoms, such as jaw claudication (pain upon moving the jaw or chewing); pain upon combing the hair or palpating the temple region of the head; episodes of AF, TIA or TVO, weight loss; loss of appetite; or non-specific retinopathy (unexplained retinal hemorrhages or cotton wool spots).[50]

One study examined biopsy-proven GCA in 170 patients during a 12-year period.[26] Ocular symptoms in patients were registered as visual loss of varying severity in 83 patients, amaurosis fugax in 26 patients, eye pain in seven patients and diplopia in five patients.

Evidence of ocular ischemia was observed in the form of arteritic anterior ischemic optic neuropathy in 69 patients, central retinal artery occlusion in 12 patients, cilioretinal artery occlusion in 12 patients, posterior ischemic optic neuropathy in six patients and general ocular ischemia in one patient.[26] In this study, almost every patient with GCA had fluorescein angiographic evidence of occlusive disease of the posterior ciliary arteries.[26] Uncovering GCA as the cause of TIA or AF may save patients from certain catastrophic vision loss from central retinal artery occlusion (CRAO) or anterior ischemic optic neuropathy (AION).[26,51]

• *Dissection of internal carotid artery.* Finally, spontaneous dissection of the cervical internal carotid artery may also cause territory ischemia and symptoms on the side of dissection. Local signs and symptoms include head, facial or neck pain; Horner's syndrome; pulsatile tinnitus; cranial nerve palsies (III, IV, V and VI); headache; ischemic stroke; TIA; AF; ischemic optic neuropathy; or retinal infarct.[52]



This patient presented with a central retinal artery occlusion.

Management of Retinal Artery Occlusion

Timely intervention is the key to visual recovery in any retinal arterial occlusion. Anecdotally, the potential for achieving any restoration of vision is greatest when the blockage is dislodged within 100 minutes of initial onset.[3,24] While frequently unsuccessful, emergent treatments are intended to increase retinal perfusion by re-establishing retinal blood flow.[1-4,53]

• *Simple management.* The traditional mechanism of increasing IOP through aggressive digital palpation with sudden release is designed to stimulate retinal autoregulatory mechanisms. In this instance, as the retinal tissues sense the general hypoxia created by the digitally applied force, the retinal vasculature dialates in an attempt to increase blood flow. When palpation is ceased, aqueous is forced from the eye, which decreases the resistance to incoming blood and increases vessel diameter. Sometimes, this will induce embolus dislodgement, permitting reperfusion of the affected retinal area.[3]

Decreasing the resistance to ocular blood flow by reducing IOP with topical and/or oral medication is another strategy for dislodging emboli. Similarly, an alternate strategy involves stimulating retinal vascular dilation by increasing blood carbon dioxide levels via breathing into a paper bag or inhaling carbogen (95% oxygen and 5% carbon dioxide).[3] Unfortunately, these measures rarely impact the final outcome.[1,3,4,24,53]

• *Conventional management.* Patients with artery occlusion must receive a complete systemic work-up to uncover the underlying cause.[4,48] An evaluation should include a complete blood count with differential and platelets; an erythrocyte sedimentation rate (ESR); c-reative protein (CRP); lipid panel; carotid artery evaluation using transcranial Doppler; prothrombin time; activated partial thromboplastin time; protein s; protein c; antiphospholipid antibody testing; homocyctein testing; antinuclear antibody and lupus anticoagulant testing; and echocardiogram and transesophageal echocardiogram.[28,29,43,54-57] It is tremendously important to obtain an ESR and CRP for elderly patients with systemic symptoms suggestive of GCA.

In general, anticoagulation therapy is the staple of treating individuals who suffer from artery occlusion secondary to coagulopathy, hyperviscosity, cardiac or other carotid sources.[42,55-58] Additionally, immunosuppressants may be appropriate for cases involving lupus or antiphospholipid antibody syndrome.[54]

The systemic management for patients who experience TIA and AF without a treatable retinal vascular event is oral anticoagulant therapy.[43,55-58] The typical management for systemic autoimmune diseases that produce these interruptive events is oral anti-inflammatory therapy, either with or without immune modulation.[20] Both therapies can be regulated by either skilled internal medicine specialists or subspecialists.

Surgical management of carotid artery disease can be accomplished via percutaneous angioplasty with stenting or endarterectomy.[23,56] Prior to surgery, however, all patients whose symptoms are determined to be within the domain of vascular interruption (AF, TIA and TVO) require prompt consultation from an internist or cardiologist to determine the definitive underlying cause and to rule out additional intervention.

Finally, momentary or fleeting interruption of vision (AF, TIA and TVO) must be differentiated from monocular retinal migraine.[19,20] A true retinal migraine is a diagnosis of exclusion that produces a fully reversible monocular visual disturbance (classic aura vs. other episodic phenomena) in

concert with a headache during a normal neuro-ophthalmic examination.[19-21] Nevertheless, it is not unreasonable to refer these patients to either a neurologist or neuro-ophthalmologist.

• *Aggressive management.* Intra-arterial thrombolysis (IAT) has the potential to produce superior visual outcomes compared with conventional treatments for retinal artery occlusion.[57-59] While the strategy of using intravenous and intra-arterial thrombolytic agents, such as urokinase, has existed for more than 20 years, there remains insufficient evidence to support its routine use.[57-59] It is worth noting that vitreous hemorrhage is a potential side effect of IAT.[57]

Hyperbaric oxygen therapy is another potential treatment for retinal artery occlusion. It is currently being tested in off-label trials, and has demonstrated increased safety and efficacy for use in retinal artery occlusion.[60,61]

A newly proposed technique using Nd:YAG laser to disrupt emboli within the central retinal artery and branch retinal arteries may help achieve rapid reperfusion of the retina.[4] Translumenal Nd:YAG embolysis (TYL) or embolectomy (TYE) has been reported to rapidly treat retinal nonperfusion secondary to embolic blockage.[4] One study demonstrated that Snellen visual acuity improved by an average of four lines in 17 of 19 patients (89%) who received TYL.[4] Eleven of the patients (58%) gained greater more than four lines.[4] Still, vitreous hemorrhage and subhyaloid hemorrhage are potential complications of TYL.[4]

The neurosensory retina is a metabolic dynamo. But, without a consistent, streaming supply of energy and oxygen, retinal tissues will begin deconstructing and become ischemic. Generally, by the time patients present for care, simple measures to restore retinal perfusion are unsuccessful.

The results of retinal artery occlusion are frequently life altering. They often are markers of runaway systemic processes that require significant control and lifestyle changes. We are uniquely positioned to provide a range of care, spanning from preventative advice to emergency therapeutic response.

Because it represents an event on the continuum of systemic vascular disease, an ocular arterial occlusion indirectly demonstrates the current status of the patient's systemic cardiovascular system. Recognizing the critical symptoms (i.e., transient visual blur, transient ischemic attack, signs consistent with migraine, episodes of amuarosis, or complaints of feeling light-headed or fainting) and employing proper measures to uncover the ultimate underlying cause may not only prevent a catastrophic visual event, but also prevent mortal complications, such as cerebrovascular accident, vascular dissection or myocardial infarction and sudden cardiac arrest. ■

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SD-OCT vs. TD-OCT: A Comparison of Retinal Imagery

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Release Date
November 2009

Expiration Date
November 30, 2010

Goal Statement
This paper analyzes and reviews five cases of retinal pathology using a side-by-side comparison of spectral domain optical coherence tomography and time domain optical coherence tomography. Additionally, it discusses the overall value of OCT in the management of various retinal conditions.

Faculty/Editorial Board
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Disclosure Statement
Dr. Shechtman is on the speakers' bureau of Carl Zeiss Meditec, Sightpath/Notal Vision and Alcon. Dr. Semes is on the advisory boards of Carl Zeiss Meditec and OptoVue.

OPTICAL COHERENCE TOMOGRAPHY has revolutionized the diagnosis and management retinal conditions. As a diagnostic tool, OCT has facilitated re-categorization of retinal diseases, such as macular hole staging.[1] Disorders of the vitreomacular interface, such as vitreomacular traction (VMT), are no longer thought to be rare entities.[2]

Also, OCT has been an invaluable tool for monitoring patients who receive anti-vascular endothelial growth factor (VEGF) therapy for neovascular abnormalities.[3] As OCT technology continues to evolve, so will our ability to diagnose and manage retinal diseases.

The new generation OCT, spectral domain, offers unsurpassed speed and unprecedented resolution.[4] In addition, SD-OCT's new software capabilities, such as video, segmentation and 3-D topographical imagery, provide additional morphological evaluations. Finally, SD-OCT allows for virtual image and cross-sectional scanned image comparison through point-by-point registration, which enhances longitudinal monitoring of the retinal condition.

But, do SD-OCT's cutting-edge features ultimately contribute to earlier diagnosis of retinal disease and enhanced patient management?

Here, we analyze and review five cases of retinal pathology using a side-by-side comparison of spectral domain (Cirrus HD-OCT, Carl Zeiss Meditec) and time domain (Stratus OCT, Carl Zeiss Meditec) OCT imagery. In addition, we discuss the overall value of OCT in the diagnosis and management of various retinal conditions as well as the advantages of SD-OCT over TD-OCT.

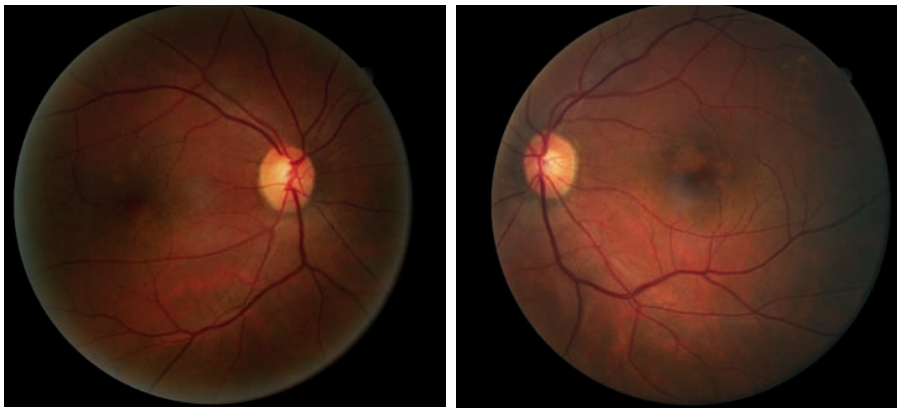
Case 1: Pigment Epithelial Detachments

• *History.* A 42-year-old Hispanic male presented for an initial exam with no visual or ocular complaints. He had no significant ocular or medical history.

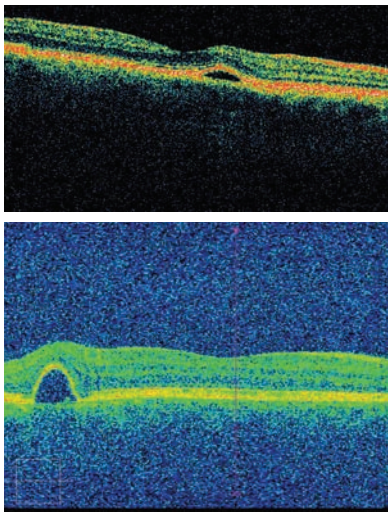
• *Diagnostic data.* His best-corrected visual acuity measured 20/20 O.U. Dilated fundus exam showed mottled retinal elevations adjacent to the fovea O.U. (*figures 1 and 2*). Amlser grid testing revealed areas of paracentral metamorphopsia in both eyes. Overlying pigment was noted on some of the retinal elevations.

Both TD-OCT and SD-OCT images of the patient's right eye revealed sloped elevation of the retinal pigment epithelium (RPE), with underlying hyporeflectivity (*figures 3 and 4*). Using the segmentation feature of the Cirrus HD-OCT on his right eye, we clearly observed several pigment epithelial detachments (PEDs) (*figure 5*).

• *Discussion.* A PED is



Figures 1 and 2. The dialated fundus exam (O.D. left, O.S. right) revealed mottled retinal elevations O.U.



Figures 3 and 4. TD-OCT (top) and SD-OCT (bottom) of our patient's right eye revealed sloped elevation of the RPE.

characterized by a serous detachment between the RPE layer and Bruch's membrane. The clinical appearance of a serous PED is described as a sharply demarcated, dome-shaped elevation associated with a reddish hue.[5] Overlying pigment, mottling or yellow deposits may accompany a PED.

Various chorioretinal diseases as well as systemic conditions (such as Cushing's syndrome) may be associated with a PED. Choroidal neovascular membrane (CNVM) is a possible sequela that is associated with a high risk for severe vision loss.[5] So, it is critical to determine the particular etiology in order to initiate an appropriate treatment.

Multiple PEDs may be observed among healthy patients, and in fact, are believed to be a variant of idiopathic central serous choroidopathy (ICSC).[6]

OCT can help to further differentiate between an ICSC and a PED. Overall advantages of the OCT in the analysis of a PED include evaluation for the presence of an associated CNV. In addition, quantifying measurements of retinal thickness can be used for continuous monitoring.

On OCT, a PED appears as a hyperreflective, elevated band due to the presence of increased retinal pigmentation found within the RPE. This elevation is more dramatic compared to the elevations of an ICSC because of tight cellular junctions within the RPE.

Frequently, however, a scan obtained on TD-OCT is limited by the region it is actually sampling (256 A-scans along six linear B-scans).[7] For example, TD-OCT may miss a small PED that resides between the six meridional sample lines.

The increased number of scans gathered on SD-OCT allows for a more thorough evaluation of retinal involvement.[8]

Moreover, SD-OCT's capability of point-by-point registration between the virtual image and the cross-sectional scanned images allows for precise follow-up.

Our patient is being followed on a bi-annual basis for stability and/or progression of the PEDs. Generally, no treatment other than observation is recommended for PED.

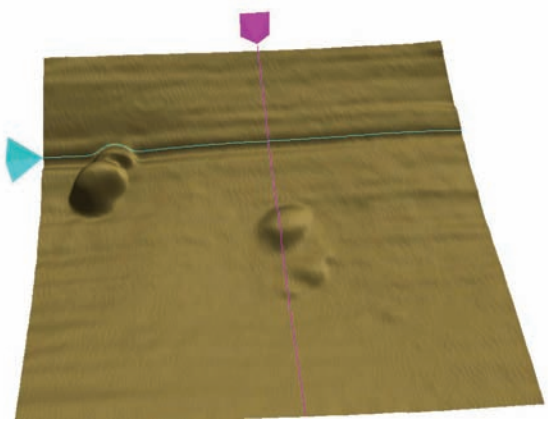
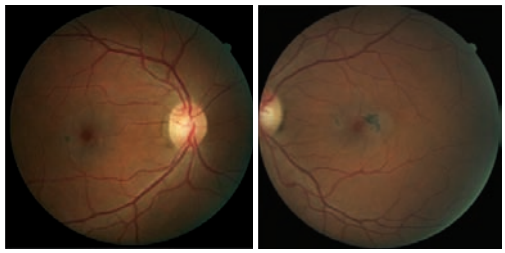


Figure 5. Note the presence of several pigment epithelial detatchments (PEDs).



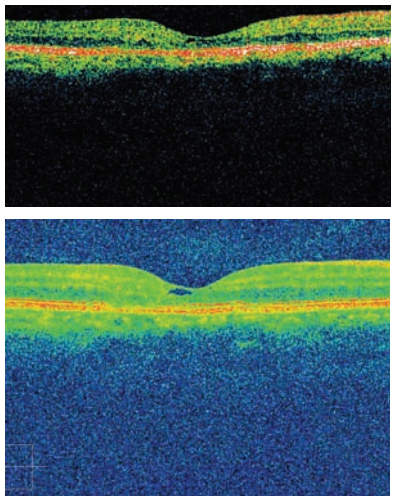
Figures 6 and 7. The dialated fundus exam (O.D. left, O.S. right) revealed an absence of the foveal light reflex and macular graying O.U.

Case 2: Idiopathic Juxtafoveal Retinal Telangiectasia

• *History.* A 54-year-old Caribbean female presented to the clinic with a six-month history of decreased vision in her left eye. Her ocular history was unremarkable, and her medical history was significant for controlled hypertension.

• *Diagnostic data.* Her best-corrected visual acuity was 20/25 O.D. and 20/50 O.S. Dilated fundus exam of both eyes revealed an absence of the foveal light reflex with associated graying appearance to the macula (*figures 6 and 7*). We also documented areas of RPE hyperplasia in both eyes.

TD-OCT of the right eye was essentially unremarkable, save a questionable, thinned foveal area (*figure 8*). However, the SD-OCT of the right eye showed a well-delineated hyporeflective space



Figures 8 and 9. TD-OCT (top) and SD-OCT (bottom) of our patient's right eye. Can you see any differences between the two images?

within the retina. This cyst was associated with an overlying draping of the internal limiting membrane (ILM). We also noted an area of displaced intraretinal RPE hyperplasia on SD-OCT (*figure 9*).

• *Discussion.* Idiopathic juxtafoveal retinal telangiectasia (IJRT) is a vascular anomaly characterized by incompetent retinal capillaries typically located temporal to the macula. These ectatic dilations of the retinal capillaries may be associated with minimal retinal leakage as well as the presence of hemorrhages or exudates.[9]

There are various subgroups and presentations of IJRT, ranging from subtle graying of the macula to areas of RPE hyperplasia and associated retinal thickening.[9,10] Conventional fluorescein angiography (FA) has been used to confirm diagnoses associated with presences of abnormal capillary network that are not visible fundoscopically.[9] Recent literature has discussed the use of OCT to help diagnose and recategorize IJRT.[10,11]

In this case, the SD-OCT illustrated the significance of enhanced resolution in facilitating a diagnosis. Furthermore, it depicted associated plaques, exudates, hemorrhage and RPE hyperplasia. Finally, SD-OCT's quantitative parameters also helped us initiate therapeutic intervention in a timely fashion. We asked the patient to return in three months to further evaluate progression on both funduscopy and OCT.

Case 3: AMD and Vitreomacular Traction

• *History.* A 72-year-old white male returned for a three-month follow-up for dry AMD. The patient had a longstanding history of dry AMD O.U. and has been taking an AREDS-formulated vitamin for five years.

• *Diagnostic data.* His best-corrected visual acuity measured 20/25 O.D. and 20/40 O.S. Dilated fundus evaluation revealed soft drusen O.D. with an associated area of retinal atrophy, and coalescent soft drusen O.S. (*figure 10*).

TD-OCT of the left eye showed RPE disruption (*figure 11*); however, SD-OCT of the left eye provided a better representation of individual modulation associated with the macular drusen (*figure 12*). In addition, disruption of both the RPE and photoreceptor inner/outer segment junction is clearly visible on SD-OCT. Of note, vitreomacular traction (VMT) was also noted, with increased associated foveal traction. VMT may further contribute to his decreased visual acuity and, most importantly, was not seen on TD-OCT.

• *Discussion.* VMT is described as a partial posterior vitreous detachment with continuous attachment to the macula. The traction on the macula commonly contributes to cystoid macular edema with subsequent decreased visual acuity. Several distinct maculopathies have been associated with VMT, including macular hole formation and epiretinal membrane.[12]

Often, a diagnosis of VMT is difficult to distinguish clinically. Even with a fundus contact lens examination, the firm, translucent adhesions of the vitreous at the macula may be essentially imperceptible. Fortunately, however the use of OCT has led to better understanding of the disease.

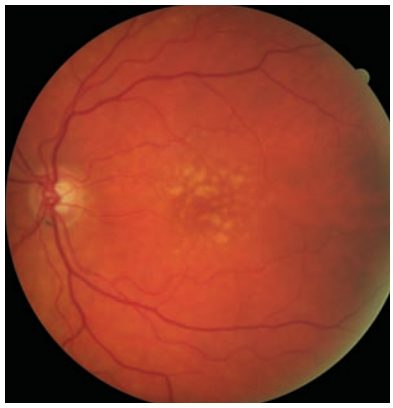
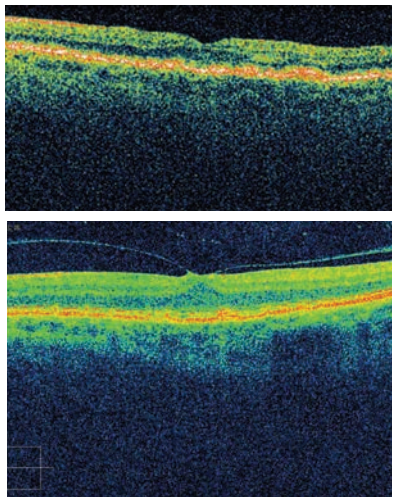


Figure 10. Dialated fundus exam of our patient's left eye demonstrated soft drusen.



Figures 11 and 12. TD-OCT (top) of our patient's left eye showed RPE disruption. In addition, the SD-OCT (bottom) revealed vitreomacular traction as well as associated foveal traction.

In general, VMT appears as a low reflective band above the retina on OCT. This band is detached both nasal and temporal to the macula, with remaining adherence to the central fovea. This firm, foveal and parafoveal attachment might be classified as either focal or multifocal.[2] Associated maculopathies may be further evaluated and monitored on OCT as well.

In this case, the high resolution of the SD-OCT clearly distinguished the vitreomacular interface. In contrast, the TD-OCT was unable to delineate the partial detachment of the posterior hyaloid.

The presence of VMT corroborates the decreased visual acuity in our patient's right eye. In addition, management may be altered in the future with regard to surgical intervention for VMT. We asked the patient to return in six months for further evaluation.

Case 4: Diabetic Macular Edema

• *History.* A 52-year-old Hispanic female presented with an eight-year history of diabetes that was managed with insulin. She was not self-monitoring her glucose levels and was unaware of her last HbA1C measurement.

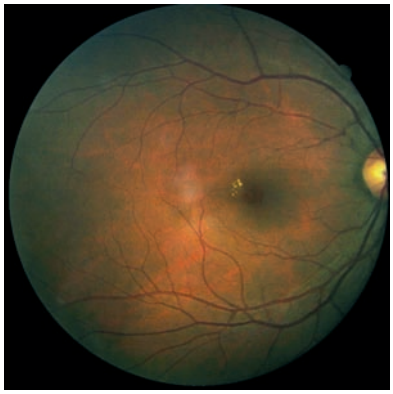
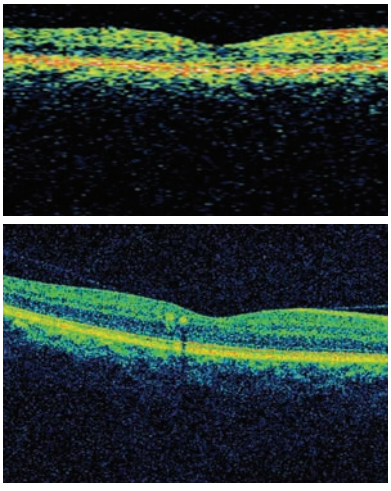


Figure 13. Our patient's dialated fundus examination revealed the presence of dot and blot hemorrhages.

She presented with no visual or ocular complaints.

• *Diagnostic data.* Best-corrected visual acuity measured 20/20 O.U. Dilated fundus examination revealed dot and blot hemorrhages in both eyes. The fundus exam also revealed an area of exudates with associated retinal disruption near the macula of her left eye (*figure 13*).

The TD-OCT of her right eye showed no abnormalities, and reported a retinal thickness of 185µm (*figure 14*). The SD-OCT of her right eye, however, revealed intraretinal hyperreflective lesions that correlated to the area of retinal exudates, and reported a retinal thickness of 284µm (*figure 15*). The SD-OCT also demonstrated a partial detachment of the posterior hyaloids O.S. (TD-OCT identifies retinal thickness as the distance between the ILM and photoreceptor layer boundaries, whereas SD-OCT indentifies retinal thickness as the distance between the ILM and the RPE layers, which is approximately 45µm thicker.[7,13,14])



Figures 14 and 15. TD-OCT (top) of our patient's right eye demonstrated no abnormalities. SD-OCT (bottom), however, revealed intraretinal hyperreflective lesions that correlated to an area of exudates.

• *Discussion.* Diabetes mellitus is a metabolic disorder characterized by hyperglycemia that causes a constellation of systemic and ocular complications. Diabetic retinopathy (DR) is the leading cause of newly diagnosed cases of blindness in young adults in the U.S.[15] Diabetic macular edema (DME) is the primary cause of decreased vision associated with DR and can occur at any stage of the disease.

DME is characterized by capillary breakdown that results in retinal vascular leakage. Hemorrhages, exudates and increased inner retinal thickness are frequent manifestations of DME.[15]

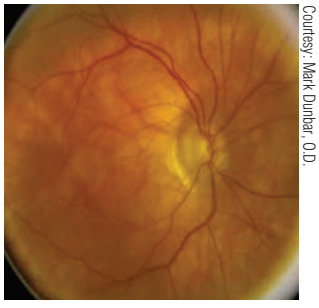
OCT is particularly useful in the diagnosis of subtle DME. Clinical features of DME seen on OCT include CME, subretinal fluid, neurosensory detachment and diffuse macular thickness. An OCT image of DME can be described as "spongy" with loss of foveal contour. The quantitative parameters of the OCT are also used to guide treatment intervention.

Due to the lower resolution of TD-OCT, the retinal boundaries are not always accurately drawn—especially when presented with retinal pathology. This may lead to disparate retinal thickness measurements when compared to measurements taken on SD-OCT, as in this case.

Additionally, SD-OCT's ability to gather 30,000 A-scans/second (in comparison to 500 A-scans/second for TD-OCT) gives a more accurate representation of macular edema. The use of the 3-D reconstruction macular thickness topography also can provide more reliable macular thickness information than TD-OCT.

As mentioned above, the increased resolution of SD-OCT permits more extensive evaluation of the vitreoretinal interface. Thus, SD-OCT allows the clinician to observe an associated epiretinal membrane or VMT more effectively.[16]

We educated the patient about her condition as well as the importance of both self-monitoring and lifestyle changes. Because of the possible presence of DME seen on SD-OCT, we scheduled her for a retinal consultation.



Courtesy: Mark Dunbar, O.D.

Figure 16. The dialated fundus examination revealed large staphyloma of the posterior poles.

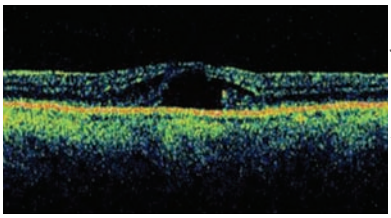
Case 5: Macular Hole

• *History.* A 57-year-old Hispanic female presented with decreased vision in her left eye. Her systemic and ocular history was unremarkable.[17]

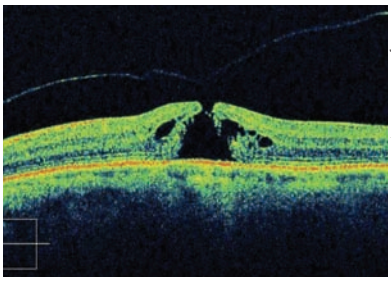
• *Diagnostic data.* The dilated fundus examination revealed large staphyloma of the posterior poles (*figure 16*). Detailed evaluation of the left macula showed the subtle appearance of an eccentric oval macular hole.

TD-OCT of the left eye revealed an early stage macular hole associated with a partial operculated detachment (*figure 17*). SD-OCT, however, exhibited greater detail, indicating that the defect was a full-thickness, stage 3 macular hole, and additionally revealed the presence of a PVD (*figure 18*).

• *Discussion.* An idiopathic macular hole represents full-thickness loss of retinal tissue within the macula. It is more commonly observed in elderly females who present with complaints of



Courtesy: Mark Dunbar, O.D.



Courtesy: Mark Dunbar, O.D.

Figures 17 and 18. TD-OCT (top) of our patient's left eye revealed an early stage macular hole. But, further analysis on SD-OCT (bottom) suggested the presence of a full-thickness, stage 3 macular hole.

blurred vision, metamorphopsia or central scotoma. There are four stages; each stage exhibits different clinical presentations.[18] For example, the typical OCT image of late-stage, full-thickness macular hole often will reveal a complete absence of foveal tissue extending to the RPE as well as adjacent intraretinal cysts and an overlying PVD.

OCT not only has enhanced our understanding of the pathogenesis of macular holes, but also has led to a re-classification of the stages, including the addition of stage 0.[1,19] A stage 0 macular hole is represented by an insertion of the posterior hyaloid on the macula, which results in minimal macular traction in an asymptomatic patient. Most importantly, this finding is essential in the identification of at-risk patients and may not be observable fundocsopically.

Additionally, OCT can help a clinician make a differential diagnosis of either a lamellar macular hole or a pseudohole. Lamellar macular holes reveal the presence of outer retinal layers above the RPE.[20] These outer retinal layers are, in fact, more clearly visualized on SD-OCT, which shows a clear separation between the inner/outer segment layer and the RPE.

In this case, for example, although TD-OCT did reveal an associated macular hole, the SD-OCT revealed a more realistic overview of the defect as well as its severity. A proper diagnosis of the stage will, in fact, help to guide the management plan.[21] Due to the advanced stage of the macular hole, we referred the patient for a retinal surgical consultation.

The increased resolution on SD-OCT allows for evaluation of subtle pathological changes and better localization.[22] SD-OCT's improved resolution can help facilitate earlier diagnosis of retinal disease as well as enhanced monitoring of disease progression than TD-OCT. Additionally, higher resolution allows for evaluation of the inner/outer segment area, which may help correlate retinal function to structural changes.[7] Rapid image capture further contributes to better image resolution through the elimination of image degradation associated with motion artifact.

Also, SD-OCT's increased number of A-scans allows for vast sampling of the retinal tissue. This advantage permits more realistic spatial correlation and mapping of any retinal condition.

Finally, SD-OCT provides improved integration of diagnostic imaging. Its advanced features help in the comprehension of retinal disease, aid in clinical diagnosis and provide greater monitoring precision.

One final word: Though SD-OCT has several clear advantages over its predecessor, TD-OCT still holds tremendous value in the diagnosis and management of retinal disease. At the end of the day, both SD-OCT and TD-OCT make it possible for us to care for our patients significantly better than ever before—and ultimately, that is what matters. ■

Dr. Shechtman is an associate professor at Nova Southeastern University College of Optometry in Ft. Lauderdale, Fla. Dr. Semes is a professor at the University of Alabama School of Optometry in Birmingham, Ala. They thank Mark Dunbar, O.D., for contributing case number 5.

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Questions

1. What is NOT an accurate distinction between time domain (TD-OCT) and spectral domain OCT (SD-OCT)?
a. Only SD-OCT provides 3-D topographical imaging capability.
b. SD-OCT is faster and gathers more data than TD-OCT.
c. Only TD-OCT provides point-by-point registration.
d. SD-OCT has video capability.

2. How does optical coherence tomography (OCT) help to diagnose a retinal pigment epithelium (RPE) detachment?
a. Sloped borders are indicative of an RPE detachment.
b. Hyperreflective hemorrhage is observed, overlying the RPE detachment.
c. Hyperreflectivity is observed below the RPE detachment.
d. Cystic-like formation is observed with the neurosensory detachment.

3. On OCT, what will a patient with idiopathic juxtafoveal retinal telangiectasia (IJRT) demonstrate?
a. Decreased RPE hyerreflectivity.
b. A spongy appearance of intraretinal layers.
c. An increased hyperrefelctive nerve fiber layer.
d. Draping of the internal limiting membrane that overlies the cystoid change.

4. When using OCT to manage IJRT, which statement is FALSE?
a. OCT facilitates diagnosis of associated findings, such as exudates.
b. OCT can be used to guide treatment intervention.
c. OCT has uncovered the role of the vitreous in development of IJRT.
d. OCT has helped re-categorize IJRT.

5. What condition typically is associated with tractional forces on the macula secondary to vitreomacular traction (VMT)?
a. Cystoid macular edema (CME).
b. Choroidal neovascular membrane formation.
c. Epiretinal membrane.
d. Intraretinal hemorrhages.

6. What OCT demonstration is indicative of VMT?
a. A low reflective band above the retina that is detached both nasal and temporal to the macula.
b. Increased hyperreflectvity of the nerve fiber layer.
c. Hyperreflective lesion within the neurosensory retina.
d. Modulations of the RPE.

7. Regarding resolution at the vitreomacular interface, what finding could be better appreciated on SD-OCT than TD-OCT?
a. The extent of a posterior hyaloid detachment.
b. An associated peripheral retinal break.
c. Increased retinal thickness.
d. Associated leakage.

8. Approximately how much thicker will a patient's central retina appear on SD-OCT than TD-OCT?
a. 25µm.
b. 35µm.
c. 45µm.
d. 55µm.

9. What clinical feature of diabetic retinopathy is NOT typically observed on OCT?
a. CME.
b. Subretinal fluid.
c. Neurosensory detachment.
d. Superficial neovascularization.

10. When evaluating a macular hole, what is NOT an advantage of OCT?
a. OCT helps determine visual function.
b. OCT helps making a differential diagnosis.
c. OCT helps to uncover and understand vitreomacular tractional involvement.
d. OCT helps to define the parameters of stage 0.

Examination Answer Sheet
Valid for credit through November 30, 2010

SD-OCT vs. TD-OCT:
A Comparison of Retinal Imagery

Directions: Select one answer for each question in the exam and completely darken the appropriate circle. A minimum score of 70% is required to earn credit. There is a $35 fee to take this course

Mail to: Optometric CE, PO Box 488, Canal Street Station, New York, NY 10013
COPE approved for 1 hour of CE Credit. Cope ID: 26863-PS.

There is an eight-to-ten week processing time for this exam.

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11. The goal statement was achieved:
○ Very Well ○ Adequately ○ Poorly

12. The information presented was:
○ Very Useful ○ Useful ○ Not Very Useful

13. The difficulty of the course was:
○ Complex ○ Appropriate ○ Basic

14. Your knowledge of the subject was increased:
○ Greatly ○ Somewhat ○ Hardly

15. The quality of the course was:
○ Excellent ○ Fair ○ Poor

How long did it take to complete this course?

Comments on this course:

Topics you would like in the future CE articles:

Please retain a copy for your records. Please print clearly.

You must choose and complete one of the following three identifier types:

① SS # ___ - ___ - ___

Last 4 digits of your SS # and date of birth

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By submitting this answer sheet, I certify that I have read the lesson in its entirety and completed the self-assessment exam personally based on the material presented. I have not obtained the answers to this exam by any fraudulent or improper means.

Signature _____ Date _____

Lesson 106416

RO-UAB-1109

Diabetic Macular Edema: New Solutions to an Old Problem?

By Steven G. Ferrucci, O.D., F.A.A.O.

DIABETIC MACULAR EDEMA (DME) is the most common cause of moderate visual loss in patients with diabetes mellitus. Each year, approximately 75,000 new cases of DME are diagnosed in the United States.[1]

Though DME is a complex and multifactorial disease, a breakdown in the blood-retinal barrier that causes increased accumulation of fluid within the retinal layers of the macula seems to be the likely underlying pathogenesis.[2,3] Other factors associated with the incidence and progression of DME include hyperglycemia, altered blood flow, ischemia and inflammation.[4,5] Furthermore, the frequency of DME increases with the duration and severity of diabetes. In fact, several studies indicate that between 10% and 15% of all patients with diabetes will develop DME during their lifetimes.[6]

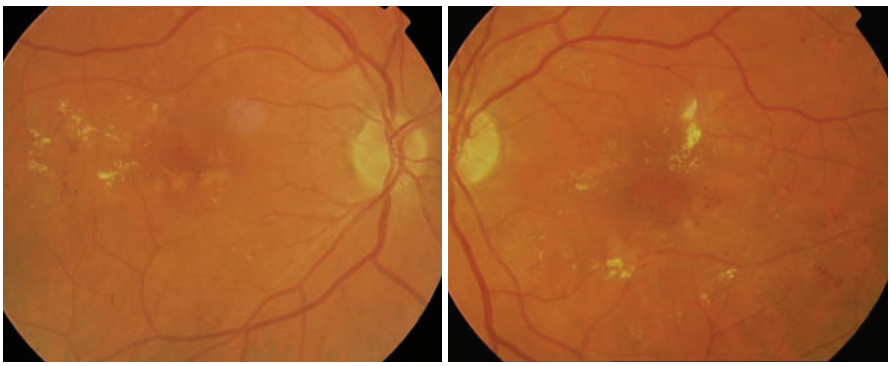
This paper provides an overview of conventional therapies for DME as well as introduces several new, cutting-edge treatment options.

Laser Photocoagulation

Traditionally, laser photocoagulation has been regarded as a gold standard treatment for DME. As documented in the Early Treatment Diabetic Retinopathy Study (ETDRS), macular photocoagulation reduced the three-year risk of moderate visual acuity loss by 50%.[7] However, many participants in ETDRS reported vision loss following photocoagulation. Even more concerning, few participants demonstrated an actual increase in visual acuity.[7]

Additionally, multiple studies of patients with diffuse DME convincingly suggest that patients do not respond well to focal or grid laser photocoagulation. In fact, one such study documented vision improvement in just 15% of treated eyes, stabilization of vision in 61% of eyes, and decreased acuity in 24% of eyes.[8]

So, due to the limitations of macular photocoagulation as well as its untoward side effects (including frequent need for re-treatment, possible central scotomas, and retinal pigment epithelium atrophy and subretinal fibrosis), alternate treatments, such as intravitreal triamcinolone acetonide (IVTA) and anti-vascular endothelial growth factor (VEGF) injections have been explored.



This patient demonstrated a bilateral presentation of diabetic macular edema.

Steroids

• *IVTA.* Corticosteroids are anti-inflammatory agents that suppress activation of the VEGF gene and downregulate its induction. Many studies point to VEGF as a major contributor in the destructive pathway that results in vascular permeability and accumulation of fluid, which ultimately manifests in the retina as DME.[9,10] Thus, corticosteroid use was investigated as a treatment for DME that did not respond to conventional laser treatment.

A preliminary study that evaluated 16 eyes with persistent macular edema demonstrated decreased macular thickness of 55% at one month, 57% at three months and 38% at six months following IVTA injection.[11] Further, mean visual acuity improved by 2.4 Snellen lines at one month, 2.1 lines at three months and 1.3 lines at six months. In another randomized study of 166 patients, 68% of the participants injected with IVTA gained at least two Snellen lines.[12]

Based on these results, many retinal specialists began using IVTA for the treatment of DME; however, more recent studies have questioned its efficacy as a reliable treatment option.[13,14]

The Diabetic Retinopathy Clinical Research Network (DRCR.net) evaluated the efficacy and safety of 1mg and 4mg doses of intravitreal triamcinolone compared with focal grid photocoagulation for the treatment of DME in 840 eyes.[13] At four months, mean visual acuity was best in the 4mg triamcinolone group.

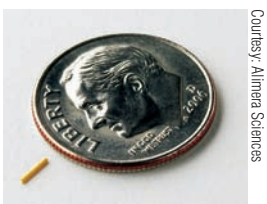
At one year, there were no statistically significant differences in mean visual acuity amongst the groups. But, at the conclusion of the study one year later, the mean visual acuity was better in the laser group than in either triamcinolone group. Most notably, there were substantially more reported complications in the triamcinolone groups, including increased IOP and cataract formation, than in the photocoagulation group.[13] Three-year follow-up data were consistent with these findings, again demonstrating no long-term benefits of triamcinolone over traditional grid or focal laser. Also, 83% of the 4mg triamcinolone group participants required cataract surgery, compared to just 31% of laser group participants.[14]

These results imply that laser photocoagulation should remain the benchmark treatment for DME. Additionally, IVTA use should likely be reserved for those patients with refractory DME that does not respond to laser treatment.

Steroid Implants

• *Illuvien.* Illuvien (Alimera Sciences) is a 3.5mm x 0.37mm flucinolone acetinonide insert that is currently under investigation for the treatment of DME. The implant was designed to administer a low daily dose of corticosteroid to the eye for up to three years. Illuvien is inserted into the posterior vitreous with a 25-gauge needle, which allows for a self-sealing wound.[15] By delivering a low, yet constant, dose of steroid, researchers believe that an anti-inflammatory response can be achieved, while avoiding complications commonly associated with steroids, such as cataract formation.[15,16]

As reported at The Association for Research in Vision and Ophthalmology (ARVO) 2009 Annual Meeting, 37 patients with DME were randomized to either a low-dose (0.23µg/day) or high-dose (0.45µg/day) Illuvien insert group. Results showed an increase in best-corrected visual acuity as well as a reduction in central macular thickness in both groups, but only the low-dose group demonstrated no evidence of IOP increase.[16] At 12-month follow-up, 23.1% of participants in the low-dose group and 27.3% of participants in the high-dose group achieved at least a 15-letter improvement in Snellen acuity. Again, no adverse IOP measurements were recorded in the low-dose group; however, 23.5% of the participants in the high-dose group experienced IOP spikes greater than 30mm Hg.[16]

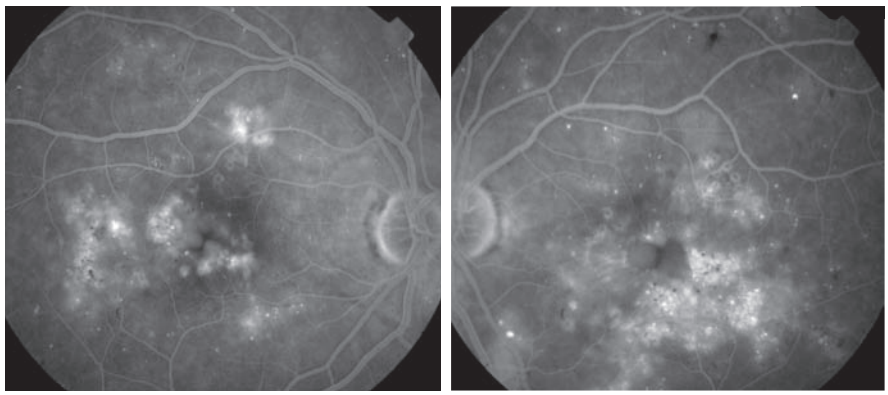


Courtesy Alimera Sciences

The Illuvien insert.

New clinical trials, including the Flucinolone Acetinonide in DME (FAME) study, are currently underway in the U.S., Canada, Europe and India. The first reports regarding safety and efficacy at 24 months are due later this year.

• *Ozurdex.* Another device that may hold some promise is Ozurdex (dexamethasone intravitreal implant, Allergan). This insert, which delivers an extended-release dose of dexamethasone, recently received FDA approval for the treatment of macular edema secondary to branch and central retinal vein occlusion. Phase II and III studies are currently underway to evaluate its efficacy against DME.



Late-phase fluorescein angiography of bilateral diabetic macular edema.

• *Retisert.* Retisert (fluocinolone acetonide, Bausch & Lomb) is also being evaluated for DME and has been FDA-approved for chronic macula edema secondary to uveitis. Phase III trials of 197 patients evaluated the efficacy of Retisert for the treatment of DME vs. standard laser treatment.

At three years, patients implanted with Retisert demonstrated a higher rate of DME resolution (58%) than patients who received laser treatment (30%).[17] Additionally, 28% of patients in the Retisert group achieved an improvement of three Snellen lines or more, compared to just 15% of patients in the laser group.

Still, the improvements did not come without complications. Ninety-five percent of phakic patients who were implanted with Retisert required cataract surgery during a three-year period, and 35% experienced medically uncontrolled IOP that required either implantation removal or a glaucoma-filtering procedure.[17]

While intravitreal steroid implants may hold genuine promise in the fight against DME, further studies are needed to evaluate not only their efficacy, but also their safety.

Anti-VEGF Agents

VEGF is associated with a breakdown of the blood retina barrier and serves as a major mediator of increased retinal permeability. Blockage of VEGF has been shown to reduce vascular permeability in animal studies.[10] Further, high levels of VEGF have been found in the aqueous humor of patients with DME.[9]

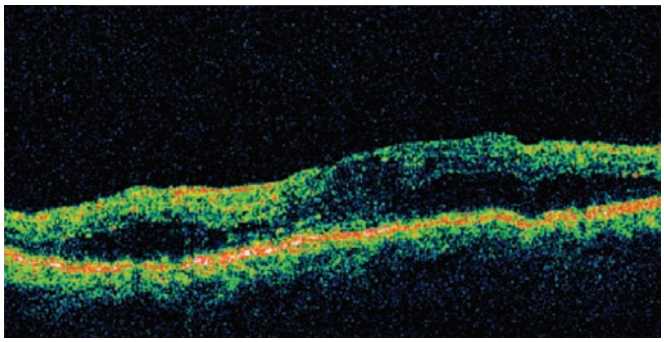
So, the inhibition of VEGF may be a promising treatment for both diabetic retinopathy as well as DME. Several studies that explore the use of intravitreal anti-VEGF agents for DME are currently underway.

• *Macugen.* Macugen (pegaptanib, OSI Pharmaceuticals) is an anti-VEGF aptamer that specifically binds to the VEGF-165 isoform. Intravitreal Macugen is currently FDA-approved for the treatment of neovascular macular degeneration, and is now being examined as an alternative treatment for DME. Results of phase II clinical trials of Macugen have demonstrated a beneficial effect on both visual acuity and retinal thickness in the treatment of DME.[18] Phase III studies are currently underway.

• *Lucentis.* Lucentis (ranibizumab, Genentech) is an anti-VEGF antibody that is currently used to treat choroidal neovascular membranes secondary to age-related macular degeneration. Several anecdotal studies and smaller case reports have praised the agent's success in reducing DME.

One such study evaluated 10 patients with chronic DME who were treated with five 0.5mg intravitreal injections of Lucentis.[19] At seven months, the patients' mean foveal thickness decreased by 85%, and their mean visual acuity improved by 12.3 Snellen letters.

In another study, four of 10 DME patients who received either 1.25mg or 2.5mg injections of Lucentis gained more than three lines of acuity at one month.[20] The patients' mean retinal thickness



Diabetic macular edema, as confirmed by optical coherence tomography.

also decreased significantly during a 24-month period, and ocular side effects consisted of only mild to moderate inflammation.

In December 2006, the Ranibizumab for Edema of the Macula in Diabetes (READ-2) study was initiated.[21] This joint study, co-sponsored by Genentech and the Juvenile Diabetes Research Group, will evaluate the long-term safety and efficacy of intraocular injections of Lucentis in patients with DME. Researchers anticipate the completion of READ-2 in December of 2009.

• *Avastin.* Avastin (bevacizumab, Genentech) is the full-length, humanized anti-body of Lucentis. Though Avastin is only FDA-approved for the treatment of metastatic colon cancer, eye care providers have been using the agent off-label for myriad ocular conditions, including AMD, proliferative diabetic retinopathy, vein occlusion and DME.

A recent study evaluated the effects of Avastin treatment on 139 patients with diffuse DME in 11 centers from eight countries during a 24-month period.[22] At its conclusion, the participants achieved a mean improvement in best-corrected visual acuity as well as a mean decrease in central retinal thickness.

A second study of 121 patients with chronic macula edema who received either photocoagulation or Avastin injection revealed similar results.[23] At one-year follow-up, participants who received Avastin demonstrated a mean improvement of 5.1 Snellen letters as well as a corresponding decrease in mean central retinal thickness.

This study also suggested that early intervention, before ischemia occurs, might yield better results. Several other studies have supported these conclusions.[16,24,25]

Still, large, randomized clinical trials with longer follow-up periods are necessary before the long-term benefits of either Avastin or Lucentis for DME are fully realized.

Many new treatment options are being explored in the fight against DME. Currently, steroid implants and intravitreal injection of anti-VEGF agents hold the greatest promise.

But, additional studies are needed to evaluate the efficacy and safety of these advanced treatments. Until then, however, laser photocoagulation will likely remain the standard of care, and the new and off-label treatments may be reserved for cases of DME that do not respond to conventional therapy or when laser is contraindicated.

Nonetheless, we must familiarize ourselves with emerging DME treatments so we can best preserve the vision of our patients with diabetes for as long as possible. ■

Dr. Ferrucci is chief of optometry and residency director at the Sepulveda VA Ambulatory Care Center & Nursing Home in California. He is also an associate professor at the Southern California College of Optometry.

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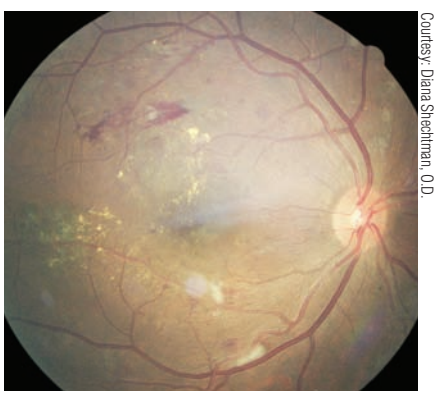

Courtesy: Diana Shechtman, O.D.

Anti-vascular endothelial growth factor (VEGF) therapy might be an effective treatment option for diabetic macular edema, as seen here.

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