Optical coherence tomography for retinal imaging in multiple sclerosis

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Abstract: Visual disturbances caused by inflammatory and demyelinating processes of the visual system, mainly in the optic nerve, are a common symptom in multiple sclerosis (MS). Optical coherence tomography (OCT) is a tool that is increasingly used for quantifying retinal damage in MS and other neurologic diseases. Based on spectral interferometry, it uses low-coherent infrared light to generate high-resolution spatial images of the retina. The retinal nerve fiber layer (RNFL) consists of unmyelinated axons that form the optic nerve, and thus represents a part of the central nervous system. OCT allows for noninvasive measurements of RNFL thickness in micrometer resolution. With the help of OCT, researchers have managed to demonstrate that eyes of MS patients show distinct RNFL thinning after an event of acute optic neuritis in MS, and even subclinical damage in eyes with no previous optic neuritis. OCT is also a useful tool in terms of providing a differential diagnosis of MS toward, for example, neuromyelitis optica, a disease that usually shows stronger retinal thinning, or Susac syndrome, which is characterized by distinct patchy thinning of the inner retinal layers. RNFL thinning is associated with magnetic resonance imaging-derived measurements of the brain, such as whole-brain atrophy, gray and white matter atrophy, and optic radiation damage. These features suggest that OCT-derived retinal measurements are a complement for measuring central nervous system neurodegeneration in the context of clinical trials – for example, with neuroprotective substances.

Keywords: visual function, multiple sclerosis, optic neuritis, retinal nerve fiber layer, neuromyelitis optica, Susac syndrome

Introduction

“Objective”, “easy to perform”, “noninvasive”, “cheap”, and “reproducible” – these are keywords that are used when referring to the application of optical coherence tomography (OCT) as a novel imaging marker for the diagnosis, differential diagnosis, and disease progression in multiple sclerosis (MS), the most common chronic inflammatory disorder of the central nervous system (CNS).¹ But what is really behind it?

Visual disturbances including blurred vision, visual field defects, and color desaturation are frequently occurring symptoms in MS and are assumed to be caused by inflammation in and axonal damage to the optic nerve as part of the CNS.²,³ When exceeding a certain threshold, this scenario may clinically appear as acute optic neuritis (ON). During the course of the disease, acute ON affects 50%–70% of MS patients.²,³ Notably, MS patients consider visual function the second most important body function,⁴ which underscores the considerable impact of visual impairment on patients’ quality of life.
Since its introduction in 1991,\textsuperscript{7} retinal OCT has emerged as a valuable part of the neuroophthalmologic imaging toolbox. It allows for spatial imaging of the retina with micrometer resolution and thus, for example, quantification of the retinal nerve fiber layer (RNFL), which represents the unmyelinated axons of the retinal ganglion cells that converge to the optic disc and form the optic nerve (Figure 1).\textsuperscript{6} In principle, OCT works as an analog to ultrasound imaging, but is based on spectral interferometry.\textsuperscript{7} Infrared low-coherent light from a laser or superluminescent diode is scattered back by the different retinal layers. By analyzing phase differences obtained from an interference pattern with a reference beam, the signal can be mathematically transformed into a depth protocol. Thus, intraretinal thickness estimates can be calculated. Of note, as a general rule, OCT data are derived from different abilities of distinct anatomical structures to reflect light and do not necessarily represent the respective anatomical structures itself.

The first OCT data from MS patients were reported in 1999.\textsuperscript{7} While early OCT studies in MS were performed with comparatively slow third generation time domain (TD)-OCT devices, which focus on the peripapillary RNFL derived from a ring scan and the total macular volume (TMV) of all layers, state-of-the-art fourth generation spectral domain (SD)-OCT devices and algorithms facilitate retinal imaging with enhanced resolution, shorter acquisition times, three-dimensional scans, and video imaging. Also, in the latest SD-OCT devices, eye tracking systems allow accurate repositioning of the scanned area, thus providing conditions for detecting even subtle changes in the range of a few micrometers in follow-up measurements. The most important advantage of SD-OCT is that it allows for intraretinal segmentation, which means that the different retinal layers can now be differentiated and measured individually (Figure 2). Thus, besides the RNFL, the bordering ganglion cell layer (GCL), often combined with the inner plexiform layer (GCIPL), became an important outcome parameter in OCT studies in MS.\textsuperscript{9-14} Importantly, comparative studies with different OCT devices revealed that data generated by TD-OCT and SD-OCT are not interchangeable.\textsuperscript{15} Thus, the technique used for acquisition should be considered when interpreting data.

The examination is noninvasive; OCT devices are – comparatively – affordable, and examinations can be performed within a few minutes. Given these features, OCT has emerged into a valuable imaging method for the detection and longitudinal monitoring of neuroaxonal pathology in MS and other diseases with a neurodegenerative component. Importantly, typical OCT findings in MS, namely RNFL reduction and GCL thinning, were also the most prominent pathological changes observed in a postmortem histological investigation of the retinas of MS patients, which thereby corroborates the validity of the OCT technique.\textsuperscript{16} Against this background, OCT is on the rise to becoming a standard outcome parameter in observational and interventional trials in MS.

The aim of this review is to briefly summarize current OCT findings in MS and ON, its role for differential diagnosis, and its suitability as an outcome parameter in clinical trials.

**Retinal damage in MS following ON**

Acute ON is the presenting symptom in 15%–20% of MS patients and occurs in up to 70% of patients during the course of the disease.\textsuperscript{2,3} For decades, temporal paling and atrophy of the optic disc was considered a characteristic morphological consequence of ON. Accordingly, numerous OCT studies consistently found that ON leads to significant thinning of the RNFL (Figure 3).\textsuperscript{17-26} According to a meta-analysis of cross-sectional TD-OCT studies that included more than 2,000 individual eyes from MS patients with a previous episode of ON,\textsuperscript{27} a mean RNFL reduction of approximately 20 μm can be expected after ON, which corresponds to a 20% loss in RNFL thickness. The favorite explanation for this observation is the retrograde degeneration of retinal axons that

**Figure 1 OCT-derived cross-sectional images of the retina.**

Notes: (A) A line scan through the fovea centralis and the optic nerve head. The left image shows the fundus image, which is acquired simultaneously to the OCT image. The orange line indicates the location of the cross-section. The right image is the respective retinal OCT scan. (B) The retinal nerve fiber layer thickness is usually acquired by a peripapillary ring scan. Image analysis provides the thickness values for the overall ring, but also for the sectors.

Abbreviations: NS, nasal-superior; N, nasal; NL, nasal-inferior; TI, temporal-inferior; T, temporal; TS, temporal-superior; OCT, optical coherence tomography.
have been damaged by an inflammatory attack to the optic nerve. More recently, the course of RNFL reduction in the context of acute ON has been evaluated in more detail using SD-OCT. After initial swelling due to edema in the acute phase of ON, RNFL thickness decreased over the following 6 months. Intraretinal segmentation demonstrated that GCIPL also decreased significantly after ON. Of note, initial swelling was restricted to RNFL, suggesting that the changes in the GCIPL are the more reliable parameter for longitudinal monitoring of ON-related retinal damage.

Retinal damage in MS without ON

While RNFL reduction after an episode of ON is not surprising, RNFL reduction was consistently observed in MS patients who had never had a clinical episode of ON, as well as in the clinically unaffected fellow eye of patients with a history of ON (Figure 3). Accordingly, the meta-analysis of cross-sectional TD-OCT studies mentioned in the “Retinal damage in MS following ON” section reported a mean RNFL reduction of approximately 7 µm in more than 3,100 eyes of MS patients without ON. We recently performed a large multicenter SD-OCT study including 414 MS patients and 94 healthy control subjects, with the objective of describing retinal findings in MS, while focusing on the influence of an ON and differences in MS subgroups. The study revealed that even in the absence of ON, the RNFL is about 10 µm thinner when compared to that of healthy controls. MS patients with a secondary progressive disease course were more severely affected than patients with relapsing–remitting...
MS; moreover, patients with primary progressive MS who, by definition, do not develop acute ON, also showed RNFL thinning. In contrast to earlier TD-OCT-derived data, which failed to demonstrate RNFL reduction in patients with clinically isolated syndrome (CIS) suggestive of early MS, a more recent SD-OCT study showed GCL thinning in a cohort of CIS patients without a history of ON and with normal visual evoked potential (VEP) latencies. These data indicate that degeneration of retinal neurons occurs very early in the course of the disease and independent of ON. While a plethora of cross-sectional OCT studies in MS exist, high-quality longitudinal data are rather sparse. According to a TD-OCT study that monitored RNFL changes in MS patients at 6-month intervals over a period of up to 4.5 years, progressive RNFL thinning occurred even in the absence of ON as a function of time with a mean annualized decrease of 1–2 µm. A similar decrease in RNFL and GCIPL thickness was recently reported in an SD-OCT study on 92 MS patients over a median follow-up period of 1 year. In contrast, a smaller longitudinal SD-OCT study failed to detect a significant change over time in a mixed cohort of patients with relapsing–remitting and secondary progressive MS. Thus, longitudinal SD-OCT data still await confirmation in a sufficiently large cohort of well-characterized MS patients over a sufficiently long period of time. In comparison, the natural course of RNFL thinning in a healthy population ranges from around 0.1–0.5 µm per year.

How can the development of retinal damage in MS patients without a concomitant or previous ON be explained? In fact, there is a lively ongoing scientific debate about this phenomenon. Currently, three favorite hypotheses are discussed, which are not mutually exclusive. The first explanation refers to a subclinical “smoldering” ON that structurally impacts the optic nerve but does not manifest as clinically apparent ON. Consequently, retrograde axonal damage results in RNFL thinning, and GCL reduction can be explained by the “dying back” of retinal ganglion cells. Another hypothesis is focused on the concept of retrograde transsynaptic degeneration of the retinal axons and neurons, respectively, which was already suggested in the 1960s. MS lesions within the posterior part of the visual pathway affect axons of the optic radiation, which leads to retrograde degeneration of second-level neurons in the lateral geniculate nucleus and then, by crossing the synapse, transsynaptically to the degeneration of the optic tract and optic nerve, respectively. This model is supported by several combined OCT and magnetic resonance imaging (MRI) studies, which are discussed later in this review. The third approach to explain subclinical retinal damage in MS is being discussed controversially and refers to a primary retinal pathology in MS in which retinal neurons are the primary target of a neurodegenerative process.

**Retinal changes in MS beyond axonal and neuronal damage**

In addition to the RNFL and GCIPL, other retinal layers may be affected in MS, although data are less clear. Changes in the inner nuclear layer (INL) revealed new insight on MS-related retinal damage: Gelfand et al reported findings of macular microcysts in the INL in 5%–6% of all MS patients’ eyes. Appearance of macular microcysts is illustrated in Figure 4. MS patients suffering from macular microcysts tended to have reduced RNFL and GCIPL, more severely impaired visual function, and worse MS disease severity scores. Several studies from other centers confirmed these results and researchers suggested that macular microcysts are a consequence of retinal ganglion cell degeneration comprising inflammatory components. Macular microcysts in MS appear to be dynamic in their extent, suggesting a

![Figure 4 Macular microcysts in a patient with recurrent optic neuritis.](image)
dependency on the acute inflammatory status of the optic nerve.\textsuperscript{42,44} It was also reported that macular microcysts are not exclusive to MS, but they also occur in other neuroinflammatory conditions such as neuromyelitis optica (NMO) and chronic relapsing inflammatory optic neuropathy, and that macular microcysts in those diseases are generally associated with ON.\textsuperscript{41,42,44} However, macular microcysts are not specific to neuroinflammatory diseases, as a comprehensive report on the complete clinical spectrum of macular microcysts has revealed.\textsuperscript{45} Similar findings have also been shown in hereditary optic neuropathy, including Leber hereditary optic neuropathy and glaucoma,\textsuperscript{46–48} pointing to vitreous traction and schisis of the INL as an alternative cause for macular microcysts.\textsuperscript{49} In our own database, none of nine patients with neuroinflammatory diseases and macular microcysts showed any signs of vitreous traction, which clearly argues against vitreous traction as a causative factor in macular microcysts.\textsuperscript{44} Detection of macular microcysts was the first evidence that neuroinflammatory disorders do not only lead to a loss of retinal axons and ganglion cells, but also to visible structural damage in further retinal layers. Even in the absence of visible macular microcysts, thickening of the INL occurs in eyes with a history of ON, which is also in correlation to gadolinium-enhancing T2-hyperintense lesions on cranial MRI, disability, and relapse rate, indicating that the INL might be a site of swelling due to acute inflammatory processes.\textsuperscript{42,43} While the INL was repeatedly shown to be a dynamic parameter for abnormalities in MS, results for the involvement of the outer retinal layers – namely, the outer plexiform layer, outer nuclear layer, and photoreceptor layer – are inconsistent. In a subgroup of MS patients with suspected primary retinal thinning named “macula thinning predominant” with normal RNFL but abnormal TMV, a reduction of these outer layers was found in comparison to healthy controls.\textsuperscript{10} However, while a similar finding was reported from a second United States cohort,\textsuperscript{40} we could not confirm the existence of this subtype in our own database.\textsuperscript{40}

**Relationship between structural retinal changes and visual function**

Visual impairment is one of the most prevalent symptoms of MS and compromises the health-related quality of life in MS patients.\textsuperscript{41,51,52} Interestingly, OCT-determined retinal disintegration correlates with the quality of life in MS patients.\textsuperscript{51} This suggests that OCT-detectable retinal damage translates into gaugeable visual dysfunction, indicating the morphological changes that we can detect by OCT are clinically relevant. Indeed, several publications describe a relation of retinal axonal or ganglion cell loss to visual function.\textsuperscript{26,31,54} In terms of visual acuity, low-contrast visual acuity determined at 1.25% and 2.5% contrast levels using low-contrast visual acuity (Sloan) charts or functional acuity contrast testing showed a stronger association with RNFL/GCL thinning than did high-contrast tests using Snellen or Early Treatment Diabetic Retinopathy Study (ETDRS) charts.\textsuperscript{53–55} Also, color vision determined by pseudoisochromatic Hardy–Rand–Rittler plates or the Lanthony D15 desaturated tests was found to be impaired in MS and is associated with RNFL thinning.\textsuperscript{56}

One widespread method to test optic nerve function include the use of VEP recorded from the visual cortex. The amplitude and latency after a visual stimulus allow for conclusions to be made on the integrity of the optic pathway. Several publications investigated whether OCT or VEP is the more sensitive tool in evaluating optic nerve damage in MS.\textsuperscript{57–59} VEP tended to be more sensitive in detecting eyes with a previous ON, whereas OCT is more objective in obtaining the subtle shades of degeneration. In consequence, the two methods are considered complementary because each represents different aspects of the pathology. RNFL thickness was also shown to correlate with visual field deficits after ON.\textsuperscript{40} A more recent technique to characterize visual function is multifocal VEP, which detects abnormalities in smaller areas using numerous stimulations presented in one measurement. In a cohort of CIS patients it was able to detect focal abnormalities even in the absence of ON.\textsuperscript{61}

As a general rule, OCT examinations should always be accompanied by a comprehensive visual function test to give an overall picture of the patient’s visual impairment.\textsuperscript{62}

**Relationship between OCT and brain atrophy**

A frequently used slogan in neurology-related OCT research is “OCT – a window to the brain?” and occasionally, provocative claims to substitute MRI by cheaper, faster, and easier-to-perform OCT are made. In 2007, the first study investigating the relationship between OCT measurements and brain atrophy showed a significant association between RNFL thickness and brain parenchymal fraction, an MRI-derived measure of brain atrophy.\textsuperscript{63} These data suggested that neurodegeneration in the brain is reflected by retinal axonal breakdown and were the starting shot for the evaluation of the capacity of OCT-based measures as surrogate markers for global neurodegeneration in MS and, subsequently, other neurodegenerative disorders.\textsuperscript{64–66} Several subsequent
TD-OCT-based publications confirmed a relationship between different MRI measurements of brain atrophy and RNFL thickness in MS patients, yet the studies varied in terms of their methods and patient cohorts.\textsuperscript{19,22,67,68} Also, an association between RNFL thickness and axonal damage in the visual cortex, as determined by magnetic resonance spectroscopy, was shown.\textsuperscript{69} While some studies\textsuperscript{60,67} focused mainly on global brain atrophy as a more robust measure of overall brain neurodegeneration, which integrates volume changes in both gray and white matter irrespective of the underlying cause, few of these early studies addressed the correlations between retinal axonal damage and gray or white matter atrophy separately.\textsuperscript{19,22,68} However, data remained inconsistent, probably as a consequence of different cohort characteristics and methodological restrictions.\textsuperscript{22,68} Results from more recent SD-OCT studies are inconsistent as well. While some researchers reported good correlations for OCT measurements with white matter atrophy (but not or less so for gray matter), others found a relationship of RNFL and GCIPL thickness with cortical gray matter volume.\textsuperscript{70–72} Furthermore, a negative correlation of INL thickness and white matter volume was reported.\textsuperscript{70} One important confounder that impacts the correlation between OCT and MRI measures of neurodegeneration is a patient’s history of ON.\textsuperscript{72} An event of ON may inflict substantial damage to the optic nerve and inner retinal layers, respectively, which is not necessarily accompanied by equivalent damage to the brain parenchyma, thereby especially disrupting the association with gray matter measurements.\textsuperscript{72} How can the quite consistently observed associations between retinal and brain damage, at least in MS eyes without an ON history, be explained? Obviously, a more global primary or secondary degenerative process that affects the whole CNS including the retina may be an explanation. Strong support for the concept of retrograde transsynaptic degeneration discussed earlier comes from a recent combined OCT and ultrahigh field MRI study, which showed a significant correlation between both thinning of the optic radiation and lesion volume within the optic radiation with RNFL reduction.\textsuperscript{72} Transsynaptic degeneration may not only occur in a retrograde direction, but it may also occur bidirectionally.\textsuperscript{38} Anterograde degeneration in the form of Wallerian degeneration following ON can transsynaptically proceed beyond the lateral geniculate nucleus via the optic radiation to the visual cortex.\textsuperscript{74,75} In summary, OCT and MRI provide differential and largely complementary information. Thus, for the time being, OCT should be viewed as an additional complementary outcome parameter instead of an alternative to MRI.

**OCT in the diagnosis and differential diagnosis of MS**

Currently, the use of OCT in the diagnosis of MS is not clearly established, and outside MS centers and clinical trials, OCT clearly still plays a subordinated role. Nevertheless, as visual dysfunction caused by inflammation or axonal damage of the optic nerve is not unique for MS – and given that it may also occur in other neuroophthalmologic disorders often misdiagnosed as MS\textsuperscript{62} – a tool to differentiate diseases on the basis of characteristic morphological retinal changes would be helpful. Indeed, several OCT studies demonstrated a capability of OCT to differentiate between retinal damage attributable to MS–ON and other neuroophthalmologic differential diagnoses, as different entities show different patterns of retinal pathology. Two important differential diagnoses of MS in which OCT has been shown to be helpful in terms of differential diagnosis, namely neuromyelitis optica spectrum disorders (NMOSD) and Susac syndrome (SuS), are exemplarily discussed in the following paragraphs.

Both NMOSD and MS are neuroinflammatory diseases with acute ON as a characteristic or even crucial manifestation.\textsuperscript{76,77} But while ON is usually unilateral in MS and is often characterized by a good prognosis,\textsuperscript{4} ON in NMOSD frequently presents bilaterally and even simultaneously. Visual impairment is often more severe and the risk of recurrence is higher.\textsuperscript{78} Several studies investigated whether different OCT patterns exist in NMOSD and MS patients. A major finding of most studies, including our own investigation of 17 patients with MS and NMOSD, respectively,\textsuperscript{79} is that RNFL reduction after ON is more pronounced in NMO than in MS (55–83 µm versus 74–95 µm, respectively).\textsuperscript{11,21,79–83} Likewise, the GCIPL is more severely affected.\textsuperscript{11,79} However, other studies failed to detect a difference in RNFL thickness between MS and NMOSD.\textsuperscript{84,85} The strong visual impairment in NMO is thought to result from a certain threshold of neuroaxonal loss, from which retinal neurons and axons no longer have the ability to sufficiently maintain visual function. Furthermore, macular microcysts occur at a higher frequency in NMOSD–ON than MS–ON (21% versus 5%, respectively), indicating a stronger presence of inflammatory processes.\textsuperscript{42,79,86} This is in line with the increased INL thickness reported in NMOSD after ON in comparison to MS.\textsuperscript{79} Interestingly, OCT results of NMOSD eyes not affected by a clinically reported ON show no or only slight differences in comparison to healthy control subjects,\textsuperscript{11,21,79,81,85} which might be indicative of either (or both) lesser diffuse direct optic nerve damage in NMOSD when compared to MS, or less pronounced retrograde transsynaptic degeneration as a...
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Conclusion and future perspectives

OCT and, in particular, the up-to-date SD-OCT technique provide detailed information at high resolution regarding the thickness, and thus structural integrity, of the different retinal layers. Given that within the retina, axons of the retinal ganglion cells are not myelinated, axonal damage can be directly quantified, rendering OCT an excellent tool to evaluate neuroaxonal damage in vivo. OCT certainly provides only limited added value in the diagnostic workup of straightforward cases. But, as different diseases may show distinct patterns of retinal pathology, OCT may be helpful in the differential diagnostic workup in difficult situations. Most importantly, in the context of MS, it is now well established that at least in the absence of ON, retinal neuroaxonal degeneration determined by OCT reflects global neurodegeneration in the CNS, suggesting OCT parameters – in particular, RNFL and GCIPL – as surrogates for measuring CNS neurodegeneration. However, the appropriateness of OCT as part of the routine monitoring of MS patients is currently controversially discussed. Moreover, the high inter- and intrapatient reproducibility of OCT data facilitates follow-up monitoring of neurodegeneration and provides a rationale for the use of OCT as an outcome parameter in clinical trials in general and in particular those addressing neurodegeneration or evaluating the neuroprotective capacity of new drugs. Indeed, an increasing number of observational and interventional studies already included changes in RNFL as secondary endpoint. An important observation that limits the use of OCT in MS research is that the correlation between retinal and CNS neurodegeneration often tends to decrease or even vanish in the context of ON, which can be explained by the dramatic impact of ON on the inner retinal layers. However, there are no longitudinal data available to substantiate the influence of ON on the relationship of retinal thinning and brain atrophy. Thus, the history of ON or acute ON in a patient enrolled in a clinical trial is a major confounder that needs to be carefully addressed. Less affected by this limitation are trials in patients with acute ON, in which OCT parameters are excellent endpoints for the evaluation of neuroprotective substances. Recently, Sühs et al were the first to use RNFL reduction in the first 16 weeks after an acute ON as the primary endpoint in an interventional randomized controlled Phase II clinical trial, and

Figure 5 Distinct patterns of macular volume loss in a patient with Susac syndrome.

Notes: (A) Retinal thickness map and OCT scan of a Susac syndrome patient. The color-coded thickness map shows a patchy thinning, mainly in the 9–12 o’clock hour sectors. The corresponding OCT image shows that the inner retinal layers have almost vanished in the respective area. For comparison, (B) the retinal thickness map and corresponding OCT scan of a healthy subject. (C) The retinal thickness map and OCT of a multiple sclerosis patient with previous optic neuritis showing severe but equally distributed retinal thinning.

Abbreviation: OCT, optical coherence tomography.

consequence of less severe affection of the posterior visual pathway in NMOSD.

SuS is a rare condition characterized by encephalopathy, visual disturbances, and hearing loss, which are caused by probable autoimmune-mediated occlusions of small vessels in the brain, retina, and inner ear, respectively. Despite the completely different pathophysiology of visual involvement in SuS and MS, the phenotype of visual impairment in SuS may resemble that of ON. In combination with clinically and radiologically evident CNS involvement, and taking into account that young women are predominantly affected both by SuS and MS, it is not surprising that patients with SuS are often misdiagnosed as having MS. Recently, a TD-OCT study comparing retinal morphology in nine SuS patients and MS patients with or without previous ON revealed distinct patterns of retinal damage in SuS and MS. All three groups showed a reduction of average RNFL thickness and TMV. However, while in MS retinal layer damage is evenly distributed over all sectors of the macula, in SuS patients, a characteristically patchy retinal thinning in certain sectors was observed, reflecting the vascular origin of the pathology. However, there were no specific retinal areas that were predominantly affected. Currently, studies using SD-OCT in SuS are underway and will provide further information on the predominantly affected retinal layers. While damage is mainly restricted to RNFL and GCIPL in MS, the architecture of the blood supply in the retina also suggests that deeper layers are involved in SuS (Figure 5).
they showed that a 3-day course of erythropoietin in addition to methylprednisolone was superior to placebo in preventing RNFL thinning after ON. Remarkably, a sample size of 40 individuals per arm was sufficient to detect a significant difference.102 Further studies with OCT parameters as primary or secondary endpoints are under way.

Disclosure

The authors report no conflicts of interest in this work.

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