·Review·

Optical coherence tomography for assessment of diabetic macular edema

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Abstract

• Optical coherence tomography (OCT) is a noninvasive objective diagnostic technique that has become a powerful method for the clinical assessment of diabetic macular edema. It is a very useful imaging technique to diagnose and follow-up diabetic macular edema (DME). The present paper aims to present an overview of the principles, progress, and uses of OCT in the diagnosis and management of DME.

• KEYWORDS: diabetic macular edema; optical coherence tomography; interferometry; volumetric optical coherence tomography

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INTRODUCTION

Diabetic retinopathy (DR) is one of the leading causes of blindness in the working-age population of most developed countries. Macular edema is the major cause of visual loss in patients with DR. The incidences of diabetic macular edema (DME) over the 10-year period are 20.1% in the younger-onset group, 25.4% in the older-onset group taking insulin and 13.9% in the older-onset group not taking insulin[1].

The treatment of DME is evolving. Currently, the standard of care is the use of photocoagulation for clinically significant macular edema (CSME) as defined by the ETDRS protocol. The standard clinical method for determining the need for focal laser photocoagulation in DME is the subjective assessment of the presence or absence of macular thickening by slit-lamp fundus stereo biomicroscopy [2]. Objective assessments of DME, such as optical coherence tomography (OCT) or retinal thickness analysis, are beginning to displace the conventional subjective methods, but the conventional methods still predominate in the more developed world and, especially, in the less developed [3,4]. With the noninvasive objective diagnostic techniques, we can determine how accurate the clinical assessment of DME is and follow changes in DME over time.

PRINCIPLES AND PROGRESS OF OCT

Since its introduction in the early 1990s, OCT has become a powerful method for imaging the internal structure of biological systems and materials. OCT is based on the principle of Michelson interferometry [5]. Low-coherence infrared light coupled to a fiberoptic travels to a beam-splitter and is directed through the ocular media to the retina and to a reference mirror, respectively. Light passing through the eye is reflected by structures in different retinal tissue layers. The distance between the beam-splitter and reference mirror is continuously varied. When the distance between the light source and retinal tissue is equal to the distance between the light source and reference mirror, the reflected light from the retinal tissue and reference mirror interact to produce an interference pattern. The interference pattern is detected and then processed into a signal. The signal is analogous to that obtained by A-scan ultrasonography using light as a source rather than sound. A two-dimensional image is built as the light source is moved across the retina[6]. The resulting data set is a two-dimensional array that represents the optical backscattering or reflection within a cross-sectional slice of the retina. These data can be digitally filtered, processed and displayed as a two-dimensional gray-scale or false-color image.

OCT was transferred to industry in 1993 and the first-generation instrument (OCT 1) was introduced to the ophthalmic marketplace by Carl Zeiss Meditec in 1996. A second-generation instrument (OCT 2) was introduced in 2000. The instrument was then re-engineered to achieve a fourfold increase in imaging speed and a third-generation instrument (Stratus OCT or OCT 3) was introduced in 2002[7]. The axial resolution of an OCT image depends on the coherence length of the light and is independent of beam focusing conditions and numerical aperture. The transverse resolution for OCT imaging is determined by the focused spot size, as in microscopy. Because OCT uses interferometry, it performs optical heterodyne detection, and extremely high

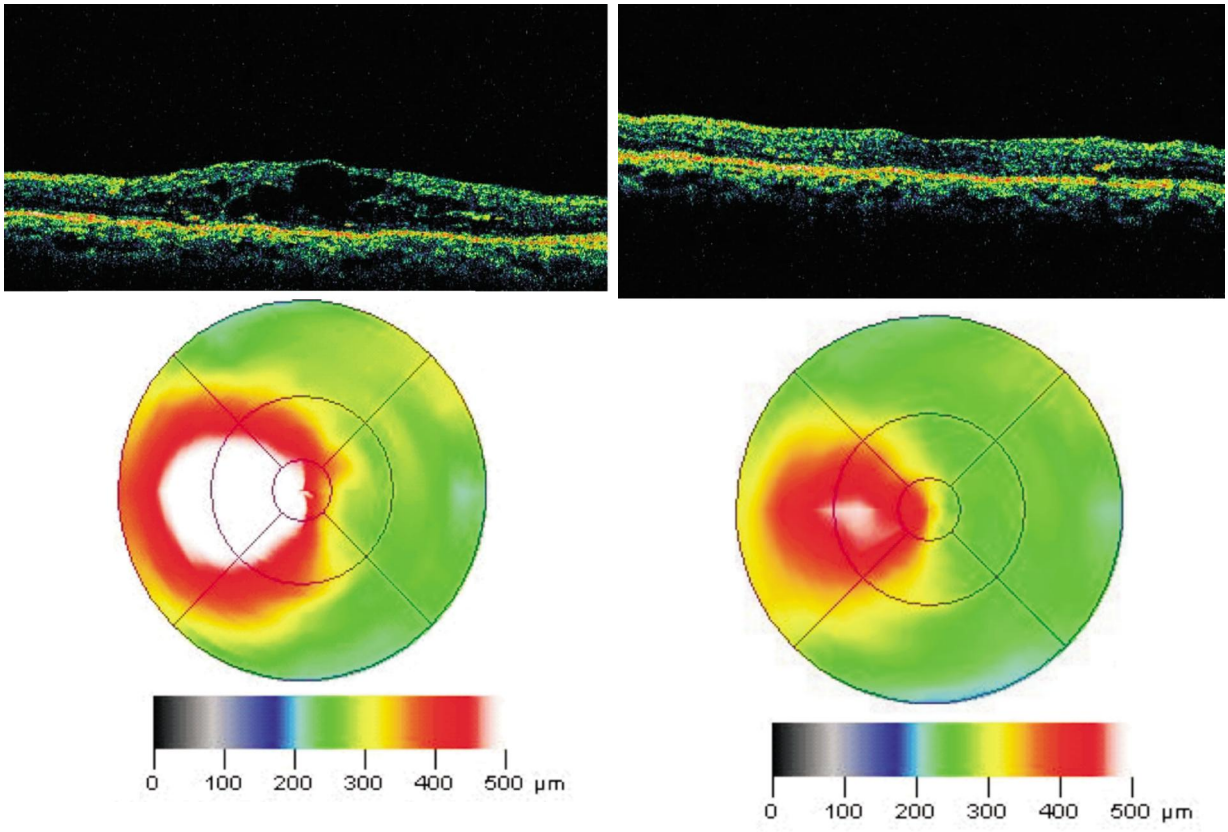

Figure 1 Optical coherence tomography can follow diabetic macular edema over time. (Left) Cross-sectional and the retinal surface map images show macular edema. The retina is protruding with prominent cystoid macular edema (CME). (Right) One month after intravitreal triamcinolone acetonide therapy, CME has resolved

sensitivities, near the quantum limit, are possible [8]. OCT 1 and OCT 2 have axial resolutions of 12μm to 15μm, while OCT 3 has a theoretical resolution ≤10μm. Current ophthalmic OCT scanners use a low coherence superluminescent diode source (820nm). On the OCT scanners, highly reflective structures are shown with bright colors (red and white), low reflective ones are displayed by darker colors (black and blue), and intermediate reflective ones appear green.

OCT for the diagnosis and management of diabetic macular edema OCT is an emerging biomedical imaging technique that generates high-resolution and cross-sectional tomographic imaging of tissue microstructure *in situ* and in real time (Figure 1)[7]. In eyes with diabetic macular edema, varying patterns are observed.

PATTERNS OF DME WITH OCT

OCT discloses that DME includes three basic structural changes: retinal swelling, cystoid macular edema, serous retinal detachment, or a combination of these patterns[9]. The retina is a compact tissue composed of neural element and glial cells [10]. Extracellular space is virtually absent because glial cells occupy all the interneural space. According to the histopathologic report in autopsy eyes with retinal edema, retinal swelling initiated the intracytoplasmic swelling of Müller cells. Sponge-like swellings in the OCT image may represent intracytoplasmic swelling of Müller cells and are observed as diffuse thickening of neurosensory retina. If retinal edema persists, liquefaction necrosis of the Müller cells ensues. Necrosis of the Müller cells and adjacent neural cells leads to cystoid cavity formation of the retina. By OCT, cystoid macular edema is seen as intraretinal cystoid spaces located not only in the outer plexiform layer but also in the inner plexiform and granular layers and even in the ganglion cell layer. DME associated with a serous retinal detachment is clearly demonstrated as a line of high reflectivity that is attached to the retinal pigment epithelium in the peripheral margin of the subretinal lenticular space. This reflective border may help the observer to differentiate the serous retinal detachment from tissue swelling. Hard exudates, composed mainly of lipid and proteinaceous material, which mainly precipitate in the outer plexiform layer, appear as spots of high reflectivity with low reflective areas behind them. However, in eyes with a serous retinal detachment, hard exudates tend to deposit not only in the retina but also in the subretinal space which are observed as highly reflective plaques adhering to the retinal pigment epithelium. No space is seen between the subretinal hard exudates and the retinal pigment epithelium[9,11-14].

Quantitative Assessment of Retinal Thickness in DME Using Volumetric Optical Coherence Tomography Another feature of OCT is the capability to measure the thickness of the central retina quantitatively, thus making it potentially of great value for the clinical assessment of macular edema in diabetic retinopathy and other diseases. The term "volumetric optical coherence tomography (VOCT)" has been coined to describe the method to quantify retinal thickness throughout the macula [6]. Using available software on the OCT 3, the retinal thickness map (RTM) scan mode and analysis function, or the fast retinal thickness map (FRTM) scan mode and analysis function is used to get a volumetric optical coherence tomogram. In each eye, six radiating cross-sectional B scans of 6mm, matching the size of the grid used for assessing retinal thickening by stereo fundus photographs, are obtained, with the center of each scan being the center of the fovea. (Figure 2) The retinal map algorithm uses measurements along six radial lines to produce a circular plot in which the foveal zone is the central circular zone of 1.00mm in diameter. Superior, nasal, inferior and temporal parafoveal zones represent annular bands in these respective sectors. The boundaries of the circular zones are inner circular zone, 1.00mm; middle circular zone, 3.00mm; outer circular zone, 6.00mm. The 9 VOCT zones are similar to zones in analysis of photographs by ETDRS graders [3]. The retinal thickness, defined as the length between inner retinal surface and retinal pigment epithelium, is measured by the computer from the tomograms. The measured thickness of the 3 tomograms in the same ring in the given quadrant is averaged to represent the retinal thickness in the corresponding area. The images of OCT are displayed in a false-color scale whereby retinal thickness at each point is represented by a different color. Bright colors (for example, red and white) represent thick areas, and dark colors (for example, blue and black) represent thin areas. Intermediate thickness areas are displayed as green and yellow. During the VOCT examination, internal fixation is used as possible, but external fixation is used occasionally if the vision is too poor for fixation in the scanned eye [6, 15]. The two OCT scan modes, standard and fast macular mapping, deliver almost the same results. Scan acquisition time is reduced from 1.28s for each of the six scans in the standard mode to less than 1.92s total examination time for all scans together in the fast mode, in which scans are acquired almost simultaneously. This reduction in examination time may improve accuracy and increase centration of the scans, especially important for patients with a central fixation disability. However, in borderline cases, fast mode results should be verified by standard mode measurements [16]. By VOCT, it may be helpful to quantify macular edema, and to assess retinal thickness changes in response to medical or surgical therapy.

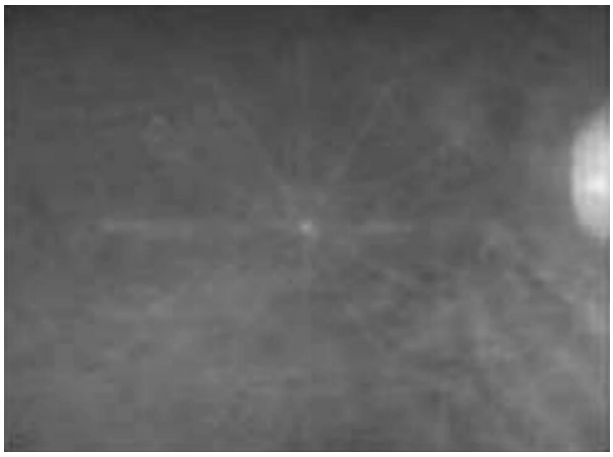

Figure 2 The fast retinal thickness map (FRTM) scan mode and analysis function is used to get a volumetric optical coherence tomogram. In each eye, six radiating cross-sectional B scans of 6mm, matching the size of the grid used for assessing retinal thickening by stereo fundus photographs, are obtained, with the center of each scan being the center of the fovea

Comparison with other Techniques DME has usually been assessed by stereo-fundus photographs and fluorescein angiography. Fluorescein angiography can demonstrate pathophysiologic aspects of retinal diseases, such as leakage from breakdown of the outer and inner blood-retina barrier with consecutive retinal swelling. As in stereo-fundus photographs, unlike OCT, quantification of the pathologic findings in the macula is difficult and imprecise. Furthermore, evaluation of stereo-fundus photographs and fluorescein angiograms is subject to a intra-and interobserver variability [16,17]. However, fluorescein angiography can provide information about the retinal leakage sites, and retinal vascular abnormalities, while fundus photography may demonstrate subtle macular lesions not seen by OCT or clinical examination [6]. Macular edema determined by OCT correlates well with visual acuity, and with leakage determined by fluorescein angiography [3,18-21]. Retinal thickening determined by stereo fundus photography also correlates well with increased retinal thickness measured by OCT [22]. The combined data from OCT, fluorescein angiography and stereo fundus photography may provide a clearer understanding of the anatomic and physiologic characteristics of diabetic macular edema. OCT, the Heidelberg Retina Tomograph (HRT) and the retinal thickness analyzer (RTA) are all objective diagnostic tools for quantitative assessment of the macula. The HRT may be more effective than OCT and RTA to image the outer retina in the presence of retinal hemorrhage and hard exudates[23]. But in HRT, the examiner may have difficulty identifying the fovea by its structure or by retinal thickness. Subretinal lesions such as retinal pigment epithelium detachments or neovascular membranes cannot be demonstrated by HRT.

Another limitation is that HRT gives results as dimensionless values, which may not reflect the anatomic reality and are not directly comparable to other methods. The retinal thickness measurements obtained by both OCT and HRT significantly correlate with visual acuity. They can differentiate between eyes with or without macular edema, with OCT showing a higher predictive value[16]. The RTA is a rapid screening instrument that generates a detailed map of retinal thickness. The major advantage of the RTA is the option to scan a relatively wide area of the retina in a short acquisition time. There is a high degree of correlation between retinal thickness obtained by OCT and that measured by RTA [24-28]. RTA may be more sensitive than OCT to detect macular thickening for patients with very early diabetic retinopathy without clinically significant macular edema. However, RTA may yield a larger number of falsely elevated retinal thickness measurements, and produces retinal images less effectively than OCT in eyes with media opacity[26, 27, 29].

SUMMARY AND FUTURE DIRECTIONS

In summary, OCT is a useful imaging technique to diagnose and manage DME. The retinal thickness measurements obtained by OCT significantly correlate with visual acuity and those produced by other methods. In the future, more functional variables, such as visual acuity, contrast sensitivity, reading speed, age- and race-specific normative data, will be needed to develop comprehensive evidence-based measurement. The comparison with other techniques, such as RTA, HRT, SLO and FAG, needs additional researches. Its usage in clinical practice requires more clinical experiences and longitudinal studies.

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