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Macular Edema
A Practical Approach

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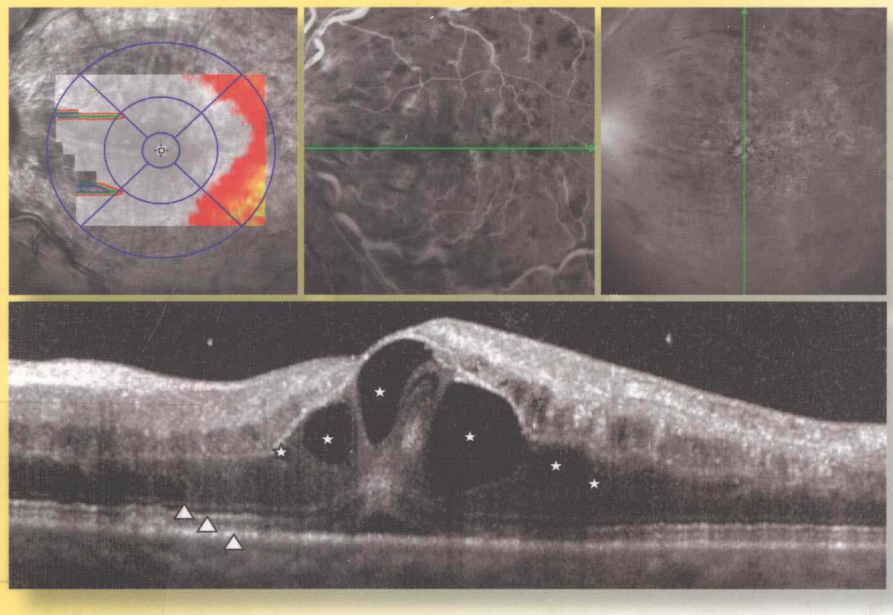

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A Practical Approach

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Preface

Macular edema has for a long time been one of the most important issues in retinal pathologies, as damage to the macula has an immediate effect on central visual acuity and may substantially affect a patient's quality of life.

For more than 40 years, clinicians have attempted to identify macular edema in its initial state and to define its various etiologies. Diagnosing macular edema with certitude at an early stage has proven difficult despite the progress in contact lens biomicroscopy.

Fluorescein angiography has been critical for detecting macular edema and currently remains the 'gold standard' for the diagnosis, identifying the characteristic stellar pattern of cystoid macular edema. Fluorescein angiography also provides a qualitative assessment of vascular leakage, which is essential for identifying treatable lesions. However, it is only since the use of laser photocoagulation that it became possible to offer an effective modality of treatment for macular edema, despite the destructive localized laser scars.

During the last decade, the clinical diagnosis of macular edema and its treatment have been greatly improved due to multiple and remarkable advances of modern imaging technologies, which allow recognition of the main etiologies of this complication. By correlating results from fluorescein angiography, optical coherence tomography, and especially spectral domain optical coherence tomography, fluid accumulation within and under the sensory retina can be confirmed and located. This fluid accumulation, frequently associated with subretinal fluid and serous retinal detachment, may not otherwise be clinically detected.

Moreover, spectral domain optical coherence tomography can characterize the presence and integrity of the external limiting membrane and the photoreceptor inner and outer segments, which is useful information for prognosis as well as a guide for treatment. The diagnosis of macular edema and its clinical forms is now based primarily on the correlation of these imaging techniques.

One of the most important innovations in the field of macular edema has been the advent of intravitreal drug delivery approaches for the treatment of posterior segment pathologies. These emerging modalities treat posterior eye disease or restore the permeability of the blood-retinal barrier by delivering drug compounds either systemically, locally, or intravitreally with anti-inflammatory or anti-vascular endothelial growth factor drugs.

Multicenter controlled clinical trials testing these new compounds as well as biologic delivery

systems and treatment strategies have already been completed or are currently under way. From this research, the care of macular edema will soon be more efficient and effective due to increased target specificity, noninvasive drug administration routes, and sustained-release compounds that will allow sufficient levels of therapeutic efficacy for longer durations.

Macular Edema: A Practical Approach describes the different patterns and etiologies of macular edema and the importance of preserving the photoreceptors at the early stage in order to retain central visual acuity. The book was designed to bring together the most recent data and evidence-based medicine while also including the multiple areas still unknown and debated.

Macular Edema: A Practical Approach presents the pathophysiological basis of macular edema and the different approaches of drug delivery to the posterior segment. Recommendations for treatment procedures or different therapies have been carefully analyzed and considered prior to inclusion.

The authors bring their personal experience and full teaching acumen to each chapter, culminating in a single book that brings to the forefront the importance of macular edema.

Macular Edema: A Practical Approach provides the ophthalmologist with a synthesis of knowledge to diagnose, determines the etiology, and offers viable treatment options for the benefit of all our patients.

Gabriel Coscas

Contents

Coscas G (ed): Macular Edema.
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Macular Edema: Definition and Basic Concepts

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Abstract

Macular edema is the result of an accumulation of fluid in the retinal layers around the fovea. It contributes to vision loss by altering the functional cell relationship in the retina and promoting an inflammatory reparative response. Macular edema may be intracellular or extracellular. Intracellular accumulation of fluid, also called cytotoxic edema, is an alteration of the cellular ionic distribution. Extracellular accumulation of fluid, which is more frequent and clinically more relevant, is directly associated with an alteration of the blood-retinal barrier (BRB). The following parameters are relevant for clinical evaluation of macular edema: extent of the macular edema (i.e., the area that shows increased retinal thickness); distribution of the edema in the macular area (i.e., focal versus diffuse macular edema); central foveal involvement (central area 500 μm); fluorescein leakage (evidence of alteration of the BRB or 'open barrier') and intraretinal cysts; signs of ischemia (broken perifoveolar capillary arcade and/or areas of capillary closure); presence or absence of vitreous traction; increase in retinal thickness and cysts in the retina (inner or outer), and chronicity of the edema (i.e., time elapsed since initial diagnosis and response to therapy). It is essential to establish associations and correlations of all the different images obtained, regardless of whether the same or different modalities are used.

Macular edema is the result of an accumulation of fluid in the retinal layers around the fovea. It contributes to vision loss by altering the functional cell relationship in the retina and promoting an inflammatory reparative response.

Macular edema is a *nonspecific sign of ocular disease* and not a specific entity. It should be viewed as a special and clinically relevant type of macular response to an altered retinal environment. In most cases, it is associated with an alteration of the blood-retinal barrier (BRB).

Macular edema may occur in a wide variety of ocular situations including uveitis, trauma, intraocular surgery, vascular retinopathies, vitreoretinal adhesions, hereditary dystrophies, diabetes, and age-related macular degeneration.

The *histopathological picture* of this condition is an accumulation of fluid in the outer plexiform (Henle's) and inner nuclear and plexiform layers of the retina (fig. 1). The increase in water content of the retinal tissue characterizing macular edema may be *intracellular* or *extracellular*. Intracellular accumulation of fluid, also called cytotoxic edema, is an alteration of the cellular ionic distribution. Extracellular accumulation of fluid, which is more frequent and clinically more relevant, is directly associated with an alteration of the BRB.

Intracellular Edema

Intracellular edema in the retina may occur when there is an intact BRB and the retinal cells are swollen due to an alteration of the cellular ionic

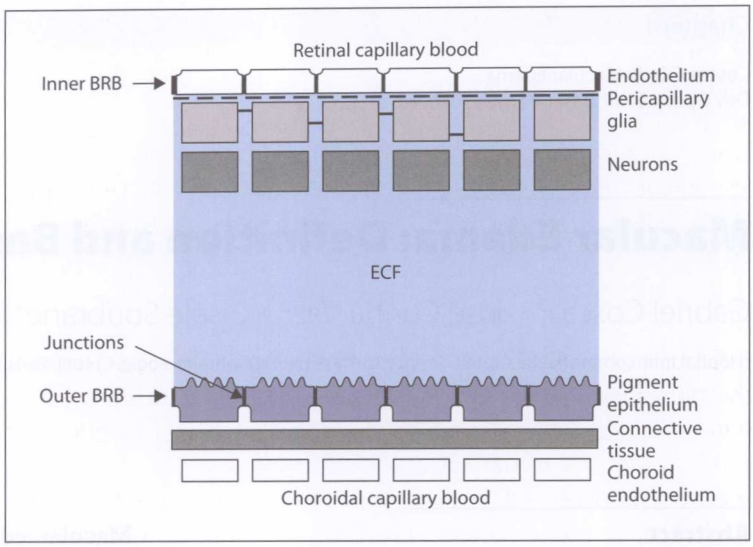

Fig. 1. Schematic presentation of the inner and outer BRBs and their relative location. ECF = Extracellular fluid.

distribution, resulting in excessive accumulation of sodium ions (Na^+) inside the cells.

This is known as cytotoxic edema. It may be induced by accumulation of excitatory neurotransmitters, such as glutamate, or excessive accumulation of lactic acid, or it may be the immediate result of *ischemia*, trauma, or toxic cell damage.

Extracellular Edema

Extracellular edema is directly associated with an open BRB (i.e., it is caused by a breakdown of the inner or outer BRB). The increase in tissue volume is due to an increase in the retinal extracellular space. Breakdown of the BRB is identified by *fluorescein leakage*, which can be detected in a clinical environment by fluorescein angiography (FA) or vitreous fluorometry measurements. Starling's law[a], which governs the movements of fluids, applies in this type of edema (Cunha-Vaz et al., 1984)[1].

After a breakdown of the BRB, the progression of retinal edema depends directly on the hydrostatic pressure difference (ΔP) and osmotic pressure difference ($\Delta\pi$) gradients. In these conditions, tissue compliance becomes more important, directly influencing the rate of edema progression. Thus, in the presence of retinal edema, it is essential to recognize whether the edema has arisen due to an intact or open BRB.

[a] Starling's law: In extracellular edema, the 'force' driving water across the capillary wall is the result of a hydrostatic pressure difference (ΔP) and an effective osmotic pressure difference ($\Delta\pi$). The equation regulating fluid movements across the BRB is: driving force = L_p [($P_{plasma} - P_{tissue}$) – σ ($\pi_{plasma} - \pi_{tissue}$)], where L_p is the membrane permeability of the BRB; σ is an osmotic reflection coefficient; P_{plasma} is blood pressure, and P_{tissue} is the retinal tissue osmotic pressure. An increase in ΔP, contributing to retinal edema, may be due to an increase in P_{plasma} and/or a decrease in P_{tissue}. An increase in P_{plasma} due to increased systemic blood pressure contributes to retinal edema formation only after loss of autoregulation of retinal blood flow and alteration of the characteristics of the BRB. A decrease in P_{tissue} is an important component that has previously not been given sufficient attention. Any loss in the cohesiveness of the retinal tissue due to pathologies, such as cyst formation, vitreous traction, or pulling at the inner limiting membrane, will lead to a decrease in P_{tissue}.

A decrease in P_{tissue} (i.e., increased retinal tissue compliance) may lead to fluid accumulation, edema formation, and an increase in retinal thickness. A decrease in $\Delta\pi$ contributing to retinal edema may occur due to increased protein accumulation in the retina after breakdown of the BRB. Extravasation of proteins will draw more water into the retina. This is the main factor provoking a decrease in $\Delta\pi$, as a reduction in plasma osmolarity high enough to contribute to edema formation is an extremely rare event.

BRB breakdown leading to macular edema may be mediated by locally released cytokines, and it induces an inflammatory reparative response creating the conditions for further release of cytokines and growth factors. The BRB cells, retinal endothelial cells, and retinal pigment epithelium (RPE) cells are both the target and producer of eicosanoids, growth factors, and cytokines.

Macular edema is one of the most serious consequences of inflammation in the retinal tissue. Inflammatory cells can alter the permeability of the tight junctions that maintain the inner and outer BRB. Cell migration may occur primarily through splitting of the junctional complexes or through the formation of channels or pores across the junctional complexes.

Clinical Evaluation of Macular Edema

The clinical evaluation of macular edema has been difficult to characterize, but evaluation has become more precise with the help of modern imaging such as FA and optical coherence tomography (OCT).

The following parameters are relevant for clinical evaluation of macular edema: extent of the macular edema (i.e., the area that shows increased retinal thickness); distribution of the edema in the macular area (i.e., focal versus diffuse macular edema); central fovea involvement (central area 500 μm); fluorescein leakage (evidence of alteration of BRB or 'open barrier') and intraretinal cysts; signs of ischemia (broken perifoveolar capillary arcade and/or areas of capillary closure); presence or absence of vitreous traction; increase in retinal thickness and cysts in the retina (inner or outer), and chronicity of the edema (i.e., time elapsed since first diagnosis and response to therapy).

Direct and Indirect Ophthalmoscopy

Direct and indirect ophthalmoscopy may show only an alteration of the foveal reflexes. Slit lamp biomicroscopy and stereoscopic fundus photography have played an important role in demonstrating changes in retinal volume in the macular area, but they are dependent on the observer's experience, and the results do not offer a reproducible measurement of the volume change (Gonzalez et al., 1995)[2].

The Early Treatment Diabetic Retinopathy Study specified the following characteristics as indicating clinically significant macular edema: (1) thickening of the retina (as seen by slit lamp biomicroscopy or stereoscopic fundus photography) at or within 500 μm of the center of the macula; (2) hard exudates at or within 500 μm of the center of the macula associated with thickening of the adjacent retina (but not residual hard exudates remaining after disappearance of retinal thickening), and (3) a zone or zones of retinal thickening 1 disk in area or larger in size, any part of which is within 1 disk diameter of the center of the macula. This definition of macular edema specifically takes into consideration the involvement of the center of the macula and its relationship to visual loss.

Fluorescein Angiography

FA documents if there is fluorescein leakage, which in turn determines whether a barrier is classified as open or intact. Clinical use of FA has contributed significantly to the present understanding of retinal disease, and it is considered the 'gold standard'.

The dye used in FA is sodium fluorescein, a small molecule that diffuses freely through the choriocapillaris and Bruch's membrane but does not diffuse through the tight junctions of the retinal endothelial cells and the RPE, which are the inner and outer BRBs. Understanding these barriers is the key to understanding and interpreting a fluorescein angiogram (Cunha-Vaz et al., 1984)[1].

FA also fundamentally contributes to our understanding of vascular retinopathy. FA will help for the identification of areas of capillary leakage and/or capillary closure or capillary dropout. Capillary closure and fluorescein leakage were first clinically identified with FA, and they are accepted as the

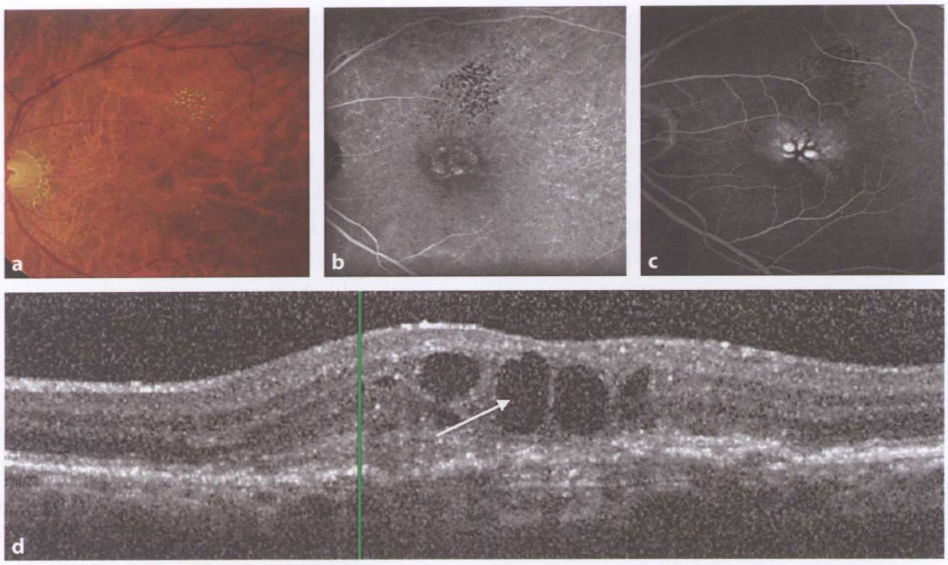

Fig. 2. CME. **a** Color photo. **b, c** FA (early and late stage); capillary dilation and leakage; fluorescein dye pools in cystoid spaces located in the outer plexiform layer (Henle's layer) and arranged radially from the fovea. **d** Spectral domain OCT (Spectralis): typical image of cystoid spaces. OCT imaging allows precise analysis of large cystoid spaces, and their location, the extent of an area of increased thickness, and the extent of the involvement of the central macula are essential in determining the presence of macular edema. Moreover, the analysis of the outer retinal layers could give valuable prognostic indications.

determinant alterations occurring in the diabetic retina, retinal vein occlusion, and other retinal vasculopathies identifying the progression of retinopathy (Kohner et al., 1970; Coscas et al., 1978)[3,4].

Intravenous injection of sodium fluorescein is generally safe and easy to perform. It is routinely used in ophthalmological clinics despite severe anaphylactic reactions that may occur on rare occasions (1 in 200,000) (Yannuzzi et al., 1986)[5].

FA is an indispensable imaging tool in determining the definitive diagnosis of macular edema (Gass, 1997)[6]. The angiographic definition distinguishes between noncystoid and cystoid macular edema (CME) (Richard et al., 1998)[7].

The noncystoid form of macular edema is characterized by diffuse abnormal permeability of the retinal capillary bed with diffuse leakage and intraretinal fluid accumulation that has not accumulated in cystoid spaces but may still do so in the later course of the disease. It is displayed as a diffusely outlined and ill-delimited area of hyperfluorescence.

In CME, early capillary dilation and leakage can be detected. In the late phase of the angiogram, fluorescein pools in cystoid spaces located in the outer plexiform layer (Henle's layer) displayed as the classic petaloid staining pattern (Guyer et al., 1999)[8]. These cystoid spaces are usually arranged radially from the fovea (fig. 2). In long-standing CME, the cystoid spaces enlarge and may merge, representing irreversible damage of the retina.

The extent of dye leakage alone does not completely correlate with functional damage and visual acuity. Duration of the edema and associated changes (RPE and the degree of ischemia) must also be taken into account.

Presence or predominance of the ischemic component needs to be analyzed with the help of FA and must be considered when signs of capillary dropout predominate in the central macular area.

Fundus imaging using *indocyanine green dye*, particularly with the scanning laser, may provide additional direct signs for macular edema but also for the precise analysis of RPE alterations and for the detection and delimitation of cystoid spaces progressively filled with the dye. Analogous to the Rosetta Stone, the key to interpretation is correlation of the data acquired from the different imaging systems.

Optical Coherence Tomography

OCT provides images of retinal structures that could not previously be obtained by any other noninvasive, noncontact, transpupillary diagnostic method. OCT allows assessment and detection of subretinal and intraretinal fluid related to changes in the inner and outer BRBs and abnormal exudation from the retinal capillary bed.

OCT provides anteroposterior images by measuring the echo time and intensity of reflected or backscattered light from intraretinal microstructures. These anteroposterior 2-dimensional or B-scan images (analogous to those of ultrasound) were demonstrated for the first time in 1991 by Huang (Huang et al., 1991)[9] and in the human retina in 1993 by Fercher (Fercher et al., 1993)[10] and Swanson (Swanson et al., 1993)[11]. These optical scans are based on the principle of low-coherence light interferometry (Puliafito et al., 1995; Schuman et al., 2004)[12,13].

Schematically, in conventional (time domain) OCT, the light beam emitted by a superluminescent diode is split into two beams by a beam splitter: an incident beam enters the ocular media and is reflected by the various layers of the fundus, while the other beam is reflected by a reference mirror. Displacement of the mirror placed on the path of the reference light beam allows analysis of structures situated at various depths during each light echo acquisition, forming an A-scan. The time necessary for this scanning and for the acquisition of these sections is the essential determinant of the quality of the signal, hence the name time domain OCT (TD-OCT).

Spectral-Domain OCT (SD-OCT), a method based on the famous Fourier transform mathematical equation (1807), eliminates the need for a moving mirror in the path of the reference beam, which allows for much more rapid image acquisition and provides excellent resolution (axial resolution of <10 μm). This property enables spectral domain SD-OCT systems to capture a large number of high-resolution images: 50 times faster than standard time domain OCT and 100 times faster than the first ultrahigh-resolution OCT. As the examination can be performed simultaneously in various planes, real high-speed 3-dimensional reconstructions can be obtained with hundreds of images per second.

Rapid scanning allows an increased number and density of scans of the retina to be obtained in a very short time, with a marked reduction of artifacts related to patient movements (eye and respiratory movements) during the examination. The use of image processing systems based on *real-time averaging* reduces the signal-to-noise ratio and increases image definition and image quality.

OCT has rapidly become a noninvasive optical imaging modality for medical diagnosis in ophthalmology, allowing in vivo visualization of the internal microstructures of the retina on these sections and evaluation of variations of *retinal thickness*. Images are obtained in 2 or 3 dimensions and represent variations of these reflections (and backscatter) of light either in a plane of section or in a volume of tissue. This anteroposterior dimension of OCT provides a spectacular complement to angiographic data.

OCT scans can visualize exudative reactions with fluid accumulation (intraretinal and/or subretinal). Comparative quantitative evaluation of these images during the course of the disease is particularly useful. OCT may allow discovery at a stage often difficult to assess by other imaging methods, considerably enhancing the ability to

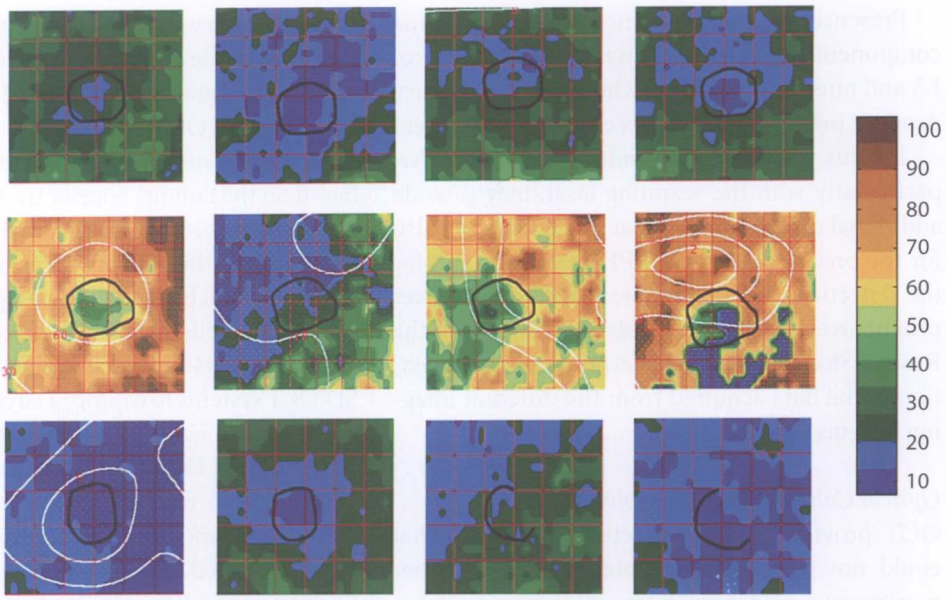

Fig. 3. Multimodal images from 3 patients (rows 1, 2, and 3) from visits 0, 12, 24, and 36 months showing the foveal avascular zone contour, retinal leakage analyzer results, and retinal thickness analyzer results. The retinal leakage analyzer color-coded maps of the BRB permeability indexes are shown. Retinal thickness analyzer views show white dot density maps of the percentage increases in retinal thickness. Patterns a, b, and c are shown on rows 1, 2, and 3, respectively.

diagnose and follow macular edema. Assessment and mapping of retinal thickness with the time domain OCT-3 Stratus has been the standard for many years and has been used in clinical studies.

After introduction of new spectral domain OCT (SD-OCT) instruments, studies have been published comparing retinal thickness measurements. These studies have demonstrated that retinal thickness measurements are dependent on the segmentation of the inner and outer retinal borders. The new spectral domain OCT systems image the outer retinal layers as 3 hyper-reflective bands: the external limiting membrane, the junction (or interface) of the photoreceptor outer and inner segments, and the RPE.

The *outer layers of the retina* can now be analyzed due to these recent technological progresses allowing high-definition, high-speed volume imaging. This allows analysis of structural changes particularly affecting photoreceptors and the IS/OS interface, thereby providing functional information on these tissues. The possibility of integrated structural imaging and functional imaging will play an increasingly important role in clinical applications (Coscas, 2009)[14].

Real-time images of the microscopic retinal tissues have been termed 'optical biopsy' and closely reflect histological sections of the macula and fovea.

Increasingly, they resemble a real anatomical representation, especially with the development of ultrahigh-resolution techniques and the upcoming combination with adaptive optics (Soubrane, 2009)[15].

In macular edema, the process begins with diffuse swelling of the outer retinal layers, advancing

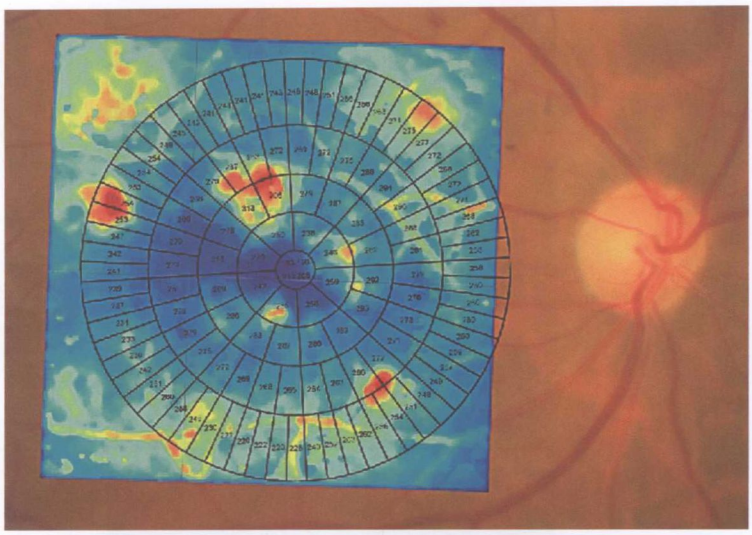

Fig. 4. Multimodal image composed of a color photograph of the eye fundus (morphology reference), a color-coded leakage map (BRB functional information), and a map of retinal thickness with average values for the earmarked areas. This image allows simultaneous correlation of both leakage and thickness in the eye fundus.

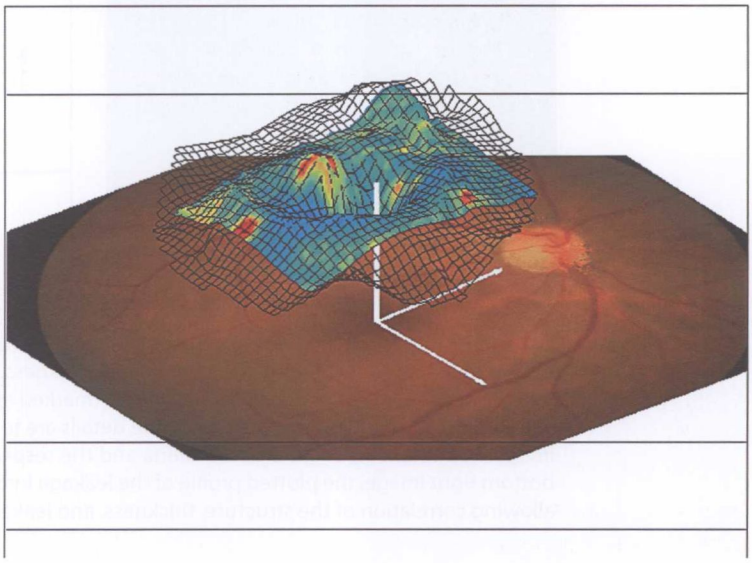

Fig. 5. The same information presented in figure 2 is now shown 3-dimensionally. The differences in the information presented is significant. Although the shape of the thickness is now clear, it occurs at the expense of having fewer details on the leakage itself and the location of both the thickness and leakage within the macular area.

to the typical image of cystoid spaces. Later, the large cystoid spaces can extend from the RPE to the internal limiting membrane and even rupture, causing macular holes. Hence, OCT is becoming a very efficient tool for following the distribution, evolution, and location of macular edema.

The extent of an area of increased thickness and the involvement of the central macula are essential to describe a clinical case of macular edema and predict visual loss. The presence of cysts and vitreous traction are particularly well documented using OCT. The analysis of the outer

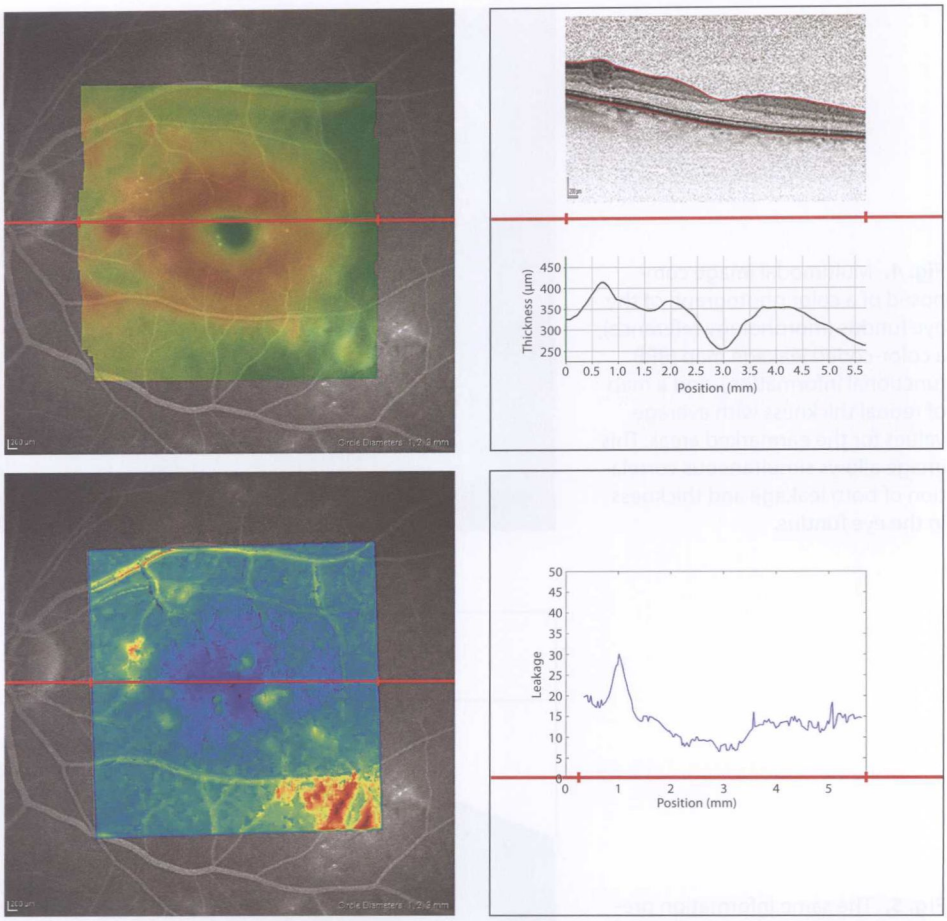

Fig. 6. This new approach on the representation of a multimodal imaging system integrates the fundus reference (left column), the color-coded thickness, and leakage maps (left column, top and bottom rows, respectively). A selected location (marked as a red horizontal line on the left column images) allows choosing the location where details are to be shown on the right. On the top right image, the detailed structure of the retina and the respective thickness profile is shown. On the bottom right image, the plotted profile of the leakage information for the same location is shown, allowing correlation of the structure, thickness, and leakage at the local level.

retinal layers may provide valuable prognostic indications (fig. 2).

To *establish a correlation between different images*, either from the same or from different modalities, it is essential to associate and to correlate them all. Multimodal macula mapping, for example, uses a variety of diagnostic tools and techniques to obtain additional information (fig. 3–6) (Lobo et al., 2004; Bernardes et al., 2002; Cunha-Vaz, 2006)[16–18].

Spectral domain OCT facilitates correlations with clinical data, angiographies, and functional investigations.

These imaging techniques are essential to guide the indications for current treatment and to assess the response to treatment.