Shedding new light on diabetic retinopathy with optical coherence tomography

van Dijk, H.W.

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Chapter 1

General introduction
General introduction

The retina enables the conversion of incoming light into a neural signal that is suitable for further processing in the visual cortex of the brain. As its function requires the retina to receive light from the outside world, the ocular structures - cornea, lens, vitreous - have to be optically transparent for optimal image formation. In reverse, this implies, that with proper techniques, the retina is also visible from the outside, making the retinal tissue accessible for imaging noninvasively. Retinal imaging has developed rapidly during the last 160 years and is a mainstay of the clinical care and management of patients with retinal as well as systemic diseases.1

Optical Coherence Tomography

In 1991, optical coherence tomography (OCT) was first described by Fujimoto and co-workers.2 The OCT technology has since then become a diagnostic imaging technique with a wide spectrum of clinical applications, including the eye, the gastrointestinal tract, pancreatico-biliary ductal system, in dermatology, and in cardiology. OCT enables the real-time, in situ visualization of tissue microstructure without the need to excise and process specimens as in conventional biopsy and histopathology.3, 4 In 1995, OCT was introduced as a non-invasive, non-contact, high resolution optical imaging technique to image structures in the eye such as the retina, cornea, choroid, and the optic nerve and has since then found increasingly widespread use in ophthalmic practice. In vivo, cross-sectional and three dimensional imaging of diseases of optic nerve and the retinal diseases and the ease with which these images can be acquired have changed the diagnostic strategies used by ophthalmologists dramatically.5, 6

OCT generates cross-sectional and three dimensional images of the retina by measuring echo time delay of back scattered light. Backscattering of light is typically caused by differences in refractive index in transitions from one tissue to another. The backscattering of light from deeper tissue can be differentiated from backscattering from more superficial tissues because it takes longer to arrive at the sensor. The speed of light is however to high (3*10^8 m/s) to measure delays in time directly. Therefore OCT is based on a technique called interferometry. In interferometry, the time delay from light reflected from inside the tissue is measured by correlating it with light that has traveled a known reference path. The basic setup consist of a low coherence light source, and a beam splitter to split the light into two beams and a detector. The light is split in a beam that illuminates the retina and which reflection represents the sample arm and a beam that is reflected by a reference mirror, the reference arm. The reflected light of both arms is recombined and will interfere at the detector, but only when the optical path lengths of both the sample arm and the reference arm are matched within the coherence length of the light source. The correlation of the sample and the reference arm reflected light – the interferogram – is highest
when the distance from the light source to the interferometer is the same for both arms. The amplitude of the interferogram is measured using a photo sensor, CCD or a CMOS sensor. By moving the reference mirror over a range of positions, multiple amplitudes are measured, each showing the amount of reflected light at a different, but known (the position of the mirror) position. Because it takes time to move the mirror to different positions, this is called time domain OCT (Stratus). The multiple amplitudes at different depths are known as an A-scan, using ultrasound terminology. To obtain 2-D slices of the retina, called B-scans, the scanning beam is moved to different positions over the retina in a linear or circular fashion, each time measuring multiple amplitudes at different depths. For 3-D imaging the scanning beam is moved across the retina to obtain an A-scan for each X and Y location resulting in a tomographic image. OCT imaging is limited by the amount of time it takes to image an A-scan. For the studies described in this thesis we used two different OCT principles, namely time-domain OCT (TD-OCT) and spectral-domain OCT (SD-OCT) (see figure 1). TD-OCT is relatively slow as compared to the later developed SD-OCT.\(^2,3\)

![Figure 1. Schematic diagram of OCT, with emphasis on splitting of the light, overlapping train of labeled bursts based on their autocorrelogram, and their interference after being reflected from retinal tissue as well as from the reference mirror (assuming the time delays of both paths are equal).](image-url)
SD-OCT is the same setup of a light source, a reference- and sample arm, but in contrast to TD-OCT the reference mirror is fixed, and a broadband low coherence light source is used. This time the depth information is encoded in the spectral signature of the light, i.e. each depth is measured by a slightly different wavelength (color), requiring a spectrometer and an inverse Fourier transform to create the A-scan. Because the mirror is stationary and all the backscatter at different depths can be measured simultaneously, the SD-OCT is faster compared to the TD-OCT. TD-OCT systems, commercially available as Stratus OCT (Carl Zeiss Meditec, Inc, Dublin, CA) featured scan rates of 400 A-scans per second with an axial resolution of 8–10 μm in tissue. In 2006, the first commercially available SD-OCT system was introduced. This technique achieves scan rates of 20000–52000 A-scans per second and a resolution of 5–7 μm in tissue. In clinical practice TD-OCT has been overtaken by SD-OCT because of its major advances in imaging speed, sensitivity and image resolution. With the exception of the study described in chapter 3 and the longitudinal study described in chapter 8, we have used SD-OCT in all studies on which we will report in the following chapters.

Diabetic Retinopathy

Many important eye diseases as well as systemic diseases manifest themselves in the retina. One of the systemic diseases that manifests in the retina is diabetes mellitus. Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action, or both, giving rise to risk of microvascular damage (retinopathy, nephropathy, cardiomyopathy, encephalopathy, and neuropathy). Diabetes mellitus, according to the current definition from the World Health Organization, is typically diagnosed if a patient has a fasting plasma glucose over 7.0 mmol/l or 2-h plasma glucose over 11.1mmol/l after a 75 g oral intake of a glucose load in the glucose tolerance test. Recent estimates indicate there were 382 million people in the world with diabetes in the year 2013 and this is projected to increase considerably by 2030. Treatment is primarily through diet changes, administration of insulin and/or anti-hyperglycemic drugs.

One of the retinal diseases in which OCT is of high diagnostic value is diabetic retinopathy (DR) and in particular diabetic macular edema (DME). DME is the most frequent cause of vision loss related to diabetes. DME is characterized by retinal thickening, hemorrhages, hard exudates and capillary microaneurysms. The fundamental treatment for DME involves strict glycemic and blood pressure control, which was demonstrated by the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study. Since the early eighties laser treatment has been the mainstay treatment option for clinically significant macular edema (CSME) after the recommendations by the Early Treatment Diabetic Retinopathy Studies (ETDRS) demonstrating a 50% reduction in moderate visual loss following focal laser photocoagulation. The ETDRS defined DME as
being “clinically significant” based upon the distribution and extent of retinal thickening and the presence of hard exudates (see Table 1).16

<table>
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<tr>
<th>Table 1. Definition of clinically significant macular edema</th>
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<td>1) Retinal thickening involving or within 500 µm of the center of the macula.</td>
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<tr>
<td>2) Hard exudates at, or within, 500 µm of the fovea, if associated with an area of retinal thickening</td>
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<tr>
<td>3) A zone or zones of retinal thickening one disc area or larger in size, any part of which is within one disc diameter of the centre of the macula</td>
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In the ETDRS, photocoagulation treatment was directed at all discrete points of retinal hyperfluorescence, focal leakage, areas of diffuse leakage and thickened retinal avascular zones identified by ophthalmoscopic examination and/or fluorescein angiography (FA) within 2 disc diameters of the center of the macula if they were associated with retinal thickening. A variety of other therapies have been studied with the aim of improving vision in more patients as well as preventing deterioration of visual acuity in most. These include surgical options, intravitreal corticosteroids and intravitreal vascular endothelial growth factor (VEGF) inhibitors.17 Surgical intervention is reserved for a minority of patients with vitreo-retinal interface pathology readily detectable with OCT. Within the last 5 years, the use of intravitreal anti-vascular endothelial growth factor (VEGF) agents, and to a lesser extend intravitreal corticosteroids have come into clinical practice for the management of DME, and several recent randomized clinical trials have shown improved effectiveness of anti-VEGF drugs compared to focal/grid laser.18, 19 The fact that often visual loss caused by CSME can be prevented through pharmacological interventions, laser, or in some cases surgical treatment, places great importance on the proper detection of patients with DME. OCT enables evaluation of the macular contour and intra- and sub-retinal fluid collections, and allows objective and accurate measurement of retinal thickness.5, 11 OCT can be used in addition to stereoscopic biomicroscopy to determine the location of DME. Chapter 2 will address the difference in threshold and dosage of photocoagulation treatment for DME when OCT is used to judge retinal thickening instead of clinical biomicroscopy.

**Diabetic retinal neurodegeneration**

Diabetic retinopathy (DR) is one of the leading causes of blindness in developed countries.20 The clinically visible onset of DR with micro-aneurysms, capillary non-perfusion, hemorrhages and/or lipoprotein exudates has led to the assumption that DR is primarily a microvascular disease. The clinical classification system for diabetic retinopathy is based on structural changes to the retinal microvasculature due to the fact that the microvasculature is visible during ophthalmoscopy, but the neuroretina is transparent.21 Thus, changes to the neuroretina in diabetic retinopathy were not recognized until the 1960s when Wolter and Bloodworth identified degenerating neurons in the retinas of post-
Since that time, there is increasing evidence of early retinal neurodegeneration in diabetes. Neuronal degeneration and early retinal dysfunction have been observed in various animal models of diabetes and in humans before the onset of diabetic vasculopathy. With optical coherence tomography (OCT), it became possible to image the human retina in vivo, and to measure the retinal thickness (RT) with high accuracy. Several groups have shown that RT is decreased in diabetes patients with no or minimal DR, compared to normal controls. As the inner retinal layers are affected differentially by diabetes it is desirable to quantify thickness of the separate layers within the retina. Fully automated algorithms have been reported for the segmentation of retinal time-domain and spectral-domain OCT scans that are capable of detecting up to 11 surface boundaries in the retina, based on differences in refractive index resulting in differences in scattering of light.

The intraretinal layers that can be identified were interpreted as follows (from the inner to outer surface): retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL)+inner segment photoreceptors (IS), outer segment photoreceptors (OS) and retinal pigment epithelium (RPE) (see Figure 2). In Chapters 3, 4 and 5 we describe studies investigating the question whether diabetes preferentially affects specific retinal layers, by means of comparing the thickness of the retinal layers in diabetic patients with no or minimal DR to those of age- and gender-matched normal controls.

The retinal neuropathy observed in diabetic patients at the structural levels is corroborated by previous functional studies showing neuroretinal functional deficits in diabetes, even before the onset of visible vascular lesions, including electroretinogram
abnormalities, loss of dark adaptation and contrast sensitivity, color vision disturbances, and abnormal microperimetry. Conventional threshold perimetry and visual function tests are relatively insensitive measures of minor neuro-visual damage. The Rarebit technique was developed by Frisen and co-workers to improve detection of localised subtle visual field defects. The Rarebit technique avoids simultaneous stimulation of more than one receptive field at once, defined as the group of photoreceptors converging on the same ganglion cell. Bright dots are presented against a dark background on a computer screen and the patient’s task is to identify the number of dots seen by clicking a mouse button. The Rarebit technique includes two tests, the Rarebit Perimetry (RBP) and the Rarebit Fovea Test (RFT). The RBP evaluates the central 30° visual field, while the RFT evaluates the central 4° visual field. In a previous study employing the Rarebit technique, Nilsson et al. detected foveal dysfunction in patients with diabetes mellitus type 1 without visible signs of vascular DR. In Chapter 6 the possible relationship between structural retinal neuropathy, as measured with OCT, and the neuroretinal deficits using the rarebit technique in patients with type 1 diabetes mellitus and no or minimal diabetic retinopathy (DR) is evaluated.

When studying changes in retinal layer thickness, it is essential to distinguish disease processes from normal age-related changes. Previous studies have shown that the thickness of the retinal layers in normal subjects correlated negatively with age. In Chapter 7 we evaluate the effect of age on the thickness of individual retinal layers such as the peripapillary RNFL thickness and pericentral GCL thickness, measured with SD-OCT, in a population of healthy individuals. In Chapter 8 we describe the results of a longitudinal study in diabetes patients investigating whether the thinning of inner retinal layers in diabetes patients that we have previously shown cross-sectionally is progressive over time, and whether there is an association with duration of diabetes, hyperglycaemic control, and the presence or change in retinal vasculopathy. Annual change in inner retinal layers was analysed using a linear mixed model adjusting for age, gender, duration of diabetes, HbA1c over time, presence and progression of DR.

In the retina, glia and neurons closely interact with the retinal vasculature to maintain the homeostasis necessary for normal neuroretinal function. The exact relationship, if there is any at all, between vascular diabetic retinopathy and diabetic retinal neuropathy is largely unknown. In Chapter 9 we will discuss the possible relationship between the vascular diabetic retinopathy and the diabetic retinal neuropathy. Furthermore, we will argue that the functional and structural measurements of retinal neurodegeneration in diabetes patients are possible candidates to serve as biomarkers for early retinal damage and other complications caused by diabetes, and could be useful in future trials exploring interventions to prevent the late vascular visual acuity-threatening complications of diabetic retinopathy.
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Chapter 1


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