Specific clinical applications of Optical coherence tomography in ophthalmology

Doctoral theses

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1. Introduction

The technology of Optical Coherence Tomography has a brief history of 20 years. The first commercial machine became available on the market in 1996. With the appearance of the third generation (StratusOCT) in 2002 the examination technique became widely accepted by the clinicians. From 2004 OCT has become part of the general ophthalmologic care. After the fourth generation developed in 2006 many companies have started producing their own machines.
The special feature of OCT is that it produces high resolution, cross-sectional images using a light source. On these images separate layers are easily distinguished by their optical reflectivity. As a result we get in vivo images of the quality of a light-microscope by using a non-invasive technique, therefore the procedure is often referred as 'optical biopsy'.

1.1. Boundary detection errors on Optical Coherence Tomography images

Measuring retinal thickness on OCT images are performed as following: After obtaining the individual scans, the system identifies the retinal pigmentepithelium (RPE) and the retinal nerve fiber layer (RNFL). Identification is done by the optical reflectivity of the layers. The identified layers are marked by continuous white lines.

In some cases, however, the software may detect the retinal boundaries incorrectly. This may be attributable to one or more of the following causes:

1. Pathologic changes of the retina that produce abnormally low or high reflectivity or shadowing, leading to erroneous boundary detection;

2. Decreased transparency of the optical media of the eye, in which the signal strength of the reflections from all retinal tissues is low and therefore differentiation of the layers is more difficult or impossible for the software; and

3. Technical failures such as poor patient cooperation, limited operator experience, or operator error, in which artifacts may be produced by the instrument's software and quantitative results and then become unreliable.

1.2. Optic pit

Optic disk pits are congenital abnormalities of the optic nerve head, characterised by a localised round or oval depression in the optic disc. The most common localisation of the depression is at the inferotemporal segment of the optic disc, 20% occurring centrally and 10% located in other regions of the optic disc. Unlike optic disc coloboma, an optic disk pit does not affect the disc margin, and the physiological optic cup remains distinct. This condition is associated with a serous retinal detachment often extending into the macular region. Recent OCT studies suggest a connection between

the retina and the subarachnoidal space at the site of the optic nerve head. According to these studies, fluid from the optic nerve channel may enter the sensory retina, creating a schisis-like separation of the retinal layers. Consecutively, retinal detachment is considered as a secondary change. Vitreous traction may also have an additional role in the pathogenesis of the retinal elevation.

1.3. Measuring central corneal thickness

Measurement of central corneal thickness (CCT) is important when planning and evaluating keratorefractive procedures. It is also important when assessing glaucoma, since the CCT affects the results of applanation tonometry and provides valuable information about glaucoma risk. Ultrasound pachymetry is currently the most widely used gold standard method for measuring corneal thickness.

Optical coherence tomography is a noninvasive and non-contact technique which was originally designed for fundus imaging; however, many studies have shown its value in measuring corneal thickness. Most of these studies were done on the OCT2000 system or used external analysis programs.

2. Aims

2.1. Boundary detection errors on Optical Coherence Tomography images in patients with diabetic retinopathy

The aim of our study was to detail the incidence of artifacts affecting retinal thickness measurements produced by OCT in patients with diabetic retinopathy.

2.2. Three-dimensional imaging of an optic disk pit using high resolution optical coherence tomography

Our aim was to map the three-dimensional structure of the optic disk pit and its fluid compartments and to clarify the origin of the coexisting fluid in an optic disc pit case by using optical coherence tomography (OCT).

2.3. Central corneal thickness measurements with optical coherence tomography and ultrasound pachymetry in healthy subjects and in patients after photorefractive keratectomy

The purpose of the study was to compare CCT measurements using OCT and US pachymetry, both in normal eyes and in eyes that had undergone photorefractive keratectomy (PRK), without using any modification to the commercially available instrument system and using a built-in analysis protocol. A secondary objective was to assess the intrasession variability of the OCT measurements.

3. Methods

3.1. Boundary detection errors on Optical Coherence Tomography images in patients with diabetic retinopathy

One hundred sixteen eyes with diabetic retinopathy of 64 consecutive patients with diabetes mellitus were included in this retrospective study. The patients (36 women and 28 men) were selected from the database of the StratusOCT measurements (performed at the Ophthalmology Department at Semmelweis University in Budapest, Hungary, during 2005) without regard to the stage of their disease. Patients were examined by two operators (MS, AS) who were actively working in the medical retina field and were experienced in the use of the StratusOCT instrument and certified by the Vienna OCT Reading Center (AS as operator, MS as operator and grader). Forty-one patients were examined by one operator (MS) and 23 by the other (AS). Mean age of the patients was 59 years (range: 20 to 79 years).

The StratusOCT instrument with the macular thickness map protocol was used for the examinations. This protocol uses six radial scan lines with a scan length of 6 mm each, set 30° apart, in an automated sequence. Each line contains 1024 sampling points axially and 512 points transversally.

After acquisition, we analysed each scan using the retinal thickness (single eye) protocol to evaluate whether there was any misdetection of the retinal boundaries, seen as a misplacement of the boundary lines. We considered any boundary detection error as an artifact. The number of artifacts and their clinical cause were recorded in each case. Each scan was graded by the same experienced grader (MS).

Statistical Methods
To study the factors influencing the number of scans with artifacts, analysis of covariance with forward stepwise variable selection was conducted. Frequency tables and cross-tabulations were used to study the causes of artifacts. Statistical analysis was done by the R system using the Sweave software package (R Development Core Team, Vienna, Austria).

3.2. Optic disk pit maculopathy (case report)

A 71-year-old woman presented with a best-corrected visual acuity (BCVA) of 20/20 in both eyes. The patient reported neither metamorphopsia nor central scotoma. Dilated fundus examination revealed the typical appearance of an optic nerve head pit in the left eye with a shallow retinal detachment not reaching the fovea. Fundus photography (FF 450 plus, Carl Zeiss Meditec), fluorescein angiography (FA, HRA2™, Heidelberg Engineering), and OCT (StratusOCT™, Carl Zeiss Meditec) were performed to document the presumed diagnosis. A second generation frequency domain high resolution OCT (HR-OCT, Cirrus OCT™ prototype, Carl Zeiss Meditec) was used for

specific analysis of alterations in the retinal microstructure. Therefore two scans (512 x 128 x 1024/3 x 1024 x4096) with an axial resolution of 6 mm were taken following a standardised scanning protocol.

Of the HR-OCT scans we used three high resolution images for demostration and we used 128 fast scans 3D for reconstruction purposes. After acquisition individual images were exported and processed with an external program.
For the reconstructions we used Food and Drug Administration–approved imaging software (3D-Doctor V4.0, Able Software Corp., Lexington, MA).

3.3. Measuring central corneal thickness using OCT and US pachymetry

In this prospective study we enrolled 20 patients who had previously undergone PRK (PRK group), as well as 20 normal subjects (normal group). All participants were Caucasians. The normal subjects had best-corrected vision of 20/20 or better and no ocular history for the examined eyes. Eyes with any ocular history (except ametropia) were excluded from the study. Each participant underwent a complete ophthalmic examination including ocular history, best-corrected visual acuity, and slit-lamp biomicroscopy. The normal group comprised 12 women and 8 men; the mean age was 30 years (minimum 19, maximum 65 years). The PRK group comprised 10 women and 10 men, mean age 33 years (minimum 20, maximum 58 years). Central corneal thickness was measured with the Stratus-OCT model 3000, software version 4.0.2 (0056) (Carl Zeiss Meditec Inc., Dublin, CA) and also with the Ultrasound Pachometer Model 855 (Humphrey Instruments Inc., San Leandro, CA)
In each case, the set of OCT scans was made first (always between 9:00 AM and 12:00 noon), and US pachymetry was performed a short time afterwards. This was always done within half an hour of the OCT measurements, to minimise any influence of diurnal variation of the corneal thickness.

Five OCT measurements were made with 5-minute latency. Each measurement used the Fast Macular Thickness scan protocol. The focus point (set using the diopter adjustment knob) was set to lie on the front surface of the anterior segment.
We processed the data by analysing each scan individually using the OCT software's built-in Scan Profile analysis protocol. In this process we selected the centre of the cornea (highest point of the corneal scans). On this A-scan presentation the anterior and posterior surface of the cornea can be determined very precisely as the most reflective point in their respective surroundings. The distance between these two points was calculated automatically by the software. We repeated this process for each of the six scans.
After analysing the five OCT sessions we thus obtained a total of 30 corneal thickness values for each eye. OCT measurements and analyses were all performed by the same experienced operator (M.S.).
Ultrasound pachymetry was used as a gold standard comparison. Ultrasound measurements were performed immediately after anesthetising the corneal surface using one drop of oxybuprocaine-hydrochloride 0.4% (Humacain 0.4%, TEVA Hungary Ltd., Budapest, Hungary). Three measurements were performed at the centre of the cornea in

an orientation perpendicular to the optical surface, and the three values were then averaged. The ultrasound measurements were all performed by the same experienced nurse practitioner.

For each eye, the six radial OCT scan measurements were summarised using three methods, namely as the mean, the trimmed mean, and the median. The best summarising method was chosen according to measurement reliability. As left-right correlation of CCT for the eyes of a given subject is very high (meaning that intersubject variability of CCT is very large compared to the intrasubject left-right variability), only a single eye of each participant was included in the analysis. Preferably the right eye data was used in the analysis, but if this was not available, data from the left eye was used.

Systematic errors of the OCT-determined CCT (OCT-CCT) were studied using a simple linear regression where confidence intervals of the intercept and slope were determined. Bland-Altman analysis was used to measure random error (and coefficient of variation) and the dependence of the error on CCT. In the US pachymetry–OCT comparison only the first OCT measurement of each session was used, since no repeated measurements are included in the proposed routine. As OCT-CCT may potentially have different accuracy in normal subjects as compared to PRK patients, accuracy was assessed in the two subject groups separately.

To assess the reproducibility of OCT measurements, intrasession variability of OCT-CCT was calculated as the within-patient standard deviation with analysis of variance (ANOVA). We compared CCT measurements of the PRK and normal group using the two-sample Student t-test.

Statistical analysis was done by the R system using the Sweave package (R Development Core Team, Vienna, Austria).

4. Results

4.1. Boundary detection errors on Optical Coherence Tomography images in patients with diabetic retinopathy

The automatic retinal thickness analysis produced reliable determination of the retinal boundaries in 64.7% of eyes, which were considered artifact-free. Artifacts were found in 35.3% of eyes.

In examining the causes of the artifacts, we found four main reasons:

1. Hard exudates
2. Cyst formation
3. Proliferation (fibrovascular proliferative tissue formation)
4. Degraded image quality (eg. due cataract)

Artifacts caused by hard exudates represented the majority of artifacts (41.5%), followed by cystoid macular edema (31.7%) and proliferation (17.0%). Artifacts due to other causes represented a smaller proportion than this.

4.2. Three-dimensional imaging of an optic disk pit using high resolution optical coherence tomography (case report)

At the patient's second visit 1 month later, BCVA had dropped to 20/125. Subretinal fluid had reached the fovea, observed with biomicroscopy. All examinations were repeated as described above to document disease progression.

Two separate fluid-filled spaces could be marked in manual segmentation analysis of consecutive HR-OCT tomograms contained in one macular scan:

1. cystoid spaces intraretinally within the outer nuclear layer and
2. subretinal fluid underneath the outer photoreceptor elements.

A three-dimensional reconstruction of the pit and the communicating locations could be created to provide precise insights into topographic relations within the relevant structures. No free communication could be detected between the perineural subarachnoid space and the intraretinal space but filtration can strongly be suspected between them. This type of communication could also be identified in 3D reconstructions of HR-OCT scans which showed a schisis of the retinal layers and a sensory retinal detachment in the two-dimensional images. The possible location of the communicating channel could clearly be localised. This location and the mild and slow leakage can also be seen on the corresponding FA image, which supports the above statement.

4.3. Central corneal thickness measurements with optical coherence tomography and ultrasound pachymetry in healthy subjects and in patients after photorefractive keratectomy

In the normal group, mean corneal thickness was 559 µm (mean 1 SD 30.69 µm) measured with US pachymetry and 560 µm (mean 1 SD 32.20 µm) measured with OCT. In the PRK group the corresponding values were 513 µm (mean 1 SD 45.61 µm) and 514 µm (mean 1 SD 47.48 µm), respectively.

As expected, using both measurement methods corneal thickness was significantly smaller in the PRK group than in the normal subjects (p=0.0007 for pachymetry and p=0.0009 for OCT-CCT, two-sample t-test with Welch correction).
The left-right intraclass correlation coefficient of pachymetry CCT was 0.97 and 0.98 in the normal and the PRK groups, respectively; thus, use of data from only a single eye of each subject appears to be justified.

One of the aims of the study was to determine the most appropriate summarising method for reducing the OCT measurements in the six scans to a single corneal thickness value. We found that the method of choice was the mean. Thus in the paragraphs below, the numeric CCT results correspond to the means of the six OCT scans.

Pachymetry-OCT comparison

The pachymetry–OCT correlations were 0.96 and 0.97 in the normal and PRK groups, respectively. The confidence intervals of the intercepts and slopes of the two regression lines were –26.4 to 114.1, 0.79 to 1.04 and –24.9 to 94.3, 0.82 to 1.05, respectively, both including zero intercept and slope of 1.0. The p values for intercept differing from 0 are 0.21 and 0.24, while the p values for slope differing from 1 are 0.19 and 0.23, respectively. Thus linear regression did not reveal any significant systematic measurement error.

In addition, we used Bland-Altman plots to compare the CCT data obtained from the OCT and pachymetry measurements. Bland-Altman analysis showed a measurement error of 8.5 µm (standard deviation) in the normal group. The measurement error did not significantly depend on the corneal thickness. The Bland-Altman difference-mean correlation was –0.18 (p=0.45), the confidence interval of the slope of the difference-mean regression line was –0.18 to 0.09 (p=0.45). The mean difference was –1.42 (confidence interval: –5.4 to 2.6), thus no significant shift in the measurement scale was detected. Largest positive and negative differences were 16.67 and –12.67, respectively. The standard deviation of the pachymetry-OCT difference shows no visible trend along the corneal thickness axis; the measurement error is virtually independent of the corneal thickness.

In the PRK group we observed similar results, SD = 11.5 µm, correlation = –0.16 (p=0.49), CI of the slope: –0.16 to 0.08 (p=0.49), mean difference = –0.30 (CI: –5.7 to 5.1), largest positive difference = 27.17, largest negative difference = –22.67. In this

group also, no significant systematic error was detected, and the measurement error again appeared to be independent of the value of corneal thickness.
The above standard deviations of measurement errors correspond to coefficients of variations of 1.5% and 2.2% for the normal and PRK groups, respectively.

Reproducibility

In order to assess the intrasession variability of the OCT method, the five consecutive OCT-CCT measurements were compared among themselves. We determined the intrasession standard deviation for each eye, and plotted it against the corresponding mean CCT.

We found that the intrasession standard deviation was independent of the CCT. The individual intrasession SD values ranged from 1.0 to 9.0 µm in the normal group, and from 1.5 to 6.2 µm in the PRK group.
The overall intrasession standard deviations in the normal and PRK groups were 4.9 µm and 3.8 µm, respectively, corresponding to coefficients of variation of 0.87% and 0.74%. The difference between the intrasession standard deviations was not significant ($p=0.14$).

5. Conclusions, summary

1. Occurrence of artifacts with time-domain OCT measurements in cases of diabetic retinopathy is not a rare phenomenon, and verification of quantitative measurements is strongly recommended.

2. Regarding Optic Pit maculopathy, we assume that the intraretinal space is progressively filled with subarachnoideal fluid, leading to a tearing force within the outer neurosensory layers. A connection between the outer nuclear layer and the subretinal space may lead to a serous retinal detachment as a secondary event. Vision loss could consecutively be induced by a serous retinal detachment.

3. High resolution OCT technology is capable to visualise discrete changes of the microarchitecture of the optic nerve as well as the retina when combined with appropriate imaging software.

4. Non-contact central corneal thickness measurements made using the StratusOCT instrument are accurate and reproducible, both in normal subjects and in post-PRK patients. The instrument system does not need any modifications to correctly detect and measure the centre of the cornea.

5. Publications

5.1 Publications related to the thesis

1. Papp A, Pregun T, Szabó A, **Schneider M**, Seres A, Vargha P, Hagyó K, Németh J. Intravitreális triamcinolon acetonid a diffúz diabeteses macula-oedema kezelésében. Szemészet 2007;144: 21-26

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5. **Schneider M**, Seres A, Borgulya G, Nemeth J. Boundary Detection Errors on Optical Coherence Tomography Images in Patients with Diabetic Retinopathy. Ophthalmic Surgery Lasers and Imaging 2010;41:54-59 IF2009: 0.615

5.2 Publications not related to the thesis

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5.3. Abstracts related to the thesis

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3. C.Ahlers, W.Geitzenauer, I.Golbaz, C.Simader, M.Bolz, S.Kolar, A.Papp, **M.Schneider**, G.Stock, U.Schmidt-Erfurth. (1791/B651) Treatment Effects of Ranibizumab (LucentisTM) in Patients With Pigment Epithelial Detachments Due to Neovascular Age Related Macular Degeneration Using High Definition Optical Coherence Tomography. ARVO 2007. május 6-10. Fort Lauderdale, Florida (Invest. Ophthalmol. Vis. Sci. 48: E-Abstract 1791.)
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5.4. Posters, lectures related to the thesis

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5.5. Posters, lectures not related to the thesis

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