In vivo examination of laser induced retinal changes in patients with diabetic retinopathy

PhD thesis

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Introduction:

For decades laser photocoagulation was the only therapy for a number or retinal diseases, and in many indications remains the most effective therapy. The first modern concept of laser photocoagulation for patients with diabetic retinapathy was published by Beetham et al. in the late 60s. These early reports on the beneficial effects of laser therapy were confirmed and the laser procedures were standardized by large multicenter randomized clinical trials such as the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS) in the 1970s and 1990s.

Early laser devices needed significant cooling and occupied almost complete rooms. With the continuous development and improvement of these devices and the introduction of newer laser masters now days lasers became small tabletop equipment, and much more accessible. Of course not just the size of the devices changed, but also the way laser energy is delivered. One of these novel laser delivery methods is short pulsed continuous laser, where instead of the conventional 100-200 ms laser pulse, the same laser energy is delivered in 10-20 ms. This enables to perform laser therapy much more time efficiently, making the procedure much less demanding for both patient and physician. Another advantage of this method of delivery is that heat diffusion and with this collateral damage can be reduced. Histologic studies in animal models showed significantly reduced collateral damage in the inner retina, and also in the area between laser spots.

Although Anti-VEGF therapy proved to be more effective than laser therapy in a number of indications, both panretinal and focal laser therapy remains an important therapeutic option, and is still part of all major international and

Hungarian guidelines.

Aims:

The aims of our research were the following:

1. examine the in vivo effects of a short duration continuous thermal laser onto the human peripheral retina using optical coherence tomography
2. examine the longitudinal healing process of laser burns, and quantify laser scar size changes over time
3. examine the immediate in vivo morphologic changes after macular grid photocoagulation using a short duration continuous thermal laser
4. examine the immediate and long term in vivo effects of non-visible sub-threshold laser burns applied by a short duration continuous thermal laser on retinal morphology
5. to describe a novel potential biomarker seen in patients with diabetic macular edema, and observe in vivo its behavior in respect to changes in macular thickness after macular photocoagulation.

Methods

1)

We performed short pulse continuous wave panretinal photocoagulation (PRP) in patients with proliferative diabetic retinopathy using a semiautomated scanning laser system (PASCAL, Pattern Scanning Laser, OptiMedica Corporation). Spatial and temporal morphologic changes in the human retina following laser therapy were examined using optical coherence tomography (OCT) (Spectralis OCT, Heidelberg Engineering). Follow-up examinations were performed at day 1 and 7, than monthly for 6 month.

2)

We performed grid and focal photocoagulation in patients with diabetic macular edema (DME) in a standardized manner using the short pulsed laser system mentioned above. Patients were examined with high-resolution OCT before and a day after laser therapy.

3)

In a prospective study we performed PRP in 10 patients using the short pulse laser system described in our 1. Examination In a study area adjacent to the temporal vessel arcades, 2x2 pattern laser spots were applied with halving the flux of the laser power in a stepwise manner starting from a power producing a typical grayish lesion. The study areas were then imaged on days one, three and seven, and on months one, two, three and six using color fundus photography, autofluorescence (AF), infrared (IR) imaging and spectral domain OCT.

4)

In a prospective study of patients with DME were treated with focal and grid laser photocoagulation. We analyzed the changes in the localization of hyper-reflective foci detected by spectral domain (SD) optical coherence tomography (OCT) during follow-up period at day 1, week 1, month 1, 2, 3 and 4 in defined areas. Further, fundus photography and infrared imaging were performed in all visits and findings correlated to OCT results

Results:

1)

Day 1 after PRP, the photocoagulation effects were sharply delineated from the surrounding unaffected retina and all spots seemed to be identical in size

and location. The area of tissue destruction was confined to the outer retinal layers, extending from the outer nuclear layer (ONL) to the retinal pigment epithelium (RPE). At 1 week, images showed a progressive loss of the affected outer retinal layers, namely, the ONL and the outer plexiform layer. Concomitant distortion of the inner nuclear and plexiform layers generated a pattern of “archways” between adjacent laser spots. The ellipsoid zone (EZ) seemed to be eliminated in the photocoagulated area, particularly at the borders of each lesion. The lesion center contained a condensed RPE and EZ segment. The ONL recovered partially, but the EZ inner and outer segments remained absent. During the long-term follow-up, RPE cells migrated to the center of the lesion, forming a hyperplastic scar. We observed a reduction in laser spot diameter during the follow-up.

2)

One day after laser therapy, immediate morphologic alterations of only the outer retinal layers, that is, the RPE, EZ, and ONL, were observed. The shape of the laser-induced lesions did not show a sagittal alteration pattern throughout all 3 of the layers, however, but rather seemed to follow an oblique pathway throughout the ONL, changing direction at the level of the external limiting membrane and proceeding sagittally through the EZ and RPE. These morphologic changes also induced biometric changes, such as a decrease in central retinal thickness combined with local thickening at the lesion site, especially in the EZ.

3)

The starting threshold power lesions were each visible on color fundus photography, IR and AF in all patients and showed characteristic changes on OCT throughout the follow up period. The halved flux laser burns (first step)

were ophthalmoscopically undetectable during the laser session, but during the follow up were always detectable on IR and AF images and sometimes on fundus photography. On OCT they showed similar changes to the supra threshold laser scars, but were much smaller in diameter, and in some instances an inward migration of the photoreceptor layer was observed.

4)

A dynamic change in the distribution pattern of hyper-reflective foci was observed over 4 months following the photocoagulation. With the decrease of retinal thickness, the dots either resolved completely or became confluent at the apical border of the outer nuclear layer (ONL), and finally formed ophthalmoscopically detectable hard exudates during extended follow-up. In the event of retinal thickening despite laser treatment, the hyper-reflective dots maintained their previous distribution throughout all retinal layers. As a fourth response, dissemination of plaques of hard exudates into multiple, separate, hyper-reflective foci were detected.

Conclusions:

1)

a) In vivo morphologic changes after panretinal laser therapy with a short duration continuous laser were comparable to result published from histological studies on animal models.

b) Lesions were sharply demarcated, and showed no collateral damage at the edges of the lesions

c) Laser lesions extended to the inner border of the outer nuclear layer, but the inner layers of the retina were not affected by direct thermal laser effect.

2)

a) During their evolution a loss of PRL and ONL thickness -suggesting photoreceptor loss-, as well as RPE atrophy around the scar was observed.

b) Laser lesions performed by a short duration continuous laser shrank considerably during the follow-up period and did not show lesion growth known to happen with laser scars of normal duration lasers.

3)

a) Laser lesions of macular grid laser were similar in morphology to panretinal lesions. The oblique orientation of the lesions in the ONL suggest, that the true thermal effect of the laser is only limited to the RPE/PRL layers, and the involvement of the ONL is mainly a consequence of retrograde cellular changes.

4)

a) Sub-threshold laser lesion created with halved fluence showed similar characteristics to threshold lesions, but were smaller in diameter, and showed less atrophic RPE changes.

b) An inward migration of the photoreceptors is possible after sub-threshold laser, as the diameter of defects in the PRL layer reduced over time.

5)

a) Intraretinal hyperreflective foci are a common finding on OCT in patients with diabetic macular edema, and show characteristic changes after laser therapy mainly influenced by the decrease or accumulation of intraretinal fluid.

b) Hyperreflective foci in diabetic macular edema may represent microexudates, and may serve as precursors of retinal hard exudates.

c) Hyperreflective foci might be an interesting biomarker in the detection of early increased lipid extravasation even before the development of macular edema or hard exudates.

List of Publications:

12.1 List of Publications related to the topic of the dissertation:

1. Kriechbaum K, Bolz M, **Deak GG**, Prager S, Scholda C, Schmidt-Erfurth U. (2010) High-Resolution Imaging of the Human Retina In Vivo after Scatter Photocoagulation Treatment Using a Semiautomated Laser System. Ophthalmology, 117: 545–551.
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2. Bolz M, Kriechbaum K, Simader C, **Deak G**, Lammer J, Treu C, Scholda C, Prünte C, Schmidt-Erfurth U. (2010) In Vivo Retinal Morphology after Grid Laser Treatment in Diabetic Macular Edema. Ophthalmology, 117: 538–544. **IF: 5,017**

3. **Deák GG**, Bolz M, Prager S, Ritter M, Kriechbaum K, Scholda C, Schmidt-Erfurth U. (2012) Photoreceptor Layer Regeneration is Detectable

in the Human Retina Imaged by SD-OCT after Laser Treatment Using Subthreshold Laser Power. Invest. Ophthalmol. Vis. Sci., 53: 7019–7025. **IF: 3,441**

4. **Deák GG**, Bolz M, Kriechbaum K, Prager S, Mylonas G, Scholda C, Schmidt-Erfurth U. (2010) Effect of Retinal Photocoagulation on Intraretinal Lipid Exudates in Diabetic Macular Edema Documented by Optical Coherence Tomography. Ophthalmology, 117: 773–779. **IF: 5,017**

12.2 List of Publications not related to the topic of the dissertation:

Deák GG, Lammer J, Prager S, Mylonas G, Bolz M, Schmidt-Erfurth U. (2014) Refractive Changes after Pharmacologic Resolution of Diabetic Macular Edema. Ophthalmology, 121: 1054–1058. **IF: 6,135**

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