Subthreshold Micropulse Laser Treatment of Human Diabetic Macular Edema: the Role of Müller Cells, Retinal Pigment Epithelium and the Inflammatory Cascade

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Purpose
The pathophysiology of the effect of subthreshold micropulse laser (SMPL) treatment of diabetic macular edema /DME) is still unknown. We investigated the effect of SMPL in DME eyes using retinal morphology data and the quantification of specific intraocular biomarkers.

Methods
Previously untreated, center-involving DME eyes (central retinal thickness: CRT< 400 µm) underwent BCVA and layer-by-layer OCT quantification. Moreover, specific retinal Müller cells and RPE biomarkers (Glial Fibrillary Acidic Protein: GFPA, Inwardly Rectifying Potassium Channel (Kir) 4.1, VEGF for Müller cells, and Pigment Epithelium Derived Factor: PEDF and Erythropoyetin: EPO for RPE), and multiple inflammatory cascade biomarkers were quantified (every three months) , versus healthy controls, in the aqueous humor (AH). SMPL was applied in a standardized fashion over all edematous areas. Fundus autofluorescence and microperimetry were used to evaluate both morphologic and functional SMPL side effects.

Results
Nineteen previously untreated DME eyes and ten controls were studied (minimum follow-up 12 months). At baseline, AH values of GFAP, Kir 4.1 and VEGF, and inflammatory biomarkers showed increased concentration in DME eyes versus controls (p< 0.005, for all). After SMPL: BCVA increased (mean: 5.6 ETDRS letters); OCT documented significant regression of CRT (p< 0.005) mostly at the level of the inner nuclear layer (p< 0.002), where the bodies of Müller cells are located. No side effects were documented. A significant reduction of Müller cells biomarkers was found (baseline vs 12 months data: GFAP: 1581.8 vs 982.1 pg/µl, p= 0.02; Kir 4.1: 177.0 vs 118.5 OD, p= 0.008; VEGF: 164.3 vs 134.7 FI, p= 0.04), with final restoration to normal values.The biomarkers of the inflammatory cascade also showed a significant reduction (p < 0.004). Retinal pigment epithelium biomarkers (PEDF and EPO) remained unchanged during follow-up (p> 0.2).

Conclusions
These results offer fully new insights about the effect of SMPL treatment of DME eyes. The resolution of DME by SMPL seems (mainly) to depend on the restoration of the activity of Müller cells and stabilization of the diabetic retinal inflammatory condition. These data strongly support the hypothesis of the key importance of Müller cells in the pathophysiology of DME.

Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings, not the study itself and the associated details.