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Peripheral Retinal Dysfunction in Diabetic Macular Edema

Running title: Peripheral visual fields in DME

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Dear Editor,

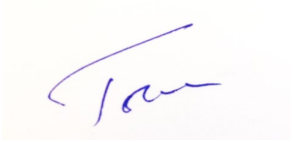
Patients with DME are treated primarily with intravitreal anti-VEGF or steroid injections (Wells et al. 2015), yet 30-40% of patients fail to fully respond to anti-VEGF treatments (Stewart 2014). Current clinical evaluation of DME is based on the extent of retinal vascular lesions and macular status as judged by optical coherence tomography (OCT), but DR affects the entire retinal neurovascular unit, including neurons, blood vessels, glial, amacrine, and Müller cells (Antonetti et al. 2012). Incomplete responses to treatment in DME may be due to the influence of angiogenic factors in addition to VEGF, or on the state of the neurovascular retina producing those factors. Hence, the rationale for this study is that comprehensive assessment of the entire neurovascular unit, including the macula and midperipheral retina, in DR and DME may provide better understand the disease and lead to more effective treatment in the future.

We employed functional and structural tests to examine the relationship between DME and peripheral visual field function in 23 subjects with DME (18 males, 5 females; mean age of 52.7 yrs (SD = 9.8) at the Kellogg Eye Center. Inclusion criteria included patients with a diagnosis of clinically significant DME as determined by a retinal specialist (based on both clinical exam and SD-OCT with macular cysts accompanied by retinal thickening. Exclusion criteria included any ocular or systemic disease other than DR that could affect vision, any previous intraocular surgery, previous treatment for diabetic retinopathy, or inability to provide written informed consent. Tests of central function included visual acuity and frequency doubling perimetry. Peripheral retinal function was tested using Octopus Perimetry, which tests up to 100^0 from the center of vision in the temporal field (assessing nasal retina), 70^0 in the nasal field (assessing temporal retina), 50^0 in the superior field (assessing inferior retina), and 70^0 in the inferior field (assessing superior retina). All subjects had OCT with measurements of central macular thickness and macular volume and color fundus photography to grade the severity of DR. Relationships between central and peripheral vision were evaluated using Pearson correlation tests. Statistical significance was set at $p<0.05$.

Four patients had mild NPDR, 11 had moderate NPDR, 5 had severe NPDR, and 3 had non-high-risk PDR. Patients with DME had an average HbA1c of 10.2 mmol/L and a range of CMT 209 mm – 560 mm and macular volume of 2.97 - 17.01 mm^3; mean ETDRS acuity was 80.7 letters. Patients had mean Octopus static peripheral perimetry sensitivity of 21.4 dB (4.9), a 4.1 dB sensitivity reduction compared to age matched normal subjects, and mean FDP sensitivity losses of 5.0 dB (10-2 protocol) and 2.5 dB (24.2 protocol) versus normal. This is a large difference considering that these are logarithmic values. Furthermore, the decreased visual field sensitivity correlated with worse visual acuity and reduced macular sensitivity via FDP (**figure 1**), but not OCT parameters or severity of DR. Moreover, reduced 10-2 and 24-2 frequency doubling perimetry showed strong correlations (R^2 linear = .505 and .456, respectively) with reduced Octopus field sensitivity. When removing the apparent outlier with an EDTRS acuity of <40, the results are similar with strong associations. However, the associations between reduced Octopus visual field sensitivity and reduced FDP 24-2 sensitivity remain statistically significant, but not those for FDP 10-2 or EDTRS visual acuity. These sensitivity losses are similar to those in persons with glaucoma (Bogunovic et al. 2015). These data suggest that perimetry detects subclinical retinal dysfunction before significant changes in acuity, since the average BCVA of the DME group was 20/25.

The findings of this study embody principles of the 2015 FDA/NEI Diabetic Retinopathy Clinical Trial Design Endpoints Workshop that argue for improved assessment of DR (Nair et al. 2016). The data suggest that patients with DME may have broader impairment of central and peripheral visual function than revealed by clinical examination, visual acuity, or OCT findings. Larger prospective studies that examine the state of the midperipheral retina in the pathogenesis and management of DME may provide greater understanding of its pathophysiology and treatment.

Yours sincerely,



Thomas W. Gardner, M.D., M.S.

References:

Antonetti DA, Klein R, and Gardner TW. Diabetic retinopathy. N Engl J Med. 2012;366(13):1227-39.

Bogunovic H, Kwon YH, Rashid A, et al. Relationships of retinal structure and humphrey 24-2 visual field thresholds in patients with glaucoma. Invest Ophthalmol Vis Sci. 2015;56(1):259-71.

Diabetic Retinopathy Clinical Research N, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015;372(13):1193-203.

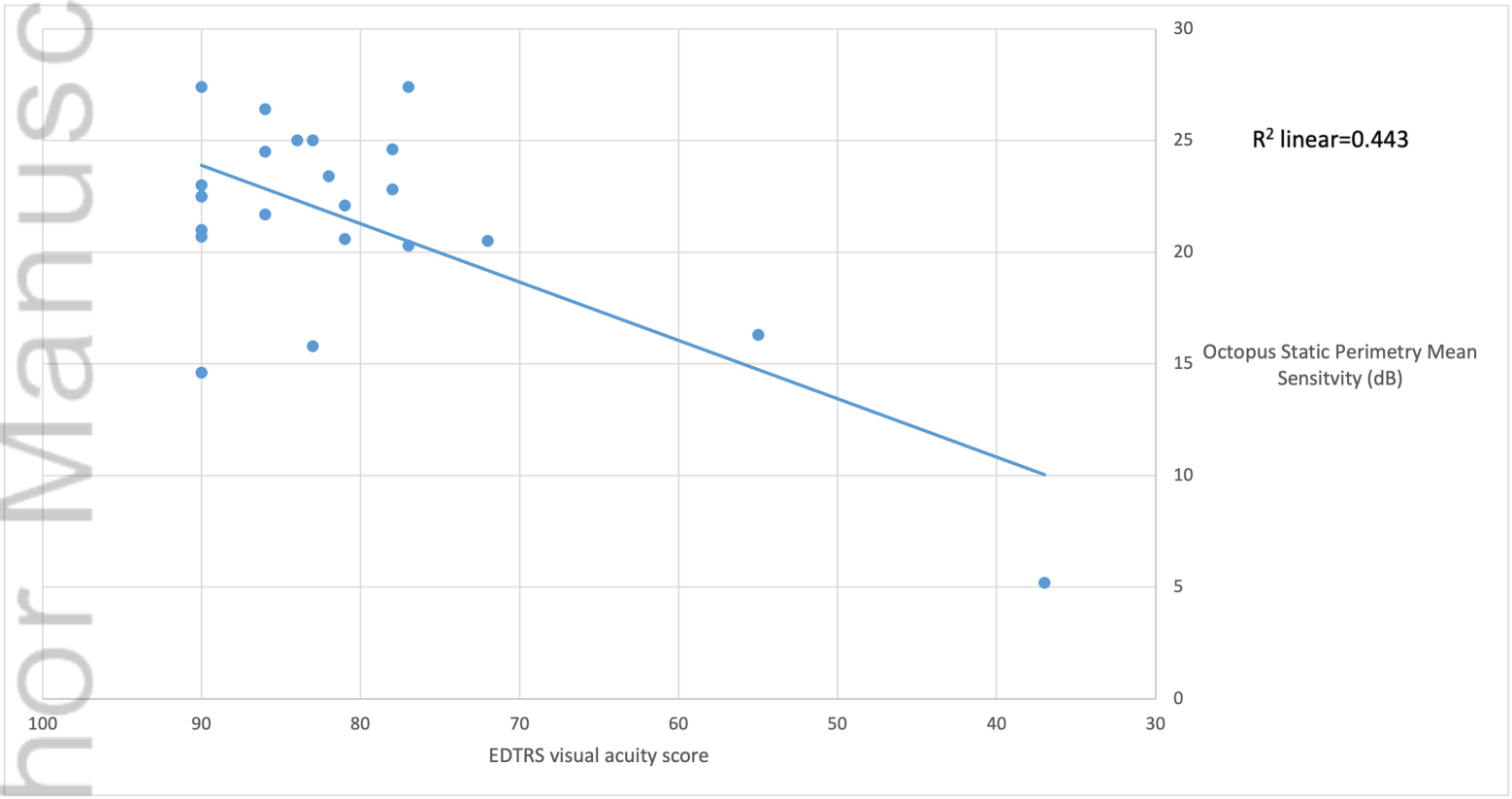
Nair P, Aiello LP, Gardner TW, Jampol LM, and Ferris III FL. Report From the NEI/FDA Diabetic Retinopathy Clinical Trial Design and Endpoints Workshop. Investigative Ophthalmology and Visual Science. 2016 Oct 1;57(13):5127-5142.

Stewart MW. Anti-VEGF therapy for diabetic macular edema. Curr Diab Rep. 2014;14(8):510.

Legend for Figure:

Figure 1 A. Pearson correlations of Octopus mean sensitivity (in decibels) and performance on EDTRS visual acuity testing (score out of 100) in 23 DME subjects ($R^2 = 0.443$; p value = 0.0003). **B.** Pearson correlation between Octopus mean sensitivity (in decibels) and FDP 24-2 mean deviation (in decibels) in 23 DME subjects ($R^2 = 0.505$, $p = 0.0006$). **C.** Pearson

correlations between Octopus mean sensitivity (in decibels) and FDP 10-2 mean deviation (in decibels) ($R^2 = 0.456$, $p = 0.0008$).



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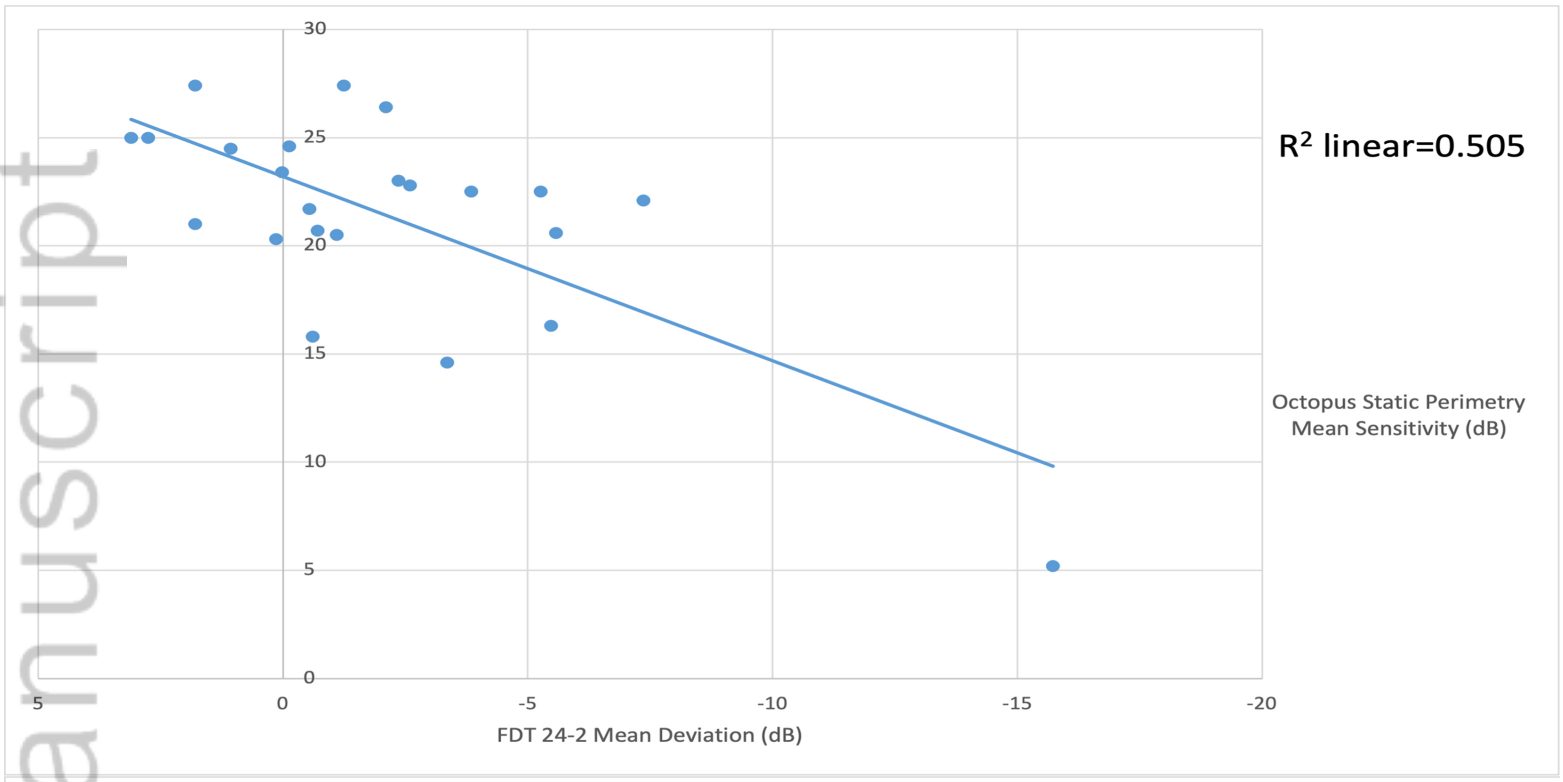

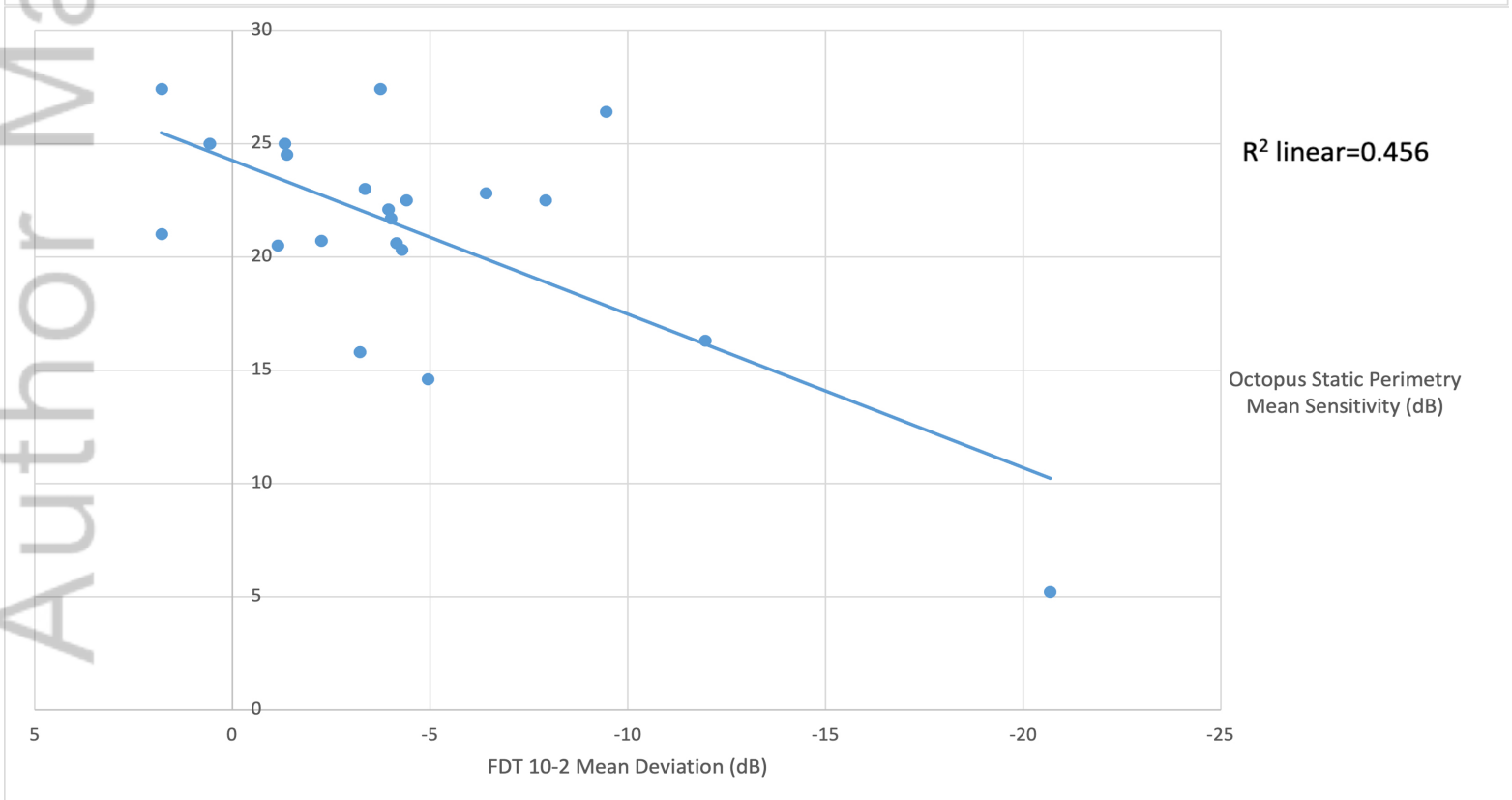

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