Dopamine and Early Retinal Dysfunction in Diabetes: Insights From a Phase 1 Study

Thomas J. Wubben

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Diabetes is a rapidly growing chronic disease worldwide, and one of its common complications, diabetic retinopathy (DR), is a leading cause of blindness in middle-aged people (1). Classically, DR has been identified by its microvascular phenotype on fundus examination in the eye clinic, which includes microaneurysms, retinal nerve-fiber layer infarcts, intraretinal hemorrhages, retinal exudation, and abnormal blood vessel growth (2). However, insights from the ever-growing body of literature on this blinding retinal disease have shown that DR effects the entire neurovascular unit that encompasses the intimate relationships between the neurons, glia, and vasculature of the retina (2). To this end, studies have demonstrated retinal dysfunction and alterations in retinal structure prior to the detection of the above described vascular abnormalities (3–6). Furthermore, by time the microvascular complications of DR are apparent, impairment in visual function and vision loss is typically already present (7). Therefore, being able to reliably detect retinal deficits prior to observable vascular changes may identify a window where interventions can be administered to slow or halt DR and prevent irreversible visual loss.

The electroretinogram (ERG) measures the electrical activity of the retina in response to a light stimulus. ERGs require trained personnel, dilation of the pupils, placement of electrodes on the cornea, and patient cooperation to limit eye movements, limiting its practicality as a screening test in retinal disorders. The ERG response that is recorded has many different components. Oscillatory potentials (OPs) are one of these components that are thought to be generated by amacrine cells in the inner retina. Additionally, these high-frequency oscillations have been shown to be delayed in different animal models of diabetes as well as in patients with diabetes without DR. In animal models, these early functional deficits were negatively correlated with retinal dopamine levels (8–12). As such, OP delays may provide a method for detecting early diabetic retinopathy prior to microvascular changes, and targeting the retinal dopaminergic system may be a novel strategy for the treatment of early DR (9,12).

To this end, in this issue of *Diabetes*, Motz et al. (13) sought to circumvent the issues that hinder the ability of ERG to act as a screening test by assessing whether a handheld ERG device with only skin electrodes and no pupil dilation had the sensitivity to detect OP delays in patients with diabetes and no DR. Also, the authors looked to address their hypothesis that dopamine deficiency contributes to early inner retinal dysfunction in participants with diabetes by examining whether levodopa, a U.S. Food and Drug Administration–approved therapeutic and precursor to dopamine, could restore these OP delays. This phase 1 clinical study included patients with a diagnosis of diabetes and no DR based on fundus photographs as well as control subjects without diabetes or confounding ocular diseases. Persons were excluded if they had a history of other diseases with underlying dopamine disturbances (i.e., Parkinson disease or major depressive disorder) or were taking other dopamine agonists or monoamine oxidase inhibitors. ERG protocols were based on this group's previous preclinical and clinical studies (9,12) with 10 min of dark adaptation found to be optimal for this screening procedure. ERGs from all control subjects without diabetes were analyzed to determine normal OP implicit times. If baseline OP implicit times from persons with diabetes fell outside the 95% CI of these normal values, the individual was randomized to low-dose (25 mg carbidopa/100 mg levodopa twice daily) or high-dose (50 mg carbidopa/200 mg levodopa twice daily) Sinemet (McKesson). Sinemet was taken for a total of 2 weeks. ERG recordings were assessed at baseline, 2 days, 2 weeks, and 4 weeks, which allowed for a 2-week washout period before the final testing. Visual acuity and contrast sensitivity were also examined, but no differences were observed between control participants and those with diabetes, and Sinemet did not alter these measures over the course of the study.

Kellogg Eye Center, Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, MI

Corresponding author: Thomas J. Wubben, twubben@med.umich.edu

See accompanying article, p. 1518.

COMMENTARY

In response to a dim flash stimulus, 52% of the recruited participants with diabetes ($n = 23$) displayed delays in OP implicit times at baseline when compared with control subjects ($n = 15$). These participants with diabetes were then randomized to either low-dose ($n = 11$) or high-dose ($n = 8$) Sinemet as above. The low-dose group demonstrated improvement in the OP implicit time delays at all time points. Interestingly, though, the high-dose group did not show statistically significant changes in the OP implicit times at any time point and actually started to revert back to the baseline value after the 2-week washout period.

The data make a sound case that this handheld ERG device that utilizes skin electrodes and no pupil dilation has the ability to detect early retinal dysfunction in persons with diabetes but no clinically detectable retinopathy. Yet, delays in OP implicit times were detected in only ~50% of the participants with diabetes. While this may be secondary to the sensitivity of the device, the lack of diabetic retinopathy was based only on fundus photographs. Considering that DR affects the entire neurovascular unit and that the disorganization of the retinal inner layers on optical coherence tomography (OCT) and the vessel density in the different capillary plexuses on OCT angiography have been suggested to be early structural biomarkers of disease, it would be interesting to parse the structure-function relationships of those participants with and without OP implicit time delays (14,15). Understanding these relationships and the correlation with progression to clinically detectable DR and visual impairment may strengthen the potential utility of this handheld device and OP delays as a screening method or even clinical marker of visual function when testing potential novel therapies in early DR.

On the other hand, caution should be used when interpreting the data regarding a treatment effect with Sinemet. While the limited number of participants in the study plays a role, the lack of a dose-response or even a consistent effect with regard to the OP delays between the Sinemet dosage groups is of concern. Furthermore, the study was of very short duration. Additional studies are needed to not only determine the dose and regimen that provides the optimal long-term effect without undue side effects, but moreover, to determine whether levodopa has any effect on the progression of DR and visual impairment over time.

Overall, this report is important and novel, showing the plausibility of using a handheld ERG device and OP delays to detect retinal dysfunction before clinically evident microvascular abnormalities in patients with diabetes and examining the use of Sinemet to improve this early retinal dysfunction. However, as discussed here and within the study, there is a need for further scientific elucidation of the structure-function relationships in those persons with diabetes with OP delays and the long-term effects of Sinemet on retinal function and progression of DR.

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