IN-OFFICE ELECTRODIAGNOSTICS FOR THE NON-GLAUCOMA PATIENT: DM, AMD, ETC

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Chief of Specialty Care Clinics

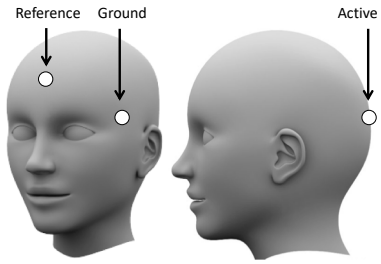
Course Outline/Objective

- What is electrodiagnostics testing?
- Visual Pathway – Basic Understanding
- VEP
- pERG
- ffERG
- mfERG
- Clinical Cases

Visually Evoked Potential (VEP)

- AKA Visually Evoked Response (VER)
  - Flash vs. Pattern
- Measures the entire visual pathway
  - From cornea to occipital lobe
- 3 electrodes
  - Ground
  - Reference
  - Measuring -> occipital lobe
    - 1" above inion

VEP Electrodes



VEP

LATENCY (ms) AMPLITUDE (μv)

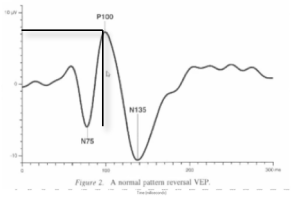
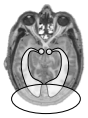


Figure 2. A normal pattern reversal VEP.



- Amplitude usually translates to the amount of axons conducting along the visual pathway
- Latency usually translates to the myelin status of the visual pathway

Why VEP?

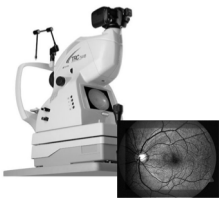
- Many optic nerve diseases are asymptomatic because central vision is not affected until late in the disease[1]
- Diagnosis and management of optic nerve disorders are often based on structural or subjective visual field tests[2]

VEP is an objective, functional test that can help discriminate between healthy and glaucomatous eyes[2]

1 Glaucoma. American Optometric Association. www.aoa.org.
2 Prata, Tiago MD, G. De Moraes MD, J. Liebmann MD, R. Ritch, C. Tello MD. (2009). Diagnostic Ability of Fast Transient Visual Evoked Potential for Glaucoma Assessment [Poster & Abstract] American Academy of Ophthalmology. 128

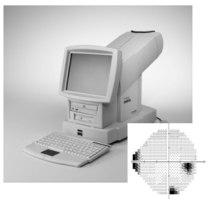
Structure

Fundus Photograph
(*Subjective*)



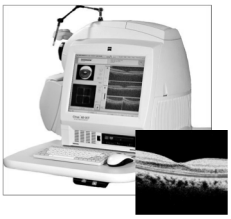
Function

Visual Field
(*Subjective*)



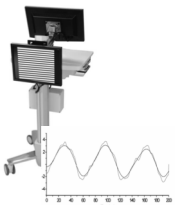
Structure

Optical Coherence Tomography
(*Objective*)



Function

ERG & VEP
(*Objective*)



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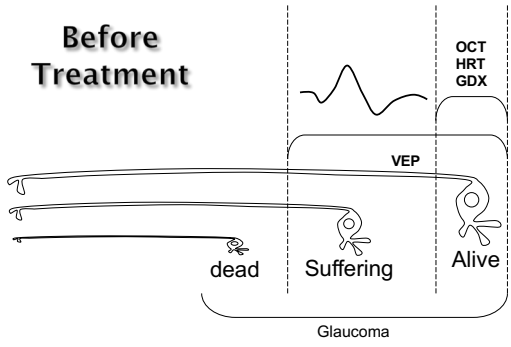

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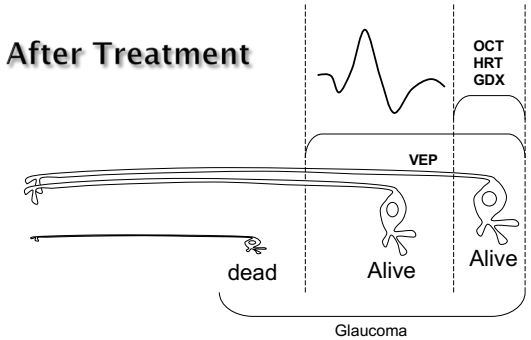

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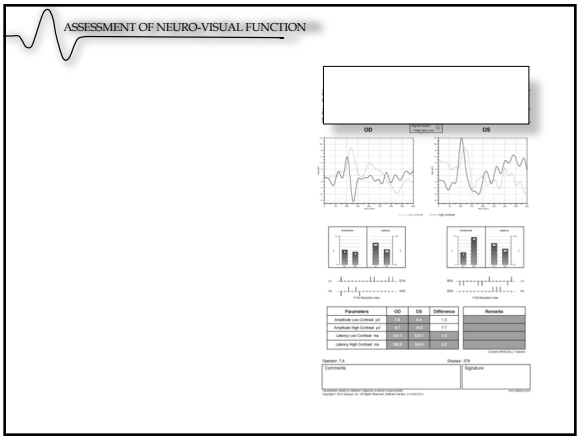
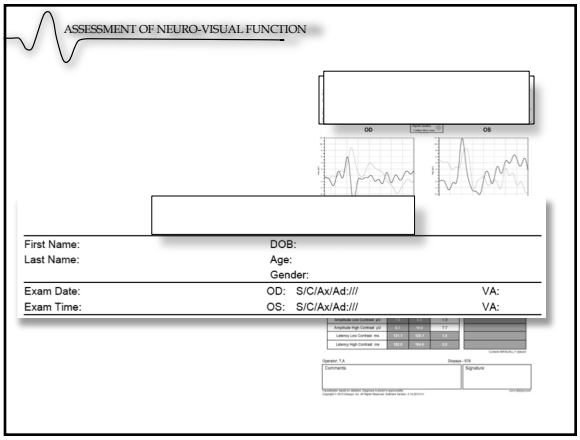
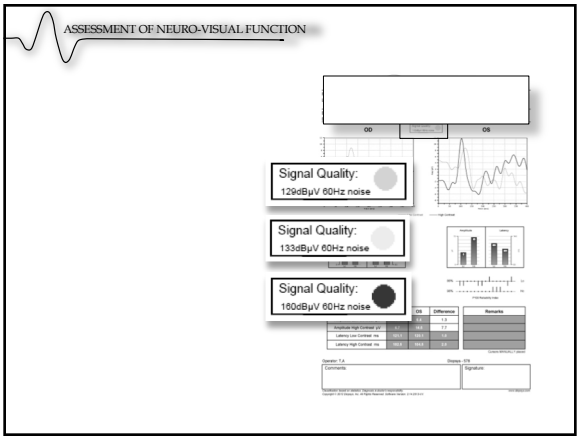
How the LX Protocol works

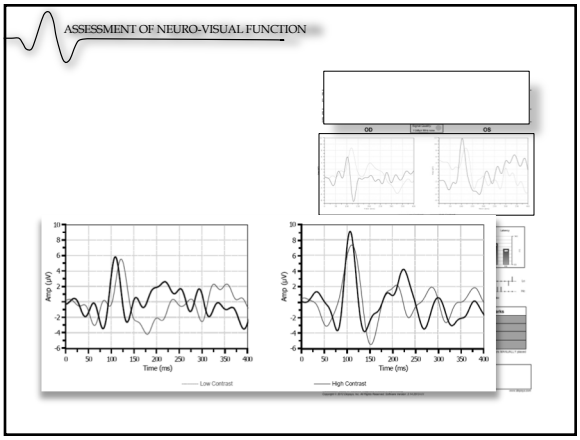
- Low contrast testing demonstrates degradation of magnocellular pathways
  - An early indication of glaucoma
- High contrast testing demonstrates degradation of parvocellular pathways
  - An early indicator of central vision loss and issues caused by problems before signal reaches optic nerve

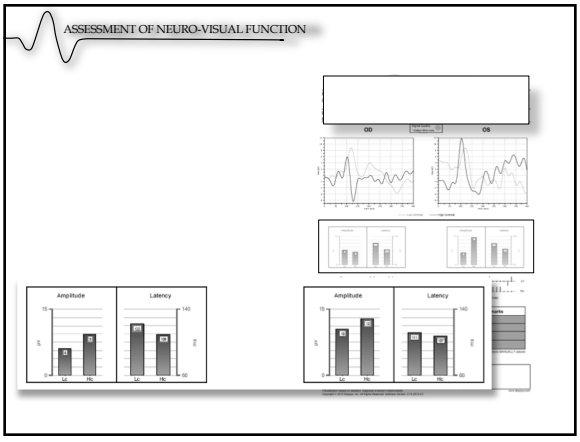
patient should be tested with best corrected vision

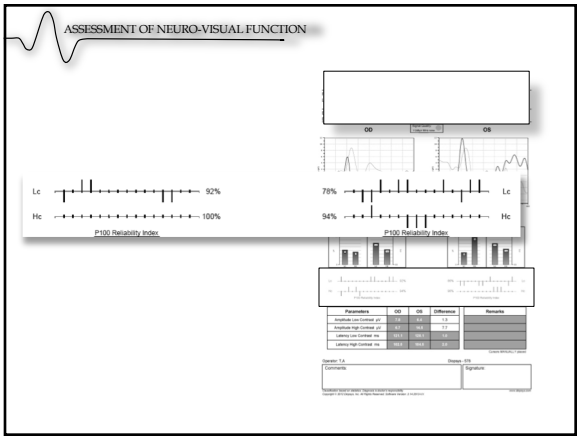


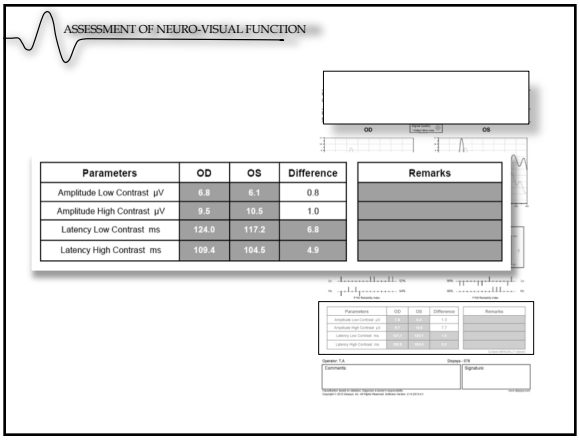


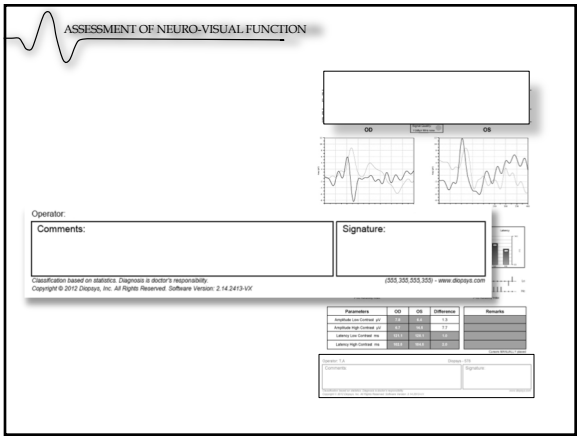





ASSESSMENT OF NEURO-VISUAL FUNCTION
OD
OS
Amplitude
Latency


ASSESSMENT OF NEURO-VISUAL FUNCTION
OD
OS
Lc
92%
Hc
100%
P100 Reliability Index
78%
Lc
94%
Hc
P100 Reliability Index


ASSESSMENT OF NEURO-VISUAL FUNCTION
OD
OS
Parameters
OD
OS
Difference
Remarks
Amplitude Low Contrast µV
6.8
6.1
0.8
Amplitude High Contrast µV
9.5
10.5
1.0
Latency Low Contrast ms
124.0
117.2
6.8
Latency High Contrast ms
109.4
104.5
4.9


ASSESSMENT OF NEURO-VISUAL FUNCTION
OD
OS
Operator:
Comments:
Signature:
Classification based on statistics. Diagnosis is doctor's responsibility.
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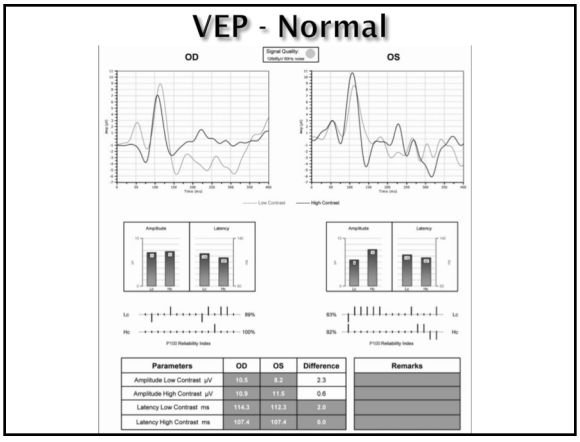
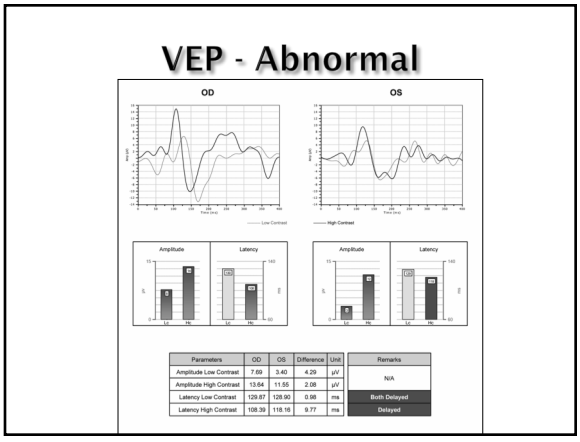
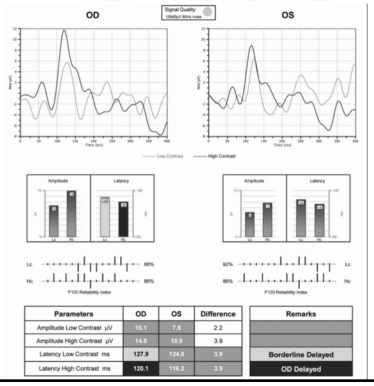
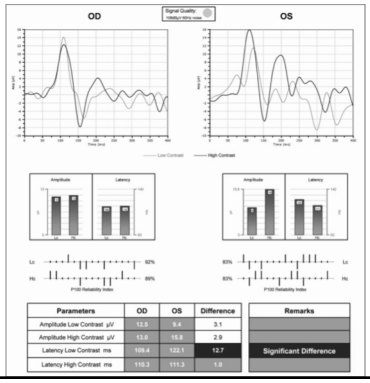

VEP - Normal
OD
OS
Signal Quality
Low Contrast
High Contrast
Amplitude
Latency
P100 Reliability Index
Parameters
OD
OS
Difference
Remarks
Amplitude Low Contrast µV
10.5
8.2
2.3
Amplitude High Contrast µV
10.9
11.5
0.6
Latency Low Contrast ms
114.3
112.3
2.0
Latency High Contrast ms
107.4
107.4
0.0


VEP - Abnormal
OD
OS
Low Contrast
High Contrast
Amplitude
Latency
Parameters
OD
OS
Difference
Unit
Remarks
Amplitude Low Contrast
7.69
3.40
4.29
µV
Amplitude High Contrast
13.64
11.55
2.08
µV
N/A
Latency Low Contrast
129.87
128.90
0.98
ms
Both Delayed
Latency High Contrast
108.39
118.16
9.77
ms
Delayed

VEP - Abnormal



VEP abnormal - Asymmetry



VEP - Summary

- VEP is an objective, functional test that can help discriminate between healthy and diseased eyes
- Indications:
  - Glaucoma
  - MS/Optic neuritis
  - Optic neuropathies
  - Unexplained vision loss
  - Transient vision loss
  - Visual field defects
  - Amblyopia/Strabismus
  - Traumatic brain injury

Pattern ERG (pERG)

- ERG's are electrical signals that are a measure of the electrophysiological activity at the retina
  - ***Mid-retinal layers, ganglion cell layer, and nerve fiber layer***
- Objectively measures retinal function**
- ERG's can help improve sensitivity and specificity in diagnosing optic neuropathies and maculopathies like glaucoma and macular degeneration when used in conjunction with other tests
- Can also help the clinician differentiate between retinal and optic nerve disorders when used in conjunction with Visual Evoked Potential (VEP).

pERG Advanced Protocols

1. Concentric Stimulus Fields
   - Drug toxicity
   - Diabetic macular edema
   - AMD
2. Contrast Sensitivity
   - Glaucoma
   - Diabetic retinopathy

pERG

1. Concentric Stimulus Fields
   - Stimulus delivered at 15 flips/second
   - BCVA
     - Pt should be properly refracted for 24″
   - 24″ testing distance
   - 100% contrast
   - Right eye (OD) then Left Eye (OS)
     - 25 seconds at 24 degrees
     - 25 seconds at 16 degrees

pERG

2. Contrast Sensitivity
   - Stimulus delivered at 15 flips/second
   - BCVA
     - Pt should be properly refracted for 24"
   - 24" testing distance
   - 85% and 15%
   - Right eye (OD) then Left Eye (OS)
     - 25 seconds at High Contrast (Hc)
     - 25 seconds at Low Contrast (Lc)

Per NIH and Bascom-Palmer:

"In patients who are glaucoma suspects, pERG signal anticipates an equivalent loss of OCT signal by several years (as many as 8 years).

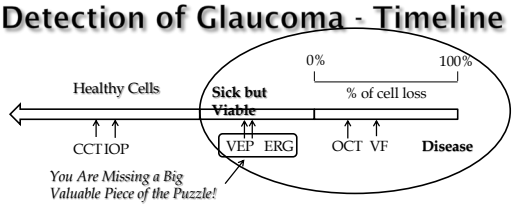
Invest Ophthalmol Vis Sci. 2013;54:2346-2352) DOI:10.1167/iovs.12-11026

Glaucoma

Progressive Loss of Retinal Ganglion Cell Function Precedes Structural Loss by Several Years in Glaucoma Suspects

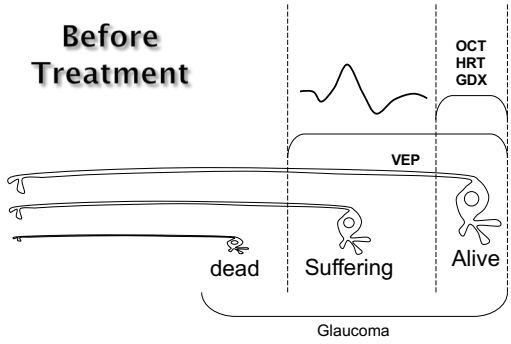
Michael E. Hood, Lori M. Ventura, William J. Feuer, Eleonore Sanitovsky, Gabriel Luna, Olga Shif, Brandon Rossa, and Vittorio Porciatti

Detection of Glaucoma - Timeline



- ERG shown to detect glaucoma while cells are alive, **up to 8 years before OCT**. (IOVS, 2013; Mar;54(3): 2346-52)
- VEP may be able to detect glaucoma slightly earlier than ERG as the disease is shown to affect LGN before retina (PNAS: 2010 Mar)
- SAP requires approx 30% (6% to 57% range) cell death to register peripheral vision loss (Ophthalmology: 2013 Apr;120(4):736-44)
- OCT detects glaucoma approximately 2 to 3 years before VF with about 15% RNFL loss (Est)

Before Treatment



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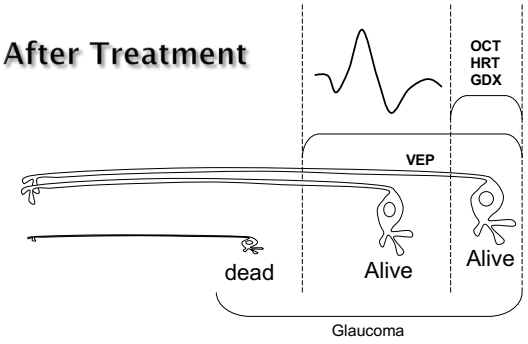
After Treatment



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pERG Indications

- Glaucoma
- Optic Neuropathies
- Maculopathies
  - AMD
  - Diabetic retinopathy
  - Diabetic macular edema
  - Macular toxicity

Review Article

Role of Electrophysiology in the Early Diagnosis and Follow-Up of Diabetic Retinopathy

Nicola Pescosolido,[1] Andrea Barbato,[2] Alessio Stefanucci,[3] and Giuseppe Buomprisco[4]

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[2]*Center of Ocular Electrophysiology, Department of Sense Organs, Faculty of Medicine and Dentistry, "Sapienza" University of Rome, Viale del Policlinico 155, 00161 Rome, Italy*
[3]*Faculty of Medicine and Dentistry, "Sapienza" University of Rome, Viale del Policlinico 155, 00161 Rome, Italy*
[4]*Department of Sense Organs, Faculty of Medicine and Dentistry, "Sapienza" University of Rome, Viale del Policlinico 155, 00161 Rome, Italy*

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Retinopathy is a severe and common complication of diabetes, representing a leading cause of blindness among working-age people in developed countries. It is estimated that the number of people with diabetic retinopathy (DR) will increase from 126.6 million in 2011 to 191 million by 2030. The pathology seems to be characterized not only by the involvement of retinal microvessels but also by a real neuropathy of central nervous system, similar to what happens to the peripheral nerves, particularly affected by diabetes. The neurophysiological techniques help to assess retinal and nervous (optic tract) function. Electroretinography (ERG) and visual evoked potentials (VEP) allow a more detailed study of the visual function and of the possible effects that diabetes can have on the visual function. These techniques have an important role both in the clinic and in research: the central nervous system, in fact, has received much less attention than the peripheral one in the study of the complications of diabetes. These techniques are safe, repeatable, quick, and objective. In addition, both the ERG (especially the oscillatory potentials and the flicker-ERG) and VEP have proved to be successful tools for the early diagnosis of the disease and, potentially, for the ophthalmologic follow-up of diabetic patients.

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Clinical science

OPEN ACCESS

The Diabetes Visual Function Supplement Study (*DiVFuSS*)

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[2]Captain James A Lovell Federal Health Care Center, North Chicago, Illinois, USA
[3]Private Practice, Olathe, Kansas, USA
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ABSTRACT

Background Diabetes is known to affect visual function before onset of retinopathy (diabetic retinopathy (DR)). Protection of visual function may signal disruption of mechanisms underlying DR.

Methods This was a 6-month randomised, controlled clinical trial of patients with type 1 and type 2 diabetes with no retinopathy or mild to moderate non-proliferative retinopathy assigned to twice daily consumption of placebo or a novel, multi-component formula containing xanthophyll pigments, antioxidants and selected botanical extracts. Measurement of contrast sensitivity, macular pigment optical density, colour discrimination, 5-2 macular threshold perimetry, Diabetic Peripheral Neuropathy Symptoms, foveal and retinal nerve fibre layer thickness, glycohaemoglobin (HbA1c), serum lipids, 25-OH-vitamin D, tumour necrosis factor α (TNF-α) and high-sensitivity C reactive protein (hsCRP) were taken at baseline and 6 months. Outcomes were assessed by differences between and within groups at baseline and at study conclusion using mean± SDs and t tests ($p<0.05$) for continuous variables.

Results There were no significant intergroup differences at baseline. At 6 months, subjects on active supplement compared with placebo had significantly better visual function on all measures (p values ranging from 0.008 to <0.0001), significant improvements in most serum lipids (p values ranging from 0.01 to 0.0004), hsCRP ($p=0.01$) and diabetic peripheral neuropathy (Fisher's exact test, $p=0.0024$) No significant changes in retinal thickness, HbA1c, total cholesterol or TNF-α were found between the groups.

Conclusions This study provides strong evidence of clinically meaningful improvements in visual function, hsCRP and peripheral neuropathy in patients with the risk of DR and its progression, evidence shows that there is no level of average blood glucose (as reflected by glycosylated haemoglobin) that is totally protective against DR. The current clinical algorithm for delaying DR and preventing STR is earlier diagnosis of diabetes, tighter metabolic control, routine dilated retinal examinations and treatment (laser photocoagulation, intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents and corticosteroids) if/when DR progresses to a level that threatens vision.

The *Age-Related Eye Disease Study* (AREDS) demonstrated that a nutritional supplement could positively influence progression of a vision-threatening eye disease, age-related macular degeneration.[1] This begs the question as to whether nutritional supplements may benefit other eye diseases, including DR. Vitamins, minerals and other micronutrients have a variety of biological functions potentially beneficial in diabetes, serving as enzymatic cofactors mediating glucose homeostasis, as regulators of cell growth and differentiation, and as building blocks of antioxidant defence. Thus, there has been renewed interest in their potential for preventing or treating a host of diabetes complications.[2]

A number of investigators have shown that diabetes affects visual function prior to the development of DR detectable by ophthalmoscopy. This includes deficits in contrast,[3 4] visual field[5 6] and colour vision sensitivity.[7–10] As such, amelioration of these visual function deficits may serve as an additional, useful biomarker for the onset and progression of retinopathy in patients with diabetes, yet no clinically evident DR, as well as those with

RESEARCH Open Access

Beneficial effects of the nutritional supplements on the development of diabetic retinopathy

Renu A Kowluru[1*], Qing Zhong[1], Julia M Santos[1], Mangayarkarasi Thandampallayam[1], Doug Putt[1] and Dennis L Gierhart[2]

Abstract

Purpose: Increased oxidative stress and inflammatory mediators are implicated in the development of diabetic retinopathy, and in rats, its development can be prevented by antioxidants. Carotenoids are some of the powerful antioxidants, and diabetes decreases lutein and zeaxanthin levels in the serum and retina. The aim of this study is to investigate the effect of carotenoid containing nutritional supplements (Nutr), which is in clinical trials for 'Diabetes Vision Function', on diabetic retinopathy.

Methods: Streptozotocin-induced diabetic rats (Wistar, male) were fed Purina 5001 supplemented with nutritional supplements containing zeaxanthin, lutein, lipoic acid, omega-3 fatty acids and other nutrients, or without any supplementation. Retinal function was analyzed at ~4 months of diabetes by electroretinography. After 11 months of diabetes, capillary cell apoptosis (TUNEL-staining) and histopathology (degenerative capillaries) were quantified in trypsin-digested retinal vasculature. Retina was also analyzed for mitochondrial damage (by quantifying gene expressions of mtDNA-encoded proteins of the electron transport chain), VEGF and inflammatory mediators, interleukin-1β and NF-κB.

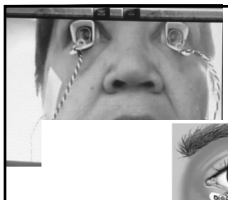
Results: Diabetes impaired retinal function decreasing the amplitudes of both a- and b-waves. In the same animals, retinal capillary cell apoptosis and degenerative capillaries were increased by 3–4 fold. Gene expressions of mtDNA encoded proteins were decreased, and VEGF, interleukin-1β and NF-κB levels were elevated. Supplementation with the nutrients prevented increased capillary cell apoptosis and vascular pathology, and ameliorated these diabetes-induced retinal abnormalities.

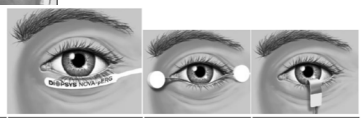
Conclusions: Nutritional supplementation prevents diabetic retinopathy, and also maintains normal retinal function, mitochondrial homeostasis and inflammatory mediators. Thus, this supplementation could represent an achievable and inexpensive adjunct therapy to also inhibit retinopathy, a slow progressing disease feared most by diabetic patients.

Keywords: Carotenoids, Diabetic retinopathy, Macular pigment, Mitochondria, Nutritional supplements, Zeaxanthin

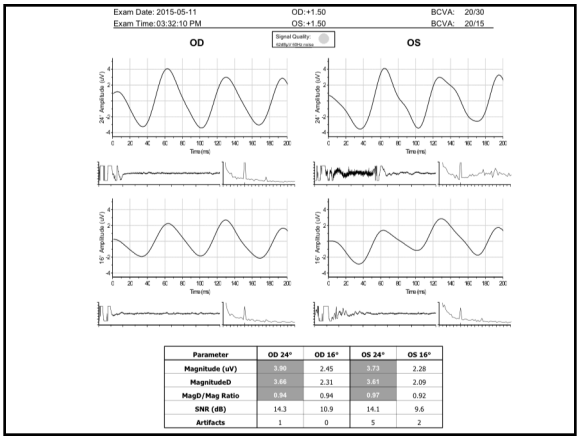
pERG Testing

pERG Lid Sensor



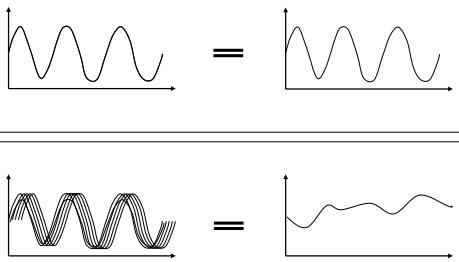


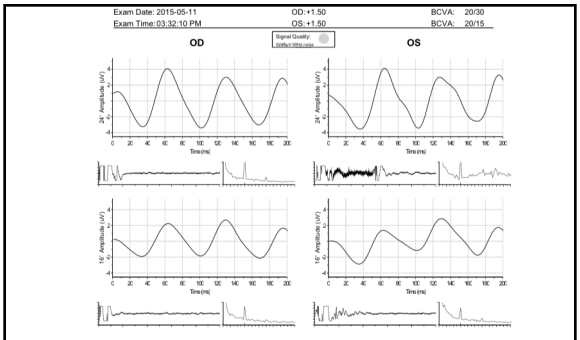
Electrode	Diopsys	DTL	Gold Foil
Position	Skin	Cornea (invasive)	Cornea (invasive)
Repeatability	Good	Sensitive to eye movements (noise)	Sensitive to eye movements (noise)
Usage	Disposable	Disposable	Disposable
Risk for Corneal Damage and Eye Irritation	Minimal	High	High
Need for Anesthetic	No	Occasionally	Frequently
Application	Easy	Very Difficult	Very Difficult



Parameter	OD 24°	OD 16°	OS 24°	OS 16°
Magnitude (uV)	3.90	2.45	3.73	2.28
MagnitudeD	3.66	2.31	3.61	2.09
MagD/Mag Ratio	0.94	0.94	0.97	0.92
SNR (dB)	14.3	10.9	14.1	9.6
Artifacts	1	0	5	2

Magnitude D





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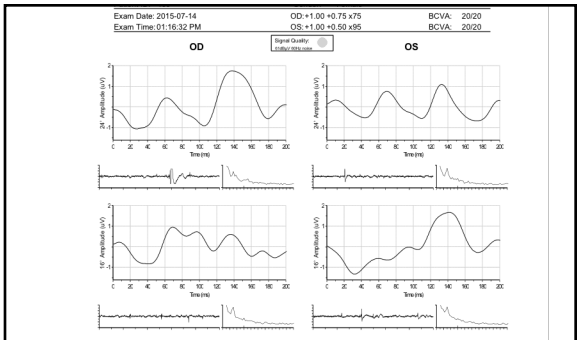
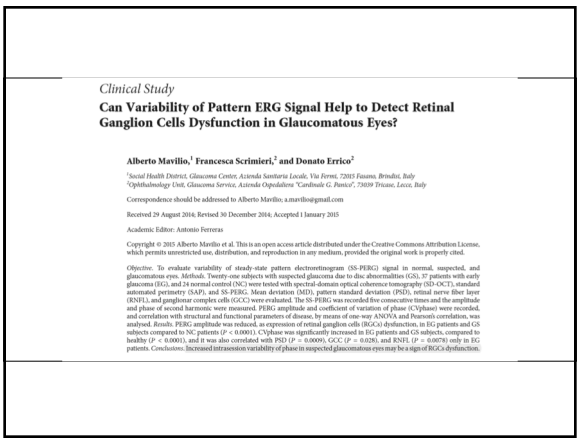


Parameter	OD 24°	OD 16°	OS 24°	OS 16°
Magnitude (uV)	1.01	1.25	1.24	1.17
MagnitudeD	0.75	0.46	0.72	0.54
MagD/Mag Ratio	0.74	0.37	0.58	0.46
SNR (dB)	0.3	2.4	2.3	1.3
Artifacts	1	0	0	0



Clinical Study

Can Variability of Pattern ERG Signal Help to Detect Retinal Ganglion Cells Dysfunction in Glaucomatous Eyes?

Alberto Mavilio,[1] Francesca Scrimieri,[2] and Donato Errico[2]

[1]*Social Health District, Glaucoma Center, Azienda Sanitaria Locale, Via Ferrni, 72015 Fasano, Brindisi, Italy*
[2]*Ophthalmology Unit, Glaucoma Service, Azienda Ospedaliera "Cardinale G. Panico", 73039 Tricase, Lecce, Italy*

Correspondence should be addressed to Alberto Mavilio, a.mavilio@gmail.com

Received 29 August 2014; Revised 30 December 2014; Accepted 1 January 2015

Academic Editor: Antonio Ferreras

Objective. To evaluate variability of steady-state pattern electroretinogram (SS-PERG) signal in normal, suspected, and glaucomatous eyes. *Methods.* Twenty-one subjects with suspected glaucoma due to disc abnormalities (GS), 37 patients with early glaucoma (EG), and 24 normal control (NC) were tested with spectral-domain optical coherence tomography (SD-OCT), standard automated perimetry (SAP), and SS-PERG. Mean deviation (MD), pattern standard deviation (PSD), retinal nerve fiber layer (RNFL), and ganglionar complex cells (GCC) were evaluated. The SS-PERG was recorded five consecutive times and the amplitude and phase of second harmonic were measured. PERG amplitude and coefficient of variation of phase (CVphase) were recorded, and correlation with structural and functional parameters of disease, by means of one-way ANOVA and Pearson's correlation, was analysed. *Results.* PERG amplitude was reduced, as expression of retinal ganglion cells (RGCs) dysfunction, in EG patients and GS subjects compared to NC patients ($P < 0.0001$). CVphase was significantly increased in EG patients and GS subjects, compared to healthy ($P < 0.0001$), and it was also correlated with PSD ($P = 0.0009$), GCC ($P = 0.028$), and RNFL ($P = 0.0078$) only in EG patients. *Conclusions.* Increased intrasession variability of phase in suspected glaucomatous eyes may be a sign of RGCs dysfunction.

Value as a Prognostic Indication of Progression of OHT to Glaucoma

Visual Field and FDT: 25-50% sensitivity

OCT: approximately 70%

PERG: 77%

Normal PERG Response

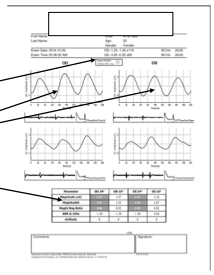
3 Quick Steps To Report Interpretation

Signal Quality – Look for a green signal

Sinusoidal Peaks – Look for 3 humps

Magnitude, MagnitudeD and MagD/Mag Ratio are colorized.

Green indicates within normal limits
Yellow indicates values are borderline
Red indicates outside normal limits



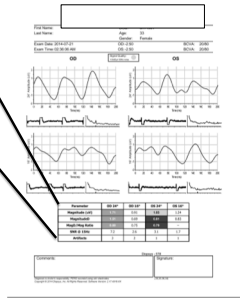
PERG Report – Data Table

Parameter	OD 24°	OD 16°	OS 24°	OS 16°
Magnitude (uV)	1.71	0.91	1.03	1.24
MagnitudeD	1.51	0.69	0.81	0.83
MagD/Mag Ratio	0.88	0.75	0.79	--
SNR @ 15Hz	7.2	2.6	3.1	1.7
Artifacts	3	2	1	1

Magnitude (uV) is defined as the strength of the patient's response at a reversal rate of 15 reversals per second.

Larger magnitudes are typically generated from normal eyes. Smaller magnitudes typically indicate pathology.

As the contrast level drops or the stimulus size decreases, the magnitude will typically decrease.



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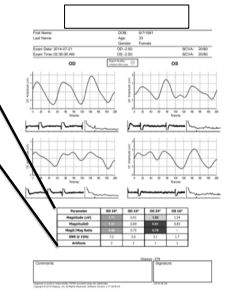
Artifacts	3	2	1	1

MagnitudeD averages the signal within the 25 second test time and takes into account the magnitude strength and the phase variability throughout the test.

In a healthy patient, the phase response tends to be consistent throughout the test. In this case, MagD is close in value to Mag.

In a patient with disease, the phase response tends to be inconsistent throughout the test - MagD will be significantly reduced in comparison with Mag.



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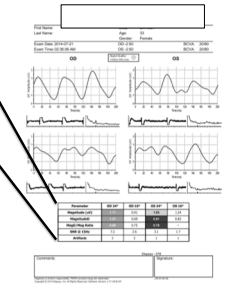
SNR @ 15Hz	7.2	2.6	3.1	1.7
Artifacts	3	2	1	1

MagD/Mag Ratio is the most repeatable measurement test-over-test. The closer the ratio is to 1.0, the lower the phase variability throughout the test, and the healthier the patient's response. Variability in phase may indicate pathology.

MagD/Mag ratio can used to monitor patients over time.



Data Table

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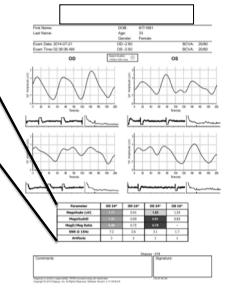
SNR @ 15Hz	7.2	2.6	3.1	1.7
Artifacts	3	2	1	1

SNR - Signal to Noise Ratio shows how strong the signal is at 15Hz compared to noise at 15Hz. Larger numbers indicate stronger PERG signals compared to the noise.

SNR values like 5, 15, >20 show strong PERG response. Numbers less than 2 are typical of a weak response.



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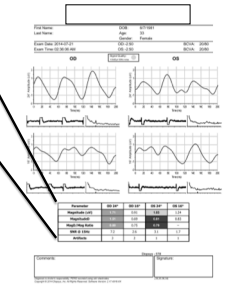
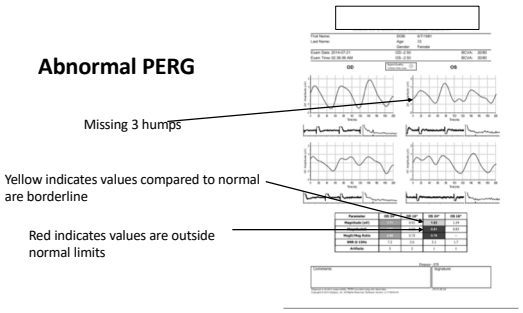
SNR @ 15Hz	7.2	2.6	3.1	1.7
Artifacts	3	2	1	1

Artifacts are caused by blinking or patient movement. They are detected and counted. A high number of artifacts will effect the amount of data that can be analyzed.

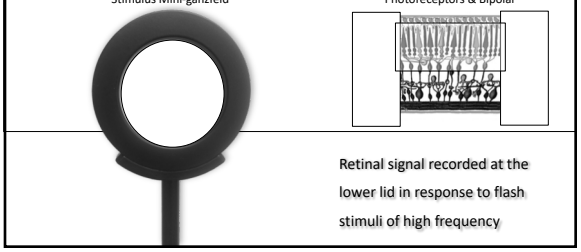
The goal is to have a low number of artifacts. We want the patient to be comfortable and blink when necessary, but not excessively. The goal is less than 10. If tests results show Artifacts greater than 10, the test should be repeated.



Abnormal PERG



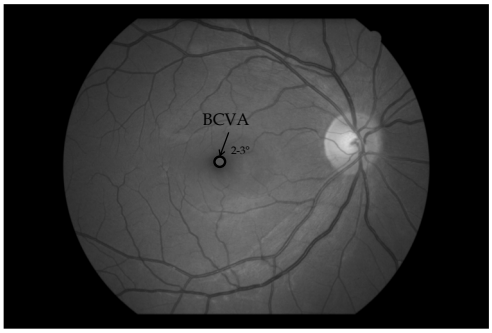
Flicker Electroretinogram (Flicker ERG)

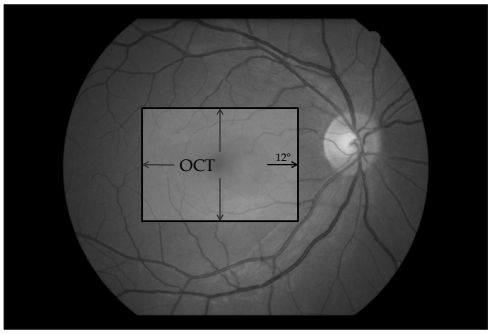


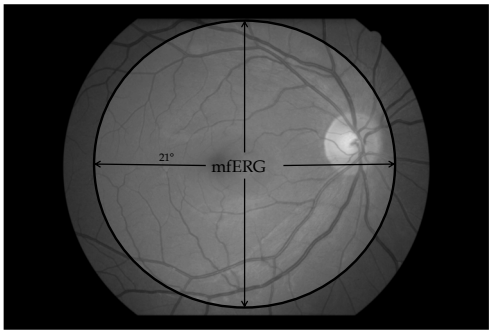
Retinal signal recorded at the lower lid in response to flash stimuli of high frequency

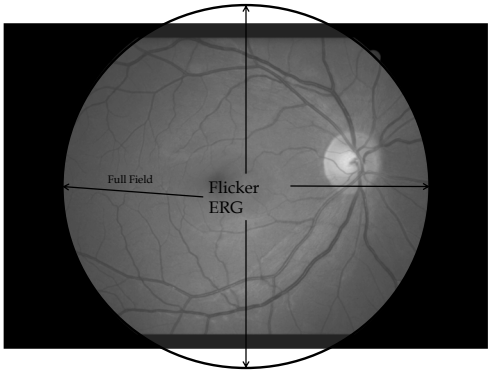
Full-field ERG (ffERG)

- Tests the outer retina
  - Photoreceptors (rod & cones)
  - Bipolar cells
- Test of overall retinal functioning
  - May not pick up small retinal issues
- Flash flicker stimulus









Full-field ERG (ffERG)

- Tests the outer retina
  - Photoreceptors (rod & cones)
  - Bipolar cells
- Test of overall retinal functioning
  - May not pick up small retinal issues
- Flash flicker stimulus

Full-field ERG (ffERG)

- ffERG indications:
  - DM & diabetic retinopathy
    - Monitoring progression
    - Monitoring improvement with treatment
  - Retinal dystrophies/disease
    - Rod/cone problems
    - RP
  - Pt symptoms:
    - Color vision issues
    - VF defects
    - Decreased vision
    - Unexplained decreased vision
  - Testing retinal function with significant media opacities
  - Indicator for prognosis following cataract surgery
    - Is the retina functioning well or not?

ERG for Early Detection

Review Article

Role of Electrophysiology in the Early Diagnosis and Follow-Up of Diabetic Retinopathy

Nicola Pescosolido,[1] Andrea Barbato,[2] Alessio Stefanucci,[3] and Giuseppe Buomprisco[4]

[1]*Department of Cardiovascular, Respiratory, Nephrologic, Anesthesiologic and Geriatric Sciences, Faculty of Medicine and Dentistry, "Sapienza" University of Rome, Viale del Policlinico 155, 00161 Rome, Italy*
[2]*Center of Ocular Electrophysiology, Department of Sense Organs, Faculty of Medicine and Dentistry, "Sapienza" University of Rome, Viale del Policlinico 155, 00161 Rome, Italy*
[3]*Faculty of Medicine and Dentistry, "Sapienza" University of Rome, Viale del Policlinico 155, 00161 Rome, Italy*
[4]*Department of Sense Organs, Faculty of Medicine and Dentistry, "Sapienza" University of Rome, Viale del Policlinico 155, 00161 Rome, Italy*

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Received 30 December 2014; Accepted 1 April 2015

Academic Editor: Secundino Cigarran

Retinopathy is a severe and common complication of diabetes, representing a leading cause of blindness among working-age people in developed countries. It is estimated that the number of people with diabetic retinopathy (DR) will increase from 126.6 million in 2011 to 191 million by 2030. The pathology seems to be characterized not only by the involvement of retinal microvessels but also by a real neuropathy of central nervous system, similar to what happens to the peripheral nerves, particularly affected by diabetes. The neurophysiological techniques help to assess retinal and nervous (optic tract) function. Electroretinography (ERG) and visual evoked potentials (VEP) allow a more detailed study of the visual function and of the possible effects that diabetes can have on the visual function. These techniques have an important role both in the clinic and in research: the central nervous system, in fact, has received much less attention than the peripheral one in the study of the complications of diabetes. These techniques are safe, repeatable, quick, and objective. In addition, both the ERG (especially the oscillatory potentials and the flicker-ERG) and VEP have proved to be successful tools for the early diagnosis of the disease and, potentially, for the ophthalmologic follow-up of diabetic patients.

ERG for Evaluating Retinal Dysfunction

The Electroretinogram in Diabetic Retinopathy

R. Tzekov, MD, PhD,[1] and G. B. Arden, MD, PhD, FRCOphth[2]

[1]*Retina Foundation of the Southwest, Dallas, Texas, USA, and* [2]*Center for Applied Vision Research, Department of Optometry and Visual Science, City University, London, United Kingdom*

Abstract. Electroretinography (ERG) is an objective method of evaluating retinal function. Since its introduction to clinical practice in the 1940s, it has become a useful and routine diagnostic clinical tool in ophthalmology. This review summarizes the role of ERG as a clinical technique for evaluating the progression of diabetic retinopathy and as a research tool for increasing our understanding of the pathophysiology of diabetic retinopathy. Most studies show unequivocally that the different types of ERG tests detect local abnormalities or widespread pathology, even in very early stages of the disease. It seems plausible that measurements from ERG recordings, particularly the oscillatory potentials, may be useful for predicting progression from nonproliferative to the more sight-threatening stages—preproliferative or proliferative—of diabetic retinopathy. Some recent work implies that the ERG can also be a useful diagnostic method for discriminating between eyes with diabetic retinopathy and those without the condition. (**Surv Ophthalmol 44**:53–60, 1999. © 1999 by Elsevier Science Inc. All rights reserved.)

Flicker ERG for Treatment Evaluation

Doc Ophthalmol
DOI 10.1007/s10633-015-9495-9

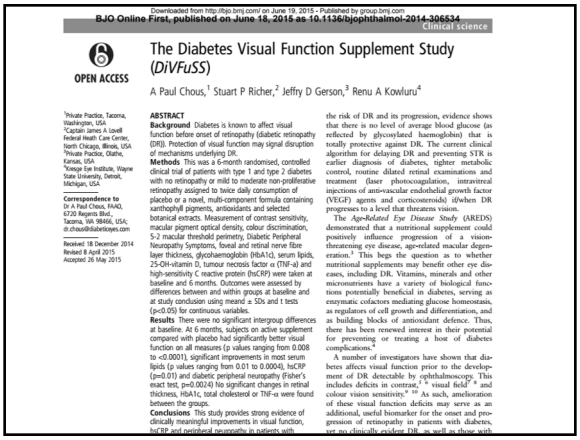
ORIGINAL RESEARCH ARTICLE

Peripheral retinal function assessed with 30-Hz flicker seems to improve after treatment with Lucentis in patients with diabetic macular oedema

Kristina Holm · Marion Schroeder · Monica Lövestam Adrian

Received: 19 December 2014 / Accepted: 5 March 2015

Abstract
Purpose To evaluate the influence of ranibizumab on the multifocal electroretinogram (Mf-ERG), full-field electroretinogram (Ff-ERG) and optical coherence tomography (OCT) in diabetic eyes ($n = 20$) with macular oedema.
Methods In 20 eyes (20 diabetic subjects) with no or background diabetic retinopathy and macular oedema (age 65.7 ± 9.8 years, duration 16.5 ± 10.0 years), the change in ETDRS letters, Mf-ERG, Ff-ERG and significantly between baseline (35.5 ± 3.6 ms) and final follow-up (34.6 ± 3.1 ms) ($p = 0.04$).
Discussion Though the central retinal thickness was reduced after three injections of ranibizumab and the subjects gained a mean of 11 ETDRS letters, there was no significant change in amplitude or implicit time in Mf-ERG. The shortened 30-Hz flicker implicit time might imply that ranibizumab has no negative impact on the entire peripheral cone function, but can improve it instead.



BJO Online First, published on June 18, 2015 as 10.1136/bjophthalmol-2014-306534
Clinical science

OPEN ACCESS

The Diabetes Visual Function Supplement Study (*DiVFuSS*)

A Paul Chous,[1] Stuart P Richer,[2] Jeffry D Gerson,[3] Renu A Kowluru[4]

[1]Private Practice, Tacoma, Washington, USA
[2]Captain James A Lovell Federal Heath Care Center, North Chicago, Illinois, USA
[3]Private Practice, Olathe, Kansas, USA
[4]Kresge Eye Institute, Wayne State University, Detroit, Michigan, USA

Correspondence to
Dr A Paul Chous, FAAO, 6720 Regents Blvd., Tacoma, WA 98466, USA; dr.chous@diabeticeyes.com

Received 18 December 2014
Revised 8 April 2015
Accepted 26 May 2015

ABSTRACT

Background Diabetes is known to affect visual function before onset of retinopathy (diabetic retinopathy (DR)). Protection of visual function may signal disruption of mechanisms underlying DR.

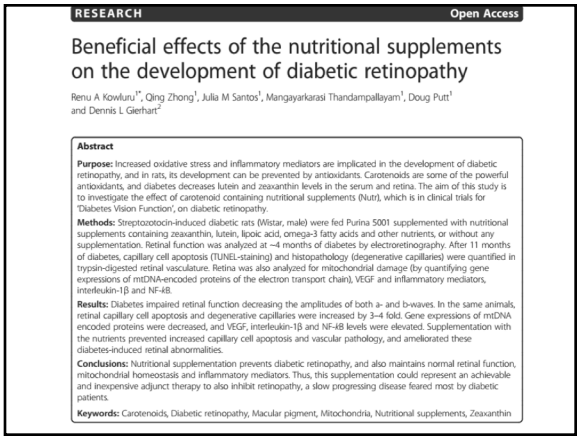
Methods This was a 6-month randomised, controlled clinical trial of patients with type 1 and type 2 diabetes with no retinopathy or mild to moderate non-proliferative retinopathy assigned to twice daily consumption of placebo or a novel, multi-component formula containing xanthophyll pigments, antioxidants and selected botanical extracts. Measurement of contrast sensitivity, macular pigment optical density, colour discrimination, 5-2 macular threshold perimetry, Diabetic Peripheral Neuropathy Symptoms, foveal and retinal nerve fibre layer thickness, glycohaemoglobin (HbA1c), serum lipids, 25-OH-vitamin D, tumour necrosis factor α (TNF-α) and high-sensitivity C reactive protein (hsCRP) were taken at baseline and 6 months. Outcomes were assessed by differences between and within groups at baseline and at study conclusion using mean± ± SDs and t tests ($p<0.05$) for continuous variables.

Results There were no significant intergroup differences at baseline. At 6 months, subjects on active supplement compared with placebo had significantly better visual function on all measures (p values ranging from 0.008 to <0.0001), significant improvements in most serum lipids (p values ranging from 0.01 to 0.0004), hsCRP ($p=0.01$) and diabetic peripheral neuropathy (Fisher's exact test, $p=0.002$-6) No significant changes in retinal thickness, HbA1c, total cholesterol or TNF-α were found between the groups.

Conclusions This study provides strong evidence of clinically meaningful improvements in visual function, hsCRP and peripheral neuropathy in patients with the risk of DR and its progression, evidence shows that there is no level of average blood glucose (as reflected by glycosylated haemoglobin) that is totally protective against DR. The current clinical algorithm for delaying DR and preventing STR is earlier diagnosis of diabetes, tighter metabolic control, routine dilated retinal examinations and treatment (laser photocoagulation, intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents and corticosteroids) if/when DR progresses to a level that threatens vision.

The *Age-Related Eye Disease Study* (AREDS) demonstrated that a nutritional supplement could positively influence progression of a vision-threatening eye disease, age-related macular degeneration.[1] This begs the question as to whether nutritional supplements may benefit other eye diseases, including DR. Vitamins, minerals and other micronutrients have a variety of biological functions potentially beneficial in diabetes, serving as enzymatic cofactors mediating glucose homeostasis, as regulators of cell growth and differentiation, and as building blocks of antioxidant defence. Thus, there has been renewed interest in their potential for preventing or treating a host of diabetes complications.[2]

A number of investigators have shown that diabetes affects visual function prior to the development of DR detectable by ophthalmoscopy. This includes deficits in contrast,[3 4] visual field[5 6] and colour vision sensitivity.[7 8] As such, amelioration of these visual function deficits may serve as an additional, useful biomarker for the onset and progression of retinopathy in patients with diabetes, yet no clinically evident DR, as well as those with



RESEARCH Open Access

Beneficial effects of the nutritional supplements on the development of diabetic retinopathy

Renu A Kowluru[1*], Qing Zhong[1], Julia M Santos[1], Mangayarkarasi Thandampallayam[1], Doug Putt[1] and Dennis L Gierhart[2]

Abstract

Purpose: Increased oxidative stress and inflammatory mediators are implicated in the development of diabetic retinopathy, and in rats, its development can be prevented by antioxidants. Carotenoids are some of the powerful antioxidants, and diabetes decreases lutein and zeaxanthin levels in the serum and retina. The aim of this study is to investigate the effect of carotenoid containing nutritional supplements (Nutr), which is in clinical trials for 'Diabetes Vision Function', on diabetic retinopathy.

Methods: Streptozotocin-induced diabetic rats (Wistar, male) were fed Purina 5001 supplemented with nutritional supplements containing zeaxanthin, lutein, lipoic acid, omega-3 fatty acids and other nutrients, or without any supplementation. Retinal function was analyzed at ~4 months of diabetes by electroretinography. After 11 months of diabetes, capillary cell apoptosis (TUNEL-staining) and histopathology (degenerative capillaries) were quantified in trypsin-digested retinal vasculature. Retina was also analyzed for mitochondrial damage (by quantifying gene expressions of mtDNA-encoded proteins of the electron transport chain), VEGF and inflammatory mediators, interleukin-1β and NF-κB.

Results: Diabetes impaired retinal function decreasing the amplitudes of both a- and b-waves. In the same animals, retinal capillary cell apoptosis and degenerative capillaries were increased by 3–4 fold. Gene expressions of mtDNA encoded proteins were decreased, and VEGF, interleukin-1β and NF-κB levels were elevated. Supplementation with the nutrients prevented increased capillary cell apoptosis and vascular pathology, and ameliorated these diabetes-induced retinal abnormalities.

Conclusions: Nutritional supplementation prevents diabetic retinopathy, and also maintains normal retinal function, mitochondrial homeostasis and inflammatory mediators. Thus, this supplementation could represent an achievable and inexpensive adjunct therapy to also inhibit retinopathy, a slow progressing disease feared most by diabetic patients.

Keywords: Carotenoids, Diabetic retinopathy, Macular pigment, Mitochondria, Nutritional supplements, Zeaxanthin

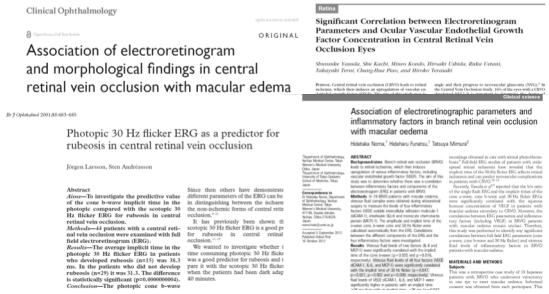
Flicker ERG Reproducibility

ICC in Healthy eyes

Protocol	Parameter	ICC
Flicker ERG	Magnitude	0.93
	Phase	0.98

Wills Eye Hospital, ARVO 2016

Retinal Evaluation in Eyes with CRVO



Clinical Ophthalmology

ORIGINAL

Association of electroretinogram and morphological findings in central retinal vein occlusion with macular edema

Br J Ophthalmol 2001;85:683–685

Photopic 30 Hz flicker ERG as a predictor for rubeosis in central retinal vein occlusion

Jörgen Larsson, Sten Andréasson

Retina

Significant Correlation between Electroretinogram Parameters and Ocular Vascular Endothelial Growth Factor Concentration in Central Retinal Vein Occlusion Eyes

Clinical science

Association of electroretinographic parameters and inflammatory factors in branch retinal vein occlusion with macular oedema

Hidetaka Noma,[1] Hideharu Funatsu,[1] Tatsuya Mimura[2]

ERG vs FA : Predictive value of Vascularization

FA:52%
ERG:94%

Acta Ophthalmologica Scandinavica 1998

Fluorescein angiography versus ERG for predicting the prognosis in Central Retinal Vein Occlusion

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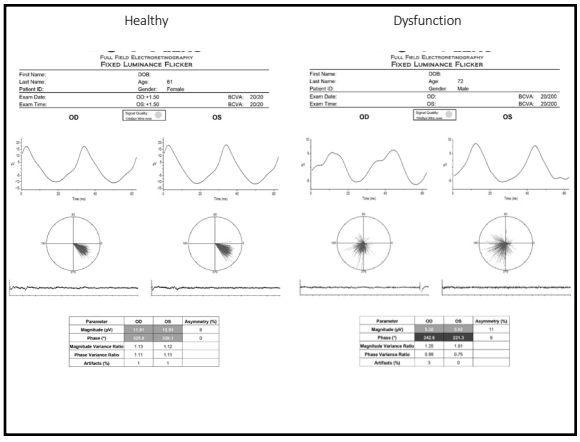
Flicker ERG is a good predictor of ischemia

Flicker ERG can be used to evaluate DR

Flicker ERG can be used to monitor patients and evaluate referals

ffERG Testing

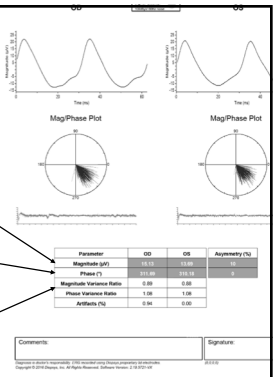


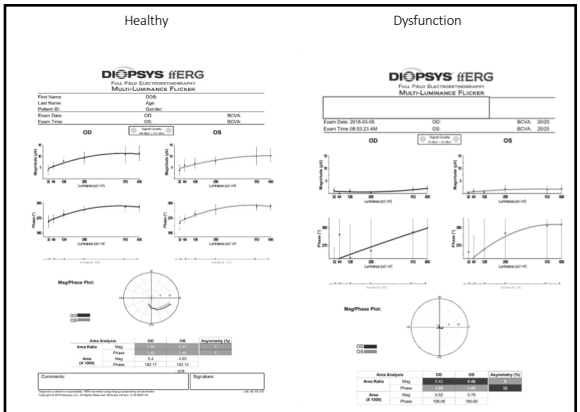
Flicker ERG Report

Magnitude is the cone/bipolar signal strength

Phase is the timing of the cone/bipolar response

Magnitude and Phase Variance represent the consistency of the strength and speed of the signal respectively

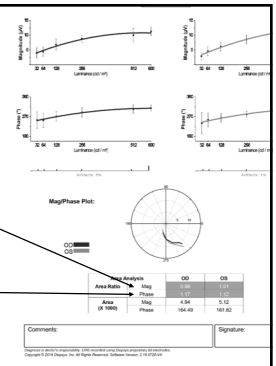




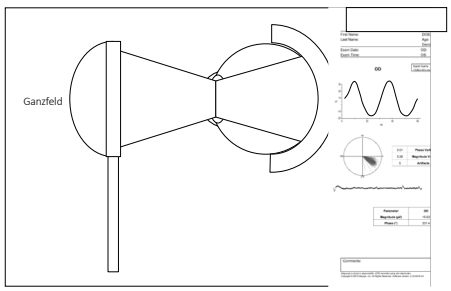
Flicker ERG Report

Magnitude area is the cone/bipolar combined signal strength of the 6 luminance levels

Phase area is the cone/bipolar combined signal timing of the 6 luminance levels

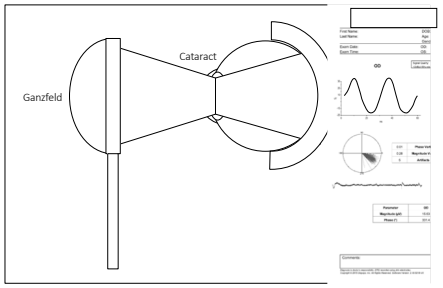


Macular Function Evaluation in Eyes Without Cataracts



1. Ratanapakorn T, Patarakittam T, Sinawat S, Sanguansak T, Bhoomibunchoo C, Kaewpanna S, Yospaiboon Y. Effect of cataract on electroretinographic response. J Med Assoc Thai. 2010;93:1196-9.
2. Pérez-Salvador García E, Pérez Salvador JL. Variability of electrophysiological readings in mature cataracts. Arch Soc Esp Oftalmol. 2002;77:543-51.

Macular Function Evaluation in Eyes With Cataracts



1. Ratanapakorn T, Patarakittam T, Sinawat S, Sanguansak T, Bhoomibunchoo C, Kaewpanna S, Yospaiboon Y. Effect of cataract on electroretinographic response. J Med Assoc Thai. 2010;93:1196-9.
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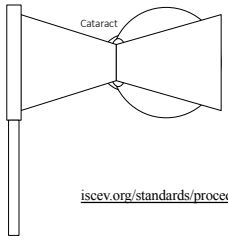
Macular Function Evaluation in Eyes With Cataracts

ISCEV* Recommend using ERG for the evaluation of retinal function in patients with media opacities.

*(*International Society of Clinical Electrophysiology of Vision*)



iscev.org/standards/proceduresguide.html

Applying to Your Practice

VEP

1. Glaucoma & glaucoma suspects
2. Unexplained vision loss
3. Transient vision loss
4. Unexplained VF defects
5. Unreliable VF
6. Optic neuropathies
7. Optic neuritis/MS
8. Amblyopia
9. TBI

PERG

1. Glaucoma & glaucoma suspects
2. Unexplained VF defects
3. Unreliable VF
4. Optic neuropathies
5. Maculopathies
   1. AMD
   2. Diabetic macular edema
   3. High risk med use (Plaquenil)
   4. Generalized DR

FFERG

1. DM & retinopathy
2. RP & its variants
3. Cone dystrophies & Rod monochromat
4. Symptoms:
   - "Night blindness"
   - Restricted peripheral fields
   - Color vision deficits
   - Unexplained decreased vision
5. To get an idea of retinal functioning in a pt with media opacity

IN-OFFICE ELECTRODIAGNOSTICS FOR THE NON-GLAUCOMA PATIENT: DM, AMD, ETC

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