REVIEW ARTICLE

Mitochondrial Retinal Imaging – What Do We Know So Far?

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Received: 19 November 2018
Accepted: 20 March 2019
Published: 06 April 2019

Abstract

Recent studies demonstrate the crucial role of mitochondria in retinal disease pathogenesis. Recently, a device was developed to non-invasively study retinal metabolic stress and measure retinal mitochondrial activity. Previous studies indicate that oxidized flavoproteins increase during metabolic stress and are a marker of mitochondrial dysfunction. This device measures oxidized flavoprotein fluorescence, which absorbs blue light and emits green autofluorescence. This review summarizes the biological rationale, technology advances, research findings, and future perspectives of mitochondrial retinal imaging.

Keywords: Age-related macular degeneration, Diabetic retinopathy, Flavoprotein fluorescence, Mitochondrial retinal imaging, Retinal metabolic analysis, Retinal mitochondrial dysfunction

INTRODUCTION

The mitochondrion is considered to be the powerhouse of eukaryotic cells. Oxidative phosphorylation produces energy, leading to adenosine triphosphate production. In addition, mitochondria perform numerous other functions in cellular homeostases such as apoptosis regulation, steroid biosynthesis, and nucleotide metabolism. For this reason, mitochondrial dysfunction can severely compromise cellular homeostasis and has been highlighted as a crucial mechanism in the pathophysiology of normal aging and pathologic processes including retinal diseases.[1,2]

Access this article online

Quick Response Code:

Website: www.ajoclinicaltrials.com

DOI: 10.25259/AJOCT-13-2018

Mitochondrial dysfunction is recognized to play a crucial role in a wide range of diseases and organs, with the most affected organs being those that have a high metabolic rate such as brain and heart.[3] For example, previous studies have shown evidence of mitochondrial involvement in the pathophysiology of neurodegenerative diseases including Parkinson's disease, Alzheimer's disease, and Huntington's disease, and in cardiac ischemia-reperfusion injury.

Recent research also highlighted the importance of mitochondria in another highly metabolic active tissue: The retina. Mitochondria are abundantly present in active retinal cells such as retinal pigmented epithelium (RPE) cells. The mitochondria play a central part in homeostasis. Reactive oxygen species (ROS) can typically alter mitochondria functions leading to respiratory chain impairment and loss of membrane potential; these changes precede apoptosis.[4]

Thus, rising comprehension of mitochondria's role in retinal functioning led to the development of a novel device to assess oxidative stress as a measure of retinal health. In contrast with

other organs, the retina medium is transparent and allows for non-invasive detection of mitochondrial dysfunction.

To date, many papers have been published testing this device in different diseases. The purpose of this review is to provide a concise source about current understandings of mitochondrial non-invasive imaging in normal and retinal diseases.

LITERATURE SEARCH

A literature search of PubMed was conducted and the papers included were published between 2008 and 2018. Articles published in peer-reviewed journals on mitochondrial retinal imaging were included. The search included the following keywords: Non-invasive detection mitochondrial dysfunction and/or mitochondria dysfunction imaging and/or retina flavoprotein fluorescence (FPF). Publications cited in the references that were relevant to our subject were also selected. After reviewing the abstracts, studies not directly related to the topic were excluded from the study.

RETINAL DISEASES AND MITOCHONDRIAL DYSFUNCTION

Multiple studies have shown the importance of mitochondria in the pathophysiology of retinal disorders such as diabetic retinopathy (DR), age-related macular degeneration (AMD), and glaucoma.

DR

In diabetes mellitus (DM), hyperglycemia induces chronic overproduction of ROS that impair antioxidant defenses,[5] damaging mitochondrial DNA (mtDNA), and disrupting mitochondrial membrane potential. This leads to cytochrome C release and initiation of apoptosis. In response, damaged mitochondria produce more ROS creating a vicious cycle of oxidative damage (Figure 1).[6,7]

AMD

Mitochondria of RPE cells are recognized to have considerable involvement in AMD development.[1] From a genetic standpoint, a variant of the gene age-related maculopathy susceptibility 2 (ARMS2) has been identified to raise disease susceptibility. This variant transcript is an unstable mRNA and decreased the production of the mitochondrial protein ARMS2 adversely affects organelle functioning. Furthermore, oxidative damage increases with aging and can induce structural mtDNA changes due to mtDNA lack of histones and introns. In the RPE cells of AMD *in vitro* models, multiple studies have shown that the mtDNA lacks appropriate repair systems and is more prone to damage, leading to a reduction of metabolic activity and increased apoptosis (Figure 1).[8-10]

Glaucoma

The optic nerve is very susceptible to mitochondrial damage considering the high metabolic needs of retinal ganglion

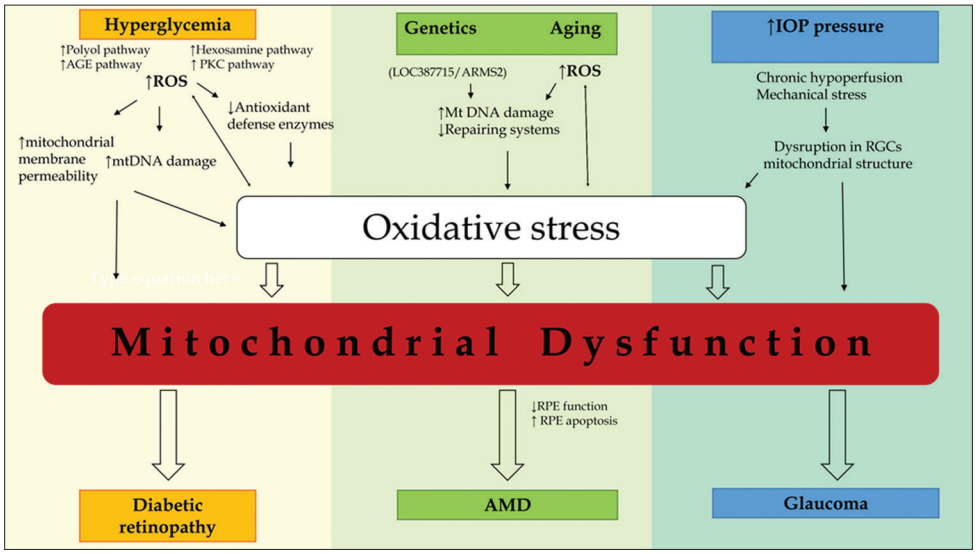

Figure 1: Synoptic image of pathophysiological pathways involving mitochondrial dysfunction. Different factors like hyperglycemia, genetics, aging and intraocular pressure can trigger the alterations that lead to an increase in oxidative stress which causes mitochondrial dysfunction. In turn, mitochondrial dysfunction increases oxidative stress and leads to a vicious cycle of oxidative damage.

Table 1: Synoptic table of device versions

Device generation	Camera	Year	Focus	Number of published papers	LSLO	Field of view
First-generation	Zeiss F4 modified	2008	Manual	4	No	3°
Second-generation	Custom optimized optical train and electronic components	2012	Manual	3	Yes	13°
Third-generation	EIDON	2018	Manual+automatic	0	Yes	23°

cells (RGCs). Increased intraocular pressure induces chronic hypoperfusion and mechanical stress that impairs mitochondrial function and structure in RGCs (Figure 1).[2]

OXIDIZED FLAVOPROTEINS AS A MEASURE OF RETINAL MITOCHONDRIAL DYSFUNCTION

The growing interest in understanding the mitochondrial role in human pathology established the need for measuring its activity or inactivity. There is a very broad spectrum of techniques that have been proposed, all of which are dependent on the precise definition authors give to the vague term "dysfunction." In the pertinent literature, dysfunction is primarily defined as uncoupling of the respiratory chain that leads to a rise in oxidative stress and subsequently to apoptosis.[1] Oxidative stress impairs mitochondrial equilibrium as increased ROS production and damage overshadows antioxidant defenses. Under these conditions, flavoproteins involved in the electron transport chain become oxidized.[11] Mitochondrial dysfunction can be estimated assessing the presence of oxidized flavoproteins, which absorbs blue light and emits green autofluorescence.[12] This measurement is called FPF and estimates oxidative stress by measuring average intensity (FPF score) and standard deviation (SD) of the autofluorescence emitted. *In vitro* studies have previously combined NAD(P)H fluorescence with FPF, but this cannot be replicated in humans because excitation wavelengths for NAD(P)H have phototoxic effects on retinal cells.[13]

Ex vivo

Several studies recognize FPF as a reliable index of mitochondrial health in non-ocular tissues including skeletal muscle, heart muscle, and brain.[14,15] In particular, FPF has been measured in animal models to evaluate the redox state of the heart during ischemia-reperfusion, skeletal muscle in aging, and neuronal activity.[16-18]

Elner *et al*. were the first to apply this technique in retinal research.[12] They induced sub-lethal stress by adding hydrogen peroxide or ceramide to human RPE cells in culture and detected an increase in FPF. This increase was prevented with antioxidants treatment beforehand, indicating that oxidation of retinal mitochondria increased FPF. Field *et al*. recently confirmed these results and also demonstrated that FPF levels increase with a mitochondrial membrane potential reduction and a pro-inflammatory cytokines upregulation, both of which precede apoptosis.[13] These findings provide a biological rationale for the presumption that mitochondrial FPF can serve as a biomarker that precedes retinal cell apoptosis and retinal structural changes. *In vitro* and *ex vivo* results indicate the potential of an instrument capable of *in vivo* non-invasive retinal measurements.

In vivo

Elner *et al*. were the first to customize a fundus camera to non-invasively measure retinal FPF in humans.[19] The first-generation prototype was a Zeiss F4 (Carl Zeiss, Oberkochen, Germany) fundus camera with modified wavelengths filters (467 nm excitation and 535 nm emission), an attached back-illuminated, electron-multiplying, and charge-coupled device camera interfacing a dedicated image capturing and analysis software. The initial captured field was 3 (Table 1).

The second-generation of the camera was a completely custom-built device with a wider field of view (13°) for FPF imaging and also the capability of obtaining a 30° infrared fundus image before the FPF picture was taken.

The third and current generation is an EIDON confocal scanner (Centervue, Padova, Italy) equipped with excitation filters of 458 ± 2 nm. This device detects a fluorescence spectrum that goes from 520 to 540 nm. This instrument has built-in imaging, measurement, and analysis capabilities and can autofocus independently for imaging. To date (October 2018), there are no peer-reviewed publications with this new model (OcuSciences Inc, technical specification document).

METABOLIC ANALYSIS OF RETINAL DISEASES

Eight peer-reviewed papers have been published regarding FPF as a biomarker in retinal diseases (Table 2).

First-generation device studies

The first-generation camera was initially used to evaluate patients with pseudotumor cerebri (PTC).[19] This study was

Table 2: Summary table of published peer-reviewed studies with FPF device

Title	Authors	Date	Population (eyes)	Captured field	Results
Retinal flavoprotein autofluorescence as a measure of retinal health	Elner *et al*.	2008	28 DM 2 AMD 2 CSR bilateral 2 RP 18 Controls	3°	FPF score is increased with both age and disease severity. DM cases without retinopathy have higher scores than controls but lower than DM cases with retinopathy. AMD, CSR, and RP cases have higher score compared to age-matched control. HRPE cells incubated with H_2O_2 or C2-ceramide have increased FPF. When pre-incubated with antioxidants the increase is blocked.
Retinal FPF correlates with mitochondrial stress, apoptosis, and chemokine expression	Field *et al*.	2011			Incubation of HRPE cells with H_2O_2 or monocytes increases FPF score and decreases mitochondrial membrane potential; these changes precede apoptosis. Incubation of human or rat neural retina with H_2O_2 increases FPF, when the antioxidant is added effect is reversed.
Flavoprotein autofluorescence detection of early ocular dysfunction	Elner *et al*.	2008	12 PTC 12 controls	3°	Patients with PTC have a higher FPF score and SD in the more affected eye while there is no difference between eyes in controls.
Rapid, non-invasive detection of diabetes-induced retinal metabolic stress	Field *et al*.	2008	42 DM 42 Controls	3°	FPF score and SD are higher in DM patients compared to age-matched controls. FPF and curve width increase with age in all the considered population.
Detection of retinal metabolic stress resulting from CSR	Field *et al*.	2009	6 CSR 6 Controls	3°	CSR eye has a higher FPF score than the unaffected eye. Both eyes have higher FPF score compared to the control group.
Non-invasive Imaging of Mitochondrial Dysfunction in Dry Age-related Macular Degeneration	Field *et al*.	2012	3 AMD 3 AMD with GA 3 Controls	15°	FPF score and SD are greater in the AMD group compared to the age-matched control group.
Non-invasive detection of mitochondrial dysfunction in OHT and primary open-angle glaucoma	Geyman *et al*.	2018	38 POAG 16 OHT 32 Controls	13°	FPF score and FPF score/RGC+thickness are increased in the OHT group compared with the control group. Only FPF score/RGC+thickness is increased in the POAG group compared to the control group.
Double-masked, placebo-controlled trial of the efficacy of a novel neuroprotective combination for reversing mitochondrial dysfunction in glaucoma	Ritch *et al*.	2018	28 Glaucoma	13°	Optic disc FPF score and SD decreases in glaucoma patients treated with an antioxidant drug (GlaucoHealth™) compared to patients treated with placebo.

(Contd...)

Table 2: *(Continued)*

Title	Authors	Date	Population (eyes)	Captured field	Results
FPF correlation with visual acuity response in patients receiving an anti-VEGF injection for diabetic macular edema	Andrade Romo *et al.*	2018	8 DM with CSDME	13°	FPF score correlates with BCVA changes after anti-VEGF treatment. While the correlation between OCT and BCVA was not significant.

FPF: Flavoprotein fluorescence, VEGF: Vascular endothelial growth factor, SD: Standard deviation, DM: Diabetes mellitus, BCVA: Best corrected visual acuity, OCT: Optical coherence tomography, OHT: Ocular hypertension, GA: Geographic atrophy, POAG: Primary open angle glaucoma, AMD: Age-related macular degeneration, RGC: Retinal ganglion cell, CSR: Central serous retinopathy

conducted on six patients with PTC (12 eyes) and six age-matched controls (12 eyes). The results showed that the more diseased eye had a higher FPF score and SD than the other eye of the diseased patient by a margin of at least 25%. This was not true in control age-matched patients, who had similar results in both eyes.

Two papers examined FPF in DM patients with the purpose of elucidating a possible relationship between FPF and DM. Elner *et al*. recruited a cohort of 21 age-matched patients (42 eyes total: 14 DM with DR, 14 DM without retinopathy, and 14 controls).[12] Their results showed a correlation between FPF score and severity of disease, with the DM with retinopathy group displaying the highest ($P = 0.04$). Field *et al*. imaged 42 patients (84 eyes total: 24 DM with DR, 18 DM without DR, and 42 age-matched controls) and confirmed that DM without DR patients had a higher FPF score and SD than controls ($P \leq 0.04$).[20] DR patients had the highest FPF score and SD ($P = 0.02$). Study investigators also examined the role of hemoglobin A1c (HBA1c), but there seemed to be no relationship between HBA1c and FPF score. These findings need to be validated since glycemic control is well known to correlate with DR progression.[21] Both studies on DM patients demonstrated a progressive increase in FPF score with age in patient groups and controls, which explains the necessity of age breakdown when analyzing results.

In the same study, Elner *et al*. also measured patients with other diseases. One case of AMD, one case of retinitis pigmentosa, and one case of central serous retinopathy (CSR) were compared with age-matched controls (12 eyes total). The diseased eyes were measured to have higher FPF score and SD. In these papers, FPF is the equivalent of their usage of "flavoprotein autofluorescence."

Another study was conducted to evaluate FPF in acute CSR.[22] Investigators recruited three patients with acute unilateral CSR (6 eyes) and three age-matched controls (6 eyes). Results showed all three affected eyes had higher FPF score compared with three unaffected eyes of diseased patients ($P < 0.001$, < 0.05, and < 0.001, respectively), which, in turn, were higher than two age-matched controls ($P < 0.001$, < 0.05) the third one was greater but not significant ($P < 0.15$).

Second-generation device studies

In 2012, Field *et al*. investigated the role of mitochondrial dysfunction in AMD using FPF.[23] They imaged six eyes from five patients with non-exudative AMD of which three had geographic atrophy (GA), and three eyes from 3 age-matched controls. The study indicated that FPF score was significantly distinguishable between AMD eyes with GA, AMD eyes without GA, and age-matched controls. The AMD eyes with GA had the highest FPF while the eyes AMD without GA eyes had higher FPF score than age-matched controls ($P = 0.02$).

In 2018, Geyman *et al*. studied FPF score changes in primary open angle glaucoma (POAG) and ocular hypertension (OHT).[24] This study involved 20 patients (38 eyes) with POAG, eight patients (16 eyes) OHT, and 18 (32 eyes) age-matched controls. FPF score was also compared against optical coherence tomography (OCT) derived RGC layer thickness. A FPF score/RGC+ thickness ratio considers the progressive thinning that occurs with disease progression. The study reported a higher FPF score and FPF score/RGC+ thickness ratio in OHT when compared to controls ($P < 0.05$ and $P < 0.01$). Only FPF score/RGC+ thickness ratio was greater in POAG patients than in controls ($P < 0.001$). Consequently, the study suggests a correlation in the POAG group between FPF score and age but did not find any correlation between FPF score and IOP or RGC+ thickness.

In 2018, Ritch *et al*.[25] assessed the changes in FPF score with a combination of antioxidant agents (GlaucoHealth™). 14 treated glaucoma patients (28 eyes) were randomized into two groups: One receiving placebo and the other GlaucoHealth™. After 1 month of treatment optic nerve, FPF score and SD were significantly decreased ($P = 0.003$ and $P = 0.01$). In contrast, there was no significant difference in visual fields and OCT ($P > 5\%$).

Finally, Andrade Romo *et al*. measured FPF before and after anti-vascular endothelial growth factor injection (bevacizumab) for diabetic macular edema.[26] In this study, of eight patients (eight eyes) with DR and clinically significant macular edema, results suggested an association between FPF score and best corrected visual acuity (BCVA) ($P < 0.000015$). On the other hand, a possible OCT and BCVA

relationship was not significant ($P < 0.13$). These studies demonstrate the potential for utilizing FPF and mitochondrial dysfunction as a novel approach to monitoring treatment progression, but FPF scores impact across multiple disease and treatment paradigms needs to be better established, and possible clinical utility must be more clearly defined.

DISCUSSION

Recent advances in a technology widely contributed to improve retinal imaging. However, the current standard of care devices focuses on the identification of structural changes rather than functional (metabolic) changes, despite the fact that functional changes often occur earlier in disease processes. The ability to analyze metabolic changes may allow for earlier anticipation of disease progression or even earlier diagnosis of previously unidentified disease as DR.[27] Field *et al.* introduced the possibility that FPF can be a better index for progression of retinopathy than HBA1c.[20] FPF analysis, first results have high potential in an area where an innovative diagnosis method is needed as demonstrated by the fact that none of the numerous functional techniques proposed for DR screening (e.g., electroretinography, microperimetry, color vision, and contrast sensitivity) have demonstrated a solid predictive value. In the same study, authors have shown a correlation between FPF and the presence of DR, but no analysis has been made to evaluate a relationship between DR severity and FPF score. Thus, FPF differences within DR severity needs to be further examined. This needs to be examined more thoroughly in not only DR but also additional retinal diseases with various stages of disease severity such as AMD. With long-term follow-up and larger sample sizes, future studies can explore FPF as a prognostic index and provide additional insight on manifestations at each disease stage that cannot be elucidated with current imaging technology.

Furthermore, preliminary results achieved in AMD, glaucoma, and CSR have shown that retinal functional alterations are present in many diseases, which pathophysiological pathways also indicate. Moreover, Ritch *et al*. demonstrated that optic disc FPF score decreases in glaucoma with antioxidant drug usage. Future studies can assess the efficacy of various treatments such as antioxidant drugs in different retinal diseases. In this scenario, mitochondrial retinal imaging represents a promising technology that transposes basic science knowledge to the clinical setting. This technology offers the possibility to perform a rapid, affordable, and non-invasive retinal functional study potentially applicable to all retinal diseases.

However, there are some divergences that merit further examination. According to the previous studies, FPF increases with aging and AMD.[12,23] In contrast, Feher *et al*. have demonstrated that the number of mitochondria decreases with aging and it is even lower in patients with AMD.[28] Based on Feher's findings, it seems counterintuitive that FPF scores increase with greater mitochondrial cell death when considering Feher's findings. However, one hypothesis is that the higher scores in more advanced stages of disease such as advance non-exudative and exudative AMD are actively indicating ongoing increases in mitochondrial dysfunction that will soon be followed by cell death. Henceforth, cell death and lower PFF scores may not be seen until a patient has experienced permanent vision loss. Additional studies are needed to clarify the correlation between a number of mitochondria and FPF. The points at which mitochondrial dysfunction level accelerates and later declines as cell death occurs for each retinal disease are subjected to uncertainty and exploration.

Moreover, a number of drawbacks are present. Two versions of the device have been used in these studies, and the field of view and FPF analysis software was different. Device model changes and the change in the field of view likely lead to differences in FPF score standardization. As a result, not all papers in the literature can be compared and examined together. Rigorous standardization of a single device that can measure FPF scores across all ophthalmic diseases is required to improve reliability and allow use in clinical settings. Present studies do not provide useful information to examine inter-individual variability. For example, FPF might be influenced by retinal mitochondrial density, lens status, lipofuscin concentration, and other factors. To define abnormal results, further studies to determine normality are needed, and any effect these factors have on FPF must be ascertained.

Finally, only eight investigations have been published, and all these studies rely on very limited sample size. Consequently, larger populations are needed to confirm the current findings.

CONCLUSION

FPF is a sensitive, albeit non-specific technology. This makes it suitable for a wide range of diseases, especially for screening and follow-up purposes. Future studies will eventually refine and solidify the present literature.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsership

Nil.

Conflicts of interest

Dr. Rishi P. Singh is on the Editorial Board of the Journal. RR: None TC: None, GH: None, RPS: Regeneron (grants and personal fees), Genentech/Roche (grants and personal fees), Alcon/Novartis (grants and personal fees), Apellis (grants),

Optos (personal fees), Zeiss (personal fees), Biogen (personal fees), during the conduct of the study.

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How to cite this article: Raimondi R, Hom GL, Conti TF, Singh RP. Mitochondrial Retinal Imaging – What Do We Know So Far?. Am J Ophthalmic Clin Trails 2019, 2(2) 1-7.