PROJECT

Supervisor: Prof. Giuseppe Querques

Title: Therapeutic Strategies for Non-neovascular Age-related Macular Degeneration: Metabolic Evaluation Through Spectrally Resolved Autofluorescence and PhotoBioModulation Treatment.

Curriculum: Clinical and Experimental Medicine

Link to the personal page of the University or relevant hospital site website: https://www.hsr.it/dottori/giuseppe-querques

https://www.unisr.it/docenti/q/querques-giuseppe

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Age-related macular degeneration (AMD) represents the leading cause of irreversible central vision loss among elderly populations in developed countries, accounting for a significant proportion of visual disability worldwide. Current estimates suggest that AMD affects approximately 170 million individuals globally, with this figure projected to increase dramatically to 288 million by 2040 due to aging populations. AMD manifests in two primary forms: neovascular AMD, characterized by pathological neovessels growth and exudation, and non-neovascular AMD, distinguished by drusen deposits and potential progression to geographic atrophy (GA). While therapeutic interventions for neovascular AMD have advanced considerably through anti-vascular endothelial growth factor (anti-VEGF) therapies, treatment options for non-neovascular AMD remain severely limited, particularly for preventing progression to advanced stages of the disease.

The scientific community's efforts in recent years have focused on identifying novel therapeutic approaches for non-neovascular AMD, with PhotoBioModulation (PBM) emerging as a promising non-invasive intervention. PBM, also known as low-level light therapy (LLLT), utilizes specific wavelengths of light (primarily within the red to near-infrared spectrum, 630-850 nm) to modulate cellular function, particularly targeting mitochondrial metabolism. Recent clinical investigations, including the LIGHTSITE trial series (I, II, and III), have demonstrated encouraging outcomes regarding PBM's potential to improve visual function and reduce disease progression in AMD. However, these studies exhibit considerable limitations including variation in treatment protocols, insufficient follow-up periods, and heterogeneous patient cohorts.

A critical gap in current research lies in the absence of objective, quantifiable biomarkers to evaluate PBM's metabolic effects on retinal tissue. Conventional imaging modalities fail to capture the metabolic changes hypothesized to underlie PBM's therapeutic mechanism. Spectrally Resolved Autofluorescence (SrAF) represents an innovative imaging technique with the capacity to quantify metabolic alterations in retinal tissue by detecting specific endogenous fluorophores, particularly flavin adenine dinucleotide (FAD), a key indicator of mitochondrial activity. Despite PBM's theoretical promise and preliminary clinical evidence, there remains a significant scientific challenge in establishing:

- Reliable biomarkers for monitoring treatment response;
- Standardized protocols for PBM application in AMD;
- Precise mechanisms of action at the cellular and tissue levels;
- Accurate methods for patient selection and stratification.

For these reasons, investigating the application of advanced metabolic imaging in the assessment of PBM for non-neovascular AMD carries significant implications for addressing this growing public health concern.

Rationale and hypothesis

Non-neovascular AMD represents a significant therapeutic challenge, with limited interventions available to prevent disease progression. PBM has emerged as a promising non-invasive treatment already used in clinical practice, but a fundamental obstacle in its optimization remains the absence of objective biomarkers to confirm and quantify its metabolic effects on retinal tissue.

The current evaluation of PBM efficacy relies primarily on functional outcomes such as visual acuity and contrast sensitivity, which may be influenced by multiple factors beyond direct therapeutic effect. Additionally, conventional imaging modalities provide limited insight into the metabolic changes hypothesized to underlie PBM's mechanism of action. This makes it difficult to determine optimal treatment intervals for maintaining therapeutic benefits.

This project addresses these limitations by proposing SrAF as an objective biomarker for PBM treatment assessment. Several characteristics support this approach:

- SrAF enables non-invasive quantification of FAD at the 575 nm wavelength band, a direct indicator of mitochondrial activity;
- Mitochondrial dysfunction represents a primary pathophysiological mechanism in disease development;

- Current clinical applications show treatment effects may diminish over time, requiring identification of optimal intervals for retreatment;

- Existing clinical evidence shows functional improvements without objective metabolic confirmation of mechanism.

We hypothesize that PBM induces significant time-dependent metabolic changes in the retina, detectable through increased FAD autofluorescence. We further hypothesize these changes will correlate with visual function improvements and anatomical stabilization. Validating SrAF as a biomarker would provide an objective means to monitor treatment response and establish individualized retreatment protocols for patients already receiving PBM therapy.

Objectives and specific aims

Overall objective: To establish SrAF as a reliable biomarker for monitoring metabolic changes induced by PBM therapy in non-neovascular AMD and determine optimal treatment intervals.

Specific aims:

- To quantify metabolic changes through SrAF measurements at the 575 nm wavelength band (FAD) following PBM treatment;

- To determine the time-course and duration of metabolic effects, establishing optimal intervals for retreatment;

- To correlate metabolic changes with functional outcomes including visual acuity and contrast sensitivity;

- To assess anatomical modifications through multimodal imaging (OCT, OCT-A, fundus autofluorescence);

- To compare SrAF biomarker changes with conventional functional and structural assessments.

Expected outcomes

We expect that SrAF will serve as a valuable biomarker for monitoring metabolic effects on mitochondrial function in patients with non-neovascular AMD, potentially providing a tool for stratifying candidates and treatment outcomes with PBM. This non-invasive approach may offer insights into retinal metabolism that could guide therapeutic strategies for early intervention in AMD progression.

Skills that the student should acquire (max. 600 characters including spaces):

- Design and conduct prospective clinical studies in Clinical and Experimental Medicine with focus on retinal pathologies;
- Perform PhotoBioModulation (PBM) laser treatments for patients with non-neovascular AMD;
- Utilize advanced retinal imaging techniques, with particular reference to Spectrally Resolved Autofluorescence (SrAF);
- Develop standardized clinical protocols for patient monitoring and determination of optimal treatment intervals;
- Critically analyze scientific literature and interpret results in the clinical context;
- Communicate scientific findings through conference presentations and publications in sector journals.

References (max. 15)

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