Non-invasive quantitative retinal imaging as potential biomarker in healthy volunteers and patients with degenerative diseases of the brain and the eye

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The general objective is to validate a new non-invasive retinal imaging tool that allows the identification of relevant biomarkers in the retina in degenerative diseases of the brain and the eye by scattering and absorption properties.

Ethical review	Approved WMO
Status	Pending
Health condition type	Glaucoma and ocular hypertension
Study type	Observational non invasive

Summary

ID

NL-OMON57452

Source
ToetsingOnline

Brief title
Retinal imaging in healthy subjects and patients

Condition

- Glaucoma and ocular hypertension
- Movement disorders (incl parkinsonism)

Synonym
retina; back part of the eye

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: TNO

Intervention

Keyword: degenerative diseases of the brain, eye diseases, retinal imaging

Outcome measures

Primary outcome

• Vascular network

• Quantitative scattering & absorption maps at 8 wavelengths

o Oxygen saturation map

o Blood volume fraction map

o Microvascular diameter map

o Scattering amplitude map

o Wavelength dependence of scattering map

• Retinal thickness measurements, in particular the total thickness, RNLF and

ganglion cell layer, inner retinal layers

• Macular volume

Secondary outcome

n.a.

Study description

Background summary

The retina, an integral part of the central nervous system, plays an essential role in visual perception but also serves as a window into the systemic and neurological health of an individual. Recent evidence suggests that imaging of

the retinal oxygenation and metabolism may be valuable for the early detection and monitoring of degenerative diseases of the brain and the eye.
The most common neurodegenerative diseases are Alzheimer*s and Parkinson*s disease. These conditions are characterized by specific protein accumulations in the brain with corresponding changes detectable in the retina using optical coherence tomography (OCT). Hadoux et al. have demonstrated that non-invasive retinal imaging using light scattering and absorption maps can discriminate between individuals with and without moderate-high brain beta-amyloid. Alzheimer*s disease is marked by the accumulation of beta-amyloid protein. While Parkinson*s disease involves the loss of dopaminergic neurons along with observable thinning of the retinal nerve fiber layer (RNFL), the main misfolding protein is phosphorylated alpha-synuclein and aggregates of this protein occur inside neurons in the border of the ganglion cell, inner nuclear and plexiform layers of the retina. All these retinal changes may reflect neurodegeneration in the brain, offering a non-invasive method for early detection and monitoring of these diseases.
Imaging of retinal metabolism and oxygenation may also provide insight in the pathophysiology of many retinal diseases. In diabetic retinopathy changes occur due to chronic hyperglycaemia, leading to narrowed retinal arteries, reduced blood flow, and eventually to more progressive retinal ischaemia. Imaging modalities like fluorescein angiography and OCT-angiography cannot reliably detect early changes, unlike retinal oximetry, in order to predict progression towards proliferative diabetic retinopathy. Characterization of retinal oxygen saturation and retinal carotenoid concentrations also serves as early biomarker in age-related macular degeneration, in which hypoxia may be an early indicator of progression of dry age-related macular degeneration towards wet age-related macular degeneration. In glaucoma, a chronic optic neuropathy associated with progressive thinning of the RNFL, damage is also associated with reduced tissue oxygenation.
The Netherlands Organization for Applied Scientific Research (TNO) has developed a novel multispectral fundus camera that aims to visualize the tissue oxygenation, biochemical composition as well as structural changes in the retina. The technology, based on multicolour spatial frequency domain imaging (mc-SFDI), yields quantitative maps of scattering (related to tissue structure and proteins such as amyloid-beta and alpha-synuclein aggregates) and absorption (related to the absolute concentrations of absorbing molecules such as oxy- and deoxyhemoglobin and carotenoids) at up to 16 preselected wavelengths. It is hypothesized that the combination of structural, functional and molecular imaging of the retina using mc-SFDI will enable early disease diagnosis, monitoring of disease progression, and eventually monitoring of longitudinal clinical treatment efficacy.
The eye offers a unique transparent window for non-invasive imaging of the retina, not only assessing its complex structure but also as a biomarker tool for broader physiological changes in the early detection and management of both retinal and neurodegenerative diseases. In this study, we aim to find differences in scattering and absorption properties in the retina between healthy volunteers and patients with degenerative diseases of the brain and the

eye, which may provide further insight into these diseases.

Study objective

The general objective is to validate a new non-invasive retinal imaging tool that allows the identification of relevant biomarkers in the retina in degenerative diseases of the brain and the eye by scattering and absorption properties.

Study design

This is a phase 0 pilot study to evaluate a novel mc-SFDI fundus camera in healthy volunteers and patients with degenerative diseases of the brain and eye. The ultimate goal of this study is to identify relevant retinal biomarkers that may contribute to early diagnosis or assessment of treatment effects in the future. A reliable and practical biomarker is expected to differentiate between healthy volunteers and participants with degenerative eye and/or brain diseases and demonstrate repeatability within a single day and across multiple days.

The study will be conducted at two sites. Participants will be screened up to 28 days before the start of the study, including an ocular examination. For the actual mc-SFDI assessment of the retina, patients with retinal disease will only be evaluated at the Rotterdam Eye Hospital, with assessments limited to one eye in principle.

Healthy volunteers, patients with Alzheimer*s disease, and patients with Parkinson*s disease will be evaluated at CHDR. Healthy volunteers and patients with Parkinson*s disease will visit CHDR for a first study visit involving two mc-SFDI assessments, followed by a second visit with only one mc-SFDI assessment. Alzheimer*s disease patients will visit CHDR only once, for one mc-SFDI assessment.

No investigational medicinal product will be administered during the study. To improve the quality of retinal imaging, tropicamide 0.5% eyedrops (up to two drops per eye) will be administered to dilate the subjects' pupils. To evaluate both the camera and the biomarkers it generates, comparisons will be made between the different study populations, and inter- and intra-subject variability will be assessed. No follow-up visits are planned.

Study burden and risks

It is not expected that the medical device (a retinal imaging device) will cause any direct harm through the mechanism of action. The acquisition will be performed by medically trained personnel in a safe and monitored environment. Also, the personnel will make sure that the properties of the device will be

considered safe (e.g. the intensity of the light will be adjusted to make sure it is well tolerated by the participants).
Tropicamide 0.5% eyedrops to dilate the pupil of subjects will be administered to improve quality of the retinal imaging. Tropicamide is an ocular parasympatholytic, which is being regularly used in routine clinical care for ophthalmological fundus examination and considered safe. The most common complaint (1-10%) after administration is a burning sensation directly after administration. Subjects will experience blurred vision in the dilated eye for 2-4 hours after administration, maximum effect is seen 15-30 minutes after instillation. A dilated pupil can be visible for up to 8 hours after administration. Very rarely (<1%) convulsions, dry mouth, tachycardia, palpitations, dysuria, hallucinations and ataxia can occur. Therefore, these eye droplets will be administered under medical supervision.
The use of topical mydriatics including tropicamide is considered safe during the pregnancy as the systemic absorption and toxicity is expected to be low. However, pregnant females will not be allowed in the study, and will be assessed using a urine pregnancy test.
Participants of the study do not benefit from participating in this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Signed informed consent prior to any study-related procedure.
- Male or female subjects aged 50-80 years old.
- Body mass index (BMI) between 18 and 30 kg/m2, inclusive at screening, and with a minimum weight of 50 kg.
- Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions.
- Applicable for Parkinson*s disease patients: Parkinson*s disease patients (Hoehn and Yahr criteria 1-3 at screening), defined as a diagnosis made by a neurologist.
- Applicable for Alzheimer*s disease patients: Alzheimer*s disease patients, defined as a diagnosis made by a neurologist or geriatric care specialist, with a score on the Mini Mental State Examination of 24 or higher.
- Applicable for diabetic retinopathy patients: diagnosis of diabetes mellitus type 1 or 2 in combination with microvascular retinal damage of any degree visualised with biomicroscopy of the retina.
- Applicable for macular degeneration patients: diagnosis of age-related macular degeneration patients, at any stage, apart from end stage wet age-related macular degeneration.
- Applicable for glaucoma patients: patients with primary open angle or normal tension glaucoma with mild to severe visual field defects will be selected

Exclusion criteria

- Evidence of any active or chronic disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (following a detailed medical history and vital signs (systolic (>150 or <70 mmHg) and diastolic blood pressure (>95 or <50 mmHg), pulse rate (<45 bpm or >110 bpm). Minor deviations from the normal range may be accepted, if judged by the Investigator to have no clinical relevance.
- For women: pregnant, or breast-feeding, or planning to become pregnant during the study. For participants at the Rotterdam Eye Hospital, this will be ascertained by medical history. For participants at CHDR, an urine pregnancy test will be performed to check for current pregnancies.
- For Alzheimer*s disease patients: Inability to willfully sign the informed consent document, supported by an MMSE < 24 at screening.

- Clinically significant eye abnormalities or conditions that could interfere with retinal imaging.
- For Alzheimer*s and Parkinson disease patients in particular: no clinical signs of glaucoma, age-related macular degeneration of diabetic retinopathy.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2025
Enrollment:	60
Type:	Anticipated

Medical products/devices used

Generic name:	an adapted commercially available CE-marked fundus camera (Topcon TRC-50DX)
Registration:	No

Ethics review

Approved WMO

Date:	29-04-2025
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL87919.058.24