# EVALUATION OF MICROVASCULAR CHANGES IN THE PERIFOVEAL VASCULAR NETWORK USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY (OCT-A) IN TYPE I DIABETES MELLITUS

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## 1. Summary of the study

The aim of this study is to investigate the role of OCTA in the evaluation of the perifoveal capillary network in a large cohort of diabetes mellitus (DM) patients and to investigate the existing relationship between advanced OCTA image analysis parameters and the demographic characteristics and systemic clinical parameters of interest, such as the metabolic control and the duration of the disease. The working hypothesis is that OCTA allows the detection of preclinical changes that are related to systemic factors such as the time of diabetes mellitus duration or the metabolic control, and that these changes reflect the microvascular alterations that present elsewhere in the body caused by diabetic microangiopathy. If the detection of these early abnormalities were possible, OCTA would lead us to modify the pharmacological treatment of these patients to avoid future microvascular complications at the retina level as well as in other organs such as the kidney glomerules or the brain capillaries.

The aim of this study is to evaluate the role of OCTA as a non-invasive method for the detection of early changes in the perifoveal capillary network and their relationship with the systemic factors in a cohort of type 1 diabetes mellitus patients.

The specific aims of this Project are:
1) To evaluate the OCTA characteristics of the perifoveal capillary network in:
a. type 1 DM patients and healthy controls
b. type 1 DM patients with and without diabetic retinopathy
c. type 1 DM patients in different moments of disease progression (evolution time)

2) To study the correlations between perifoveal capillary network characteristics and the systemic factors, such as demographic factors, metabolic control and cardiovascular risk factors in type 1 DM.

## 2. Results achieved

To summarize the results obtained, according to the objectives described in the original project we have demonstrated the different characteristics of the perifoveal capillary network in type 1 DM patients compared to healthy controls[1,2] (objective 1A) and more

concisely the differences in type 1 DM patients with and without diabetic retinopathy[3] (objective 1B), as well as the relationship between the perifoveal capillary network and the DM evolution time (objective 1C). We also demonstrated an existing relationship between the perifoveal capillary network and some systemic factors such as the metabolic control (HbA1c) [4,5] or the cardiovascular risk factors[6] in type 1 DM patients (objective 2). Additionally, we have demonstrated the existing relationship between the measurements obtained in the different scanned areas, both with the built-in commercial software[7,8,9] and research software.[10,11,12,13]

After the formal 3-year period an extension was requested to present the final memory of the project, as several articles were still under review and some of the doctoral theses were in the final phase for presentation. In the last year, one additional original article has been published in an indexed journal with impact factor and one doctoral thesis (PhD) has been presented in the University of Barcelona (Marina Barraso-Rodrigo, presentation date 12/3/2021). Currently, three more articles are under review and two more doctoral theses are being developed, one in the final phase with estimated presentation date in the third quarter of 2021 and another one in 2022.

## 3. Relevance and future implications

The results of the study have allowed us to accomplish all the objectives detailed in the original project. Beyond these achieved objectives, the main result of the project is the creation of a high-quality data biobank, which is a unique cohort worldwide for the study of microvascular complications of type 1 DM. This dataset comprises a vast repository of retinal images of type 1 DM patients and healthy controls, linked to the corresponding systemic blood data that allows the identification of groups at risk of disease progression, the investigation of novel disease biomarkers, and the detection of microvascular damage in early stages, with prospective follow up data started in the 2nd and 3rd years of the project. Currently, we are submitting further grant applications to continue the longitudinal prospective follow-up of the study cohort, which would provide additional value to the project.

The implications of this research results are important in three areas, representing improvements in the diagnosis and management of type 1 DM patients and the development of new research lines.

First, the objective identification of the status of the vessel density and other perifoveal vascular network parameters assessed by OCTA overcomes the limitations of the traditional clinical diabetic retinopathy classification. This classification is not continuous (it has 5 categorical levels: no retinopathy, mild, moderate and severe non-proliferative retinopathy and proliferative retinopathy), it is subjective and depends on the identification of changes seen in funduscopy by the ophthalmologist, which represents a problem for standardization and benchmarking of results between cohorts. As we demonstrated with our results, OCTA allows the objective continuous quantification of different parameters (vessel density, perfusion density, changes in the foveal avascular zone) that is independent of the evaluating physician, being applicable in all study cohorts and sites of the world. Due to the novelty of the imaging technique there are very few data repositories of OCTA worldwide, and the existing ones are often much smaller (n<200 eyes) and frequently of type 2 DM patients (the most common type of disease, accounting for 85-90% of cases) studies in type 1 DM cohorts being rare. Our study cohort is the largest published OCTA series in type 1 DM worldwide (n=1200 eyes), and has allowed us to establish the cut-off points for each of these OCTA parameters with a corresponding diagnostic probability of presenting diabetic retinopathy objectively, with a single OCTA image. In this research line, a new project has been designed to implement the capture of OCTA images locally as part of the routine check-up in the diabetes unit, with the aim of avoiding unnecessary false positive referrals to the ophthalmology service in the routine screening program with non-mydriatic cameras.

Second, a new research line is directed to identifying novel biomarkers in OCTA images, beyond the usual parameters incorporated in the built-in commercial software of the OCT devices. With this aim, we are processing the OCTA images with MatLab®-based software to evaluate novel parameters and assess whether any of these present greater sensitivity or specificity to classify patients with diabetic retinopathy compared to standard OCTA parameters. We are also evaluating 3D reconstructions of the OCTA macular cubes to identify novel biomarkers of DM such as the surface or volume of the retinal vessels as a way to quantify these and evaluate how they are associated to the

conventional OCTA parameters, the usual clinical classifications and other systemic parameters of interest. For these advanced analyses, we are developing collaborations with other academic centers such as the University of Washington (Seattle, Washington, USA), the Institute of Molecular and Clinical Ophthalmology (IOB) of Basel (Switzerland), and specialized companies in the retinal imaging sector such as Voxeleron LLC (Pleasanton, CA, USA) and RetinAI (Bern, Switzerland), in order to maximize the results of the project.

Finally, the third research line derived from the project is centered in the application of artificial intelligence algorithms for the study of associations between retinal images (retinographies, OCT and OCTA) and clinical data of interest collected during the study. In the preliminary studies we developed methods to identify the diagnostic capacity of each of these imaging techniques to identify diabetic retinopathy cases using single, sequential or combined techniques, with the aim of developing the optimal circuit to identify cases in a populational screening program. Additionally, we are evaluating the ability of the algorithms to identify blood parameters of interest from the retinal images to explore the use of OCTA images as a non-invasive monitoring tool of the systemic disease. To further develop our investigations in these fields we are developing collaborations with academic centers such as the Intelligent Data Science and Artificial Intelligence (IDEAI) Research Center of Universitat Politècnica de Catalunya (UPC), as well as centers of excellence such as the Moorfields Eye Hospital (London, United Kingdom).

## 4. Generated scientific bibliography

**Doctoral Theses (1 doctoral thesis presented, 2 theses in process)**
Doctoral thesis presented: Marina Barraso-Rodrigo
Title: "EVALUACIÓN DEL FLUJO VASCULAR EN LA RED CAPILAR PERIFOVEAL MEDIANTE ANGIOGRAFÍA DE COHERENCIA OPTICA EN LA DIABETES MELLITUS TIPO 1"

Directors: Javier Zarranz-Ventura, Alfredo Adan-Civera
Presentation date: 12 March 2021 – University of Barcelona

Panel:

President: Pere Romero-Aroca (Universitat Rovira i Virgili)

Secretary: Lluis Arias Barquet (Universitat de Barcelona)

Member: Barbara Delàs Alós (Consorci Sanitari de Terrassa)

Reserve 1: Marc Baget Bernàldiz (Universitat Rovira I Virgili)

Reserve 2: Miguel Angel Zapata (Universitat Autònoma de Barcelona)

## Doctoral theses in process

Anibal Alé-Chilet (in process).

Sara Marín Martínez (in process).

## Articles

1.     Barraso M, Alé-Chilet A, Hernandez T, Oliva C, Vinagre I, Ortega E, Figueras-Roca M, Sala-Puigdollers A, Esquinas C, Esmatjes E, Adan A, Zarranz-Ventura J. "OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY IN TYPE 1 DIABETES MELLITUS. REPORT 1: DIABETIC RETINOPATHY"
Transl Vis Sci Technol 2020;9:34
Doi: 10.1167/tvst.9.10.34
PMID: PMC7533741


2.     Zarranz-Ventura J, Barraso M, Alé-Chilet A, Hernandez T, Oliva C, Gascón J, Sala-Puigdollers A, Figueras-Roca M, Vinagre I, Ortega E, Esmatjes E, Adan A. "EVALUATION OF MICROVASCULAR CHANGES IN THE PERIFOVEAL VASCULAR NETWORK USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY (OCTA) IN TYPE I DIABETES MELLITUS: A LARGE SCALE PROSPECTIVE TRIAL"
BMC Med Imaging. 2019 Nov 21;19(1):91.
doi: 10.1186/s12880-019-0391-8.
PMID: 31752726


3.     Barraso M, Alé-Chilet A, Hernandez T, Oliva C, Adán A, Zarranz-Ventura J. "EVALUACIÓN DE LA RED VASCULAR PERIFOVEAL CON ANGIOGRAFÍA DE TOMOGRAFÍA DE COHERENCIA ÓPTICA EN PACIENTES CON DIABETES MELLITUS TIPO 1 Y RELACIÓN CON EL GRADO DE RETINOPATÍA".
Annals d'Oftalmologia 2018;26(4):339-347.

Best Presentation Award, 48è Congrés de la Societat Catalana de Oftalmologia (November 2017)

**Book chapters**

Alé-Chilet A, Barraso M, Hernandez T, Oliva C, Zarranz-Ventura J

Chapter 12. "OCTA EN RETINOPATIA DIABÉTICA NO PROLIFERATIVA".

In: Adan A, Zarranz-Ventura J. "ANGIOGRAFIA POR TOMOGRAFIA DE COHERENCIA OPTICA".

Mesa Redonda 2017. Sociedad Española de Oftalmología.

Editor: Sociedad Española de Oftalmología. Zaragoza, September 2017.

ISBN: 978-84-89085-64-0.

**Clinical trial registry**

National Institute of Health, United States National Library of Medicine ([www.ClinicalTrials.gov](www.ClinicalTrials.gov))

Study ID: NCT03422965

**Scientific meeting communications: 32 communications in 13 meetings**

48è Congrés de la Societat Catalana d'Oftalmologia.

Barcelona, 23-25 November 2017

2 communications

XXII Congreso de la Sociedad Española de Retina y Vítreo.

Santander, 2-3 March 2018

1 communication

2018 Imaging in the Eye Conference, Association for Research in Vision & Ophthalmology (ARVO) 2018 Annual Meeting.

Honolulu, Hawaii, USA. April 29th 2018

1 communication

Association for Research in Vision & Ophthalmology (ARVO) 2018 Annual Meeting.

Honolulu, Hawaii, USA. April 29th-May 3rd 2018

3 communications

World Ophthalmology Congress (WOC) 2018.

Barcelona, Spain. June 16-19 2018

3 communications

European Society of Retina Specialists EURETINA 18th Annual Meeting.

Vienna, Austria. September 20-23 2018

5 communications

49è Congrés de la Societat Catalana d'Oftalmologia.

Barcelona, 22-24 November 2018

4 communications

IV Reunion SERV40, Sociedad Española de Retina y Vítreo.

Madrid, 7 March 2019

1 communication

XXIII Congreso de la Sociedad Española de Retina y Vítreo.

Madrid, 8-9 March 2019

3 communications

Association for Research in Vision & Ophthalmology (ARVO) 2019 Annual Meeting.

Vancouver, Canada. April 28th-May 2nd 2019

1 communication

European Society of Retina Specialists EURETINA 19th Annual Meeting.

Paris, France. September 5-8 2019

4 communications

American Academy of Ophthalmology 2019 Annual Meeting.

San Francisco, USA. 12-15 October 2019

1 communication

50º Congrés de la Societat Catalana d'Oftalmologia.

Barcelona, 28-29 November 2019

3 communications

**Awards**

Best communication award Congrés de la Societat Catalana d'Oftalmologia 2017. Marina Barraso.

"Evaluación de la red vascular perifoveal con angiografía de tomografía de coherencia óptica en pacientes con diabetes mellitus tipo 1 y relación con el grado de retinopatía". 48è Congrés de la Societat Catalana d'Oftalmologia.
Barcelona, 23-25 November 2017

Best communication award Congrés Societat Catalana d'Oftalmologia 2018. Anibal Alé-Chilet.

"Impacto del área de escaneo en las medidas de flujo del plexo capilar superficial y profundo determinado con softwares avanzados de investigación basados en MatLab® en imágenes de Angiografía por Tomografía de Coherencia Óptica (OCTA) en ojos diabéticos".
49è Congrés de la Societat Catalana d'Oftalmologia.
Barcelona, 22-24 November 2018