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# Estudio de la coroides mediante tomografía de coherencia óptica swept source en sujetos sanos y pacientes diabéticos tipo 2

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# ESTUDIO DE LA COROIDES MEDIANTE TOMOGRAFÍA DE COHERENCIA ÓPTICA SWEPT SOURCE EN SUJETOS SANOS Y PACIENTES DIABÉTICOS TIPO 2


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**UNIVERSIDAD DE ZARAGOZA**
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# Estudio de la Coroides mediante Tomografía de Coherencia Óptica Swept Source en Sujetos Sanos y Pacientes Diabéticos Tipo 2

Doctoral Thesis,

aiming for the **International PhD** degree

presented by **Francisco de Asís Bartol-Puyal** MD

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# 0) Acknowledges

PATRI QVI, ETSI IN ARTE EXERCENDA VESTIGIA NON PERSECVTVS SVM, SEMPER MIHI OPEM TVLIT.

Ta mi mare, qui onque el suyo treball no se beiga, a siu los mios alazez. Perque sin la suya aduya, res ese siu posiblle.

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# 1)Presentation of the Thesis

This doctoral thesis was developed as a compendium thesis. It is composed of four published articles in scientific journals with impact factor according to the Journal Citation Reports. These articles belong to the same line of investigation and the thesis adhered to the rules of the University of Zaragoza.

This doctoral thesis comprises the following articles:

1. Abadía B, Calvo P, Bartol-Puyal F, Verdes G, Suñén I, Ferreras, A. Repeatability of choroidal thickness measurements assessed with swept-source optical coherence tomography in healthy and diabetic individuals. Retina. 2019 Apr;39(4):786-79e.
2. Abadía B, Suñén I, Calvo P, Bartol F, Verdes G, Ferreras A. Choroidal thickness measured using swept-source optical coherence tomography is reduced in patients with type 2 diabetes. PLoS One. 2018 Feb 2;13(2):e0191977.
3. Abadia B, Bartol-Puyal F, Calvo P, Verdes G, Isanta C, Pablo L. Mapping choroidal thickness in patients with type 2 diabetes. Can J Ophthalmol. 2019 Aug 9. pii: S0008-4182(19)30344-8
4. Bartol-Puyal F, Isanta C, Ruiz-Moreno Ó, Abadía B, Calvo P, Pablo L. Distribution of Choroidal Thinning in High Myopia, Diabetes Mellitus, and Aging: A Swept-Source OCT Study. J Ophthalmol. 2019 Aug 15;2019:3567813.

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# 3) Abbreviations

2D = Two-dimension

3D = Three-dimension

AL = Axial length

BCVA = Best corrected visual acuity

COV = Coefficient of variation

CT = Choroidal thickness

DM = Diabetes mellitus

DME = Diabetic macular oedema

DR = Diabetic retinopathy

DRI = Deep Range Imaging

EDI = Enhanced Depth-Imaging

ETDRS = Early Treatment Diabetic Retinopathy Study

HbA1c = Glycosylated haemoglobin

ICC = Intraclass correlation coefficient

IOP = Intraocular pressure

IRMA = Intraretinal microvascular abnormality

JCR = Journal Citation Reports

NPDR = Non-proliferative diabetic retinopathy

OCT = Optical coherence tomography

PDR = Proliferative diabetic retinopathy

RT = Retinal thickness

SD = Standard deviation

SD-OCT = Spectral-domain optical coherence tomography

SS-OCT = Swept-source optical coherence tomography

T2D = Type 2 diabetes

TABS = Topcon Advanced Boundary Segmentation

TD-OCT = Time-domain optical coherence tomography

VA = Visual acuity

VEGF = Vascular endothelial growth factor

# 4) Summary of the Thesis

## a) Summary of the thesis (EN)

Type 2 diabetes (T2D) is a disease with a multisystemic affection, which can be classified into macro and microangiopathy. The former include ischemic cardiopathy, cerebrovascular accident and peripheral artery disease. The latter comprise nephropathy, peripheral polyneuropathy and diabetic retinopathy (DR). Based on the international classification,[1] DR is divided into five steps:[2] no DR, mild, moderate, severe and proliferative diabetic retinopathy (PDR). Mild, moderate and severe are classified as non-proliferative DR (NPDR). Another additional retinal manifestation is diabetic macular oedema (DME), which usually implies a poorer visual acuity (VA). DME is reversible if correctly treated in time.

Optical coherence tomography (OCT) has been found very useful for detecting DME, as well as for measuring retinal thickness (RT). The development of swept-source optical coherence tomography (SS-OCT) and the enhanced depth-imaging (EDI) technology have enabled deep and accurate analyses of the choroid.[3] The previous version of OCT was the spectral-domain OCT (SD-OCT) and it had lower axial resolution compared to SS-OCT, showing inaccurate segmentation of the choroid, unless the EDI mode was enabled. The choroid is mainly made up of blood vessels and it carries blood supply to the external retinal layers. For the last years, the choroid has been thoroughly evaluated and its thickness has been related to multiple physiological conditions, and ocular and systemic diseases. Most studies agree that CT is reduced in T2D eyes.[4–6] Nevertheless, it still remains unclear how DME affects CT. Moreover, it has been suggested that the choroid may follow an irregular pattern,[7–9] but no further research has been conducted so far assessing its precise topography and how it varies with different conditions and diseases.

The main subject of the four articles making up this doctoral thesis was the study of the choroid and its topography with SS-OCT in healthy and T2D patients. The purposes were the following: to assess the intrasession repeatability of choroidal thickness (CT) measurements with SS-OCT in healthy individuals and in T2D patients

with DR, to compare CT between healthy subjects and T2D patients with different stages of DR, with and without DME, to determine and compare the topographic features of CT between T2D patients and age-matched healthy controls, to evaluate the relationship between macular CT and HbA1c levels and duration of diabetes, and to compare CT in the macular region between young healthy, aged healthy and T2D individuals.

A cross-sectional study was performed at the Miguel Servet University Hospital in Zaragoza (Spain) between November 2015 and November 2017, with different study groups enrolled. Inclusion criteria for the first group were T2D patients between 55 and 75 years old, with an AL ≤ 26mm, < 6 D of myopia and < 2 D of cylinder. In case of DME, a minimum central RT of 300 μm was required. Inclusion criteria for the second group were the same but without the presence of T2D. Inclusion criteria for the third study group included young healthy volunteers between 18 and 35 years old with an AL ≤ 26 mm, < 6 D of myopia and < 2 D of cylinder. For all of them, exclusion criteria were: any ocular pathology, previous ophthalmological treatment or surgery, amblyopia, a race different from Caucasian, pregnancy or puerperium, endocrine or neurological disease, cancer history, systemic treatment with corticosteroids, immunosuppressive drugs, biologic therapies and previous treatment with potentially toxic drugs to the retina and/or optic nerve.

All OCT scans were acquired through dilated pupils at the same day time and by the same experienced technician. Two types of captures were performed: a horizontal 12-mm line and a macular 6x6 mm cube. In the horizontal line scan, 11 manual measurements of CT were obtained. In the macular cube, CT were obtained both in the Early Treatment Diabetic Retinopathy Study (ETDRS) grid and in a grid of 30x30 little cubes, from which two-dimension (2D) and three-dimension (3D) representations were generated and a new choroidal division was established for CT comparisons.

Below is a summary of the four articles:

1. **Abadía B, Calvo P, Bartol-Puyal F, Verdes G, Suñén I, Ferreras, A. Repeatability of choroidal thickness measurements assessed with swept-source optical coherence tomography in healthy and diabetic individuals. Retina. 2019 Apr;39(4):786-793.**

This was a cross-sectional study including 50 eyes of 33 healthy subjects and 60 eyes of 43 T2D patients, and whose purpose was to assess the intrasession repeatability of CT measurements obtained using SS-OCT in T2D patients and in healthy controls. Among the diabetic group, 7 patients had no DR, 13 had mild, 32 had moderate, 5 had severe, and 3 proliferative DR. Half of the T2D patients had DME. Repeatability was analysed after measuring CT in three different scans which had been consecutively obtained in a single session and automatically delineated by the internal software. Over a horizontal 12-mm line, 11 locations with 500-μm intervals were measured with the caliper by the same operator.

Mean age was 68.02±8.80 years old in the healthy group, and 66.28±7.80 years old in the T2D group (p=0.28). Mean subfoveal CT in healthy subjects and in T2D patients was 222.97±79.90 μm and 192.67±74.30 μm, respectively (p=0.013). The intraclass correlation coefficient (ICC), the coefficient of variation (COV) and the test-retest variability were calculated. All ICC were higher than 0.95 and 0.99, respectively. COV were less than 4.4% and 1.8%, respectively. The test-retest variability ranged from 0.76 μm to 11.12 μm, and from 0.64 μm to 6.29 μm, respectively. No significant differences were found in the intrasession repeatability of any choroidal measurement between healthy subjects and T2D patients.

In conclusion, SS-OCT provided excellent intrasession repeatability of CT measurements in healthy and T2D patients.

2. **Abadia B, Suñen I, Calvo P, Bartol F, Verdes G, Ferreras A. Choroidal thickness measured using swept-source optical coherence tomography is reduced in patients with type 2 diabetes. PLoS One. 2018 Feb 2;13(2):e0191977.**

This was a cross-sectional study comprising 157 eyes of 94 T2D patients and 71 eyes of 38 healthy subjects. Its objective was to compare CT between T2D patients and age-matched healthy controls.

Among the 157 T2D eyes, 48 had DME. 49 eyes had no DR, 27 had mild NPDR, 60 had moderate NPDR, 14 had severe NPDR and 7 PDR. On every SS-OCT image, 11 CT measurements were manually performed. One was subfoveal, five nasal and five temporal, with 500-μm intervals between them. Besides comparing CT between the three study groups, a correlation analysis was performed between diabetes duration, glycosylated haemoglobin (HbA1c) levels and CT. A masking was performed so that the operator could not identify whose patient was that slab.

Mean age was 67.60±8.10 years and there were no differences in age, AL or blood pressure between groups ($p>0.05$). Mean diabetes duration was 16.6±9.5 years, while mean HbA1c was 7.7±1.3%. Overall, the choroid was significantly thinner in T2D patients. Individuals with DME had reduced choroidal thickness in all measurements, except at 2000 and 2500-μm nasal positions, compared to healthy controls. There was a moderate correlation between CT and HbA1c levels in DME patients ($r=0.342$, $p=0.017$ in subfoveal position). Diabetes duration did not correlate significantly with CT. In both groups, the choroid revealed a similar pattern: it was the thickest at the subfoveal position, followed by temporal and nasal. These results were similar to other studies.[10–12]

In conclusion, SS-OCT measurements revealed that the choroid was significantly thinner in T2D patients, moderate NPDR patients, and DME patients than in healthy individuals.

3. **Abadia B, Bartol-Puyal F, Calvo P, Verdes G, Isanta C, Pablo L. Mapping choroidal thickness in patients with type 2 diabetes. Can J Ophthalmol. 2019 Aug 9. pii: S0008-4182(19)30344-8**

This was a cross-sectional study whose objective was to determine and compare topographic features of CT between T2D patients and aged-matched healthy controls based on SS-OCT. 66 eyes of 33 healthy individuals and 192 eyes of 96 T2D patients were enrolled. 36 eyes had no DR, 26 had mild NPDR, 25 had moderate NPDR, 5 had severe NPDR and 4 had PDR. None of them had DME.

A macular 6x6 mm cube was scanned with SS-OCT and choroid was automatically segmented and its thickness automatically measured. The scanned area was divided into different zones based on CT, and equivalent zones were compared between groups. In addition, 3D maps were created to represent the choroid.

There were no differences in age or AL ($p>0.05$). Mean age was 66.83±7.31 years old in the healthy group, and 67.94±7.93 years old in the T2D group. Overall, CT was significantly thinner in T2D patients ($p<0.05$). Outside the fovea, the mean CT was thicker in the superior hemiretina and decreased inferiorly, temporally and nasally, with minimum thickness in the most distant points.

These results were similar to those stating that CT is thinner in diabetes mellitus (DM) patients, but it was the first time that it was displayed in exhaustive 3D maps originated from data obtained from SS-OCT with automatic segmentation and measurements.

In conclusion, CT follows an ellipsoid pattern in both nondiabetic and diabetic eyes, with diffuse thinning in the latter. Understanding these differences is important for future studies aimed at explaining the pathophysiology and relationship between choroid and DR.

4. **Bartol-Puyal F, Isanta C, Ruiz-Moreno Ó, Abadía B, Calvo P, Pablo L. Distribution of Choroidal Thinning in High Myopia, Diabetes Mellitus, and Aging: A Swept-Source OCT Study. J Ophthalmol. 2019 Aug 15;2019:3567813.**

This was a cross-sectional study comparing the macular choroidal thinning between young healthy, aged healthy, young high myopic, and aged T2D patients using the ETDRS grid and 3D maps. The first study group comprised 102 eyes of 51 young healthy subjects, the second included 60 eyes of 30 aged healthy subjects, the third was composed of 110 eyes of 55 T2D patients, and the fourth consisted of 24 eyes of 12 young high myopic patients.

CT values were obtained in grids of 30x30 cubes of 200x200 μm every cube, which were automatically provided by the OCT, and 3D maps were created to represent CT. This was also obtained in every ETDRS grid sector. Mean age was 27.31±3.95, 66.41±7.54, 27.69±3.89, and 66.48±7.59 years in the four groups, respectively. CT was not shown to be uniform, as superior and central zones were thicker in all groups. All ETDRS sectors were always thicker ($p<0.05$) in young healthy individuals than in the others. It was found that the choroidal sector which got thinner was the inferior in case of age (103.28 μm decrease), the inferior-nasal in high myopia (86.19 μm decrease), and the temporal in T2D (55.57 μm decrease).

Young healthy subjects' choroid was used as a reference and divided into different zones according to the mean CT in every macular cube. Five nasal and five temporal zones were delimited. Comparisons of CT between equivalent zones revealed that choroid got thinner in those regions where it was thicker in healthy subjects.

Choroidal 3D representations showed different patterns: a 'mountain range' pattern in young healthy individuals, a 'mountain peak' in aged healthy individuals, an 'inverted gorge' pattern in young high myopic patients, and a 'gathered hills' pattern in aged T2D patients. Some authors had tried to make topographic descriptions or choroidal maps but it was the first time that such an in-depth map has been created. Furthermore, it was the first time that different topographic patterns have been defined.

In conclusion, not all choroidal regions are affected in a similar way, as it depends on the pathology. For a better understanding and a more exhaustive analysis, 3D maps are a useful tool. Further studies should be performed to explain the pathophysiology of these different choroidal patterns.

## b) Resumen de la tesis (ES)

La DM 2 es una enfermedad con afectación multisistémica, que puede clasificarse en macro y microangiopatía. La primera incluye cardiopatía isquémica, accidente cerebrovascular y enfermedad arterial periférica. La segunda incluye nefropatía, polineuropatía periférica y retinopatía diabética. Según la clasificación internacional, la retinopatía diabética se divide en cinco escalones: sin retinopatía, leve, moderada, grave y proliferativa. La retinopatía diabética leve, moderada y grave están incluidas en el grupo de retinopatía diabética no proliferativa. Otra manifestación retiniana adicional es el edema macular diabético, que normalmente supone una peor agudeza visual y es reversible si se trata a tiempo.

La tomografía de coherencia óptica (OCT) ha resultado ser muy útil para detectar edema macular diabético, así como para medir el espesor retiniano. El desarrollo de la OCT swept-source (SS-OCT) y la tecnología EDI han permitido análisis profundos y precisos de la coroides. La versión previa de OCT era la OCT de dominio espectral (SD-OCT) y tenía menor resolución axial en comparación con la SS-OCT, con segmentación imprecisa de la coroides, a menos que se habilitara el modo EDI. La coroides está compuesta principalmente por vasos sanguíneos y lleva aporte sanguíneo a las capas externas retinianas. Durante los últimos años, se ha examinado la coroides de forma exhaustiva y se ha relacionado su grosor con múltiples condiciones fisiológicas, y enfermedades oculares y sistémicas. La mayoría de los estudios han encontrado que está adelgazada en el caso de la DM 2. Sin embargo, todavía no está claro cómo afecta el edema macular diabético al grosor coroideo. Asimismo, se ha sugerido que la coroides sigue un patrón irregular pero hasta ahora no se han llevado a cabo más investigaciones que definan su topografía de forma precisa y cómo varía con las diferentes condiciones y enfermedades.

El tema principal de los cuatro artículos que comprende esta tesis doctoral fue el estudio de la coroides y sus características anatómicas evaluadas con SS-OCT en individuos sanos y pacientes con DM 2. Los objetivos fueron los siguientes: verificar la repetitibilidad intratest de las mediciones de grosor coroideo con SS-OCT en individuos sanos y pacientes con DM 2 con retinopatía diabética, comparar el grosor

coroideo entre sanos y pacientes con DM 2, y analizar el grosor coroideo por toda la mácula en pacientes con DM 2 y controles sanos ajustados por edad.

Se realizó un estudio transversal en el Hospital Universitario Miguel Servet en Zaragoza (España) entre noviembre de 2015 y noviembre de 2017, en el que se reclutaron varios grupos de estudio. Los criterios de inclusión para el primer grupo fueron pacientes con DM 2 entre 55 y 75 años, con una longitud axial ≤ 26 mm, < 6 D de miopía y < 2 D de cilindro. En caso de edema macular diabético, era necesario un mínimo de 300 µm centrales de espesor retiniano. Los criterios de inclusión para el segundo grupo fueron los mismos pero sin la presencia de DM 2. Los criterios de inclusión para el tercero fueron voluntarios jóvenes sanos de entre 18 y 35 años con una longitud axial ≤ 26 mm, < 6 D de miopía y < 2 D de cilindro. Para todos ellos, los criterios de exclusión fueron: cualquier patología ocular, tratamiento o cirugía ocular previa, ambliopía, raza diferente de la caucásica, embarazo o puerperio, enfermedad endocrinológica o neurológica, historia de cáncer, tratamiento sistémico con corticoides, fármacos inmunosupresores, terapias biológicas y tratamiento previo con fármacos potencialmente tóxicos para la retina y/o el nervio óptico.

Todos los exámenes en OCT se adquirieron a través de pupilas dilatadas a la misma hora del día y por el mismo técnico experimentado. Se realizaron dos tipos de capturas: una línea horizontal de 12 mm y un cubo macular de 6x6 mm. En el primero, se obtuvieron 11 mediciones manuales de grosor coroideo. En el segundo, se obtuvieron los grosores tanto en la rejilla ETDRS como en otra de 30x30 cubos pequeños, a partir de los cuales se crearon representaciones 2D y 3D, y se estableció una nueva división coroidea para efectuar comparaciones.

A continuación está el resumen de los cuatro artículos:

1. **Abadía B, Calvo P, Bartol-Puyal F, Verdes G, Suñén I, Ferreras, A. Repeatability of choroidal thickness measurements assessed with swept-source optical coherence tomography in healthy and diabetic individuals. Retina. 2019 Apr;39(4):786-793.**

Este es un estudio transversal que incluye 50 ojos de 33 individuos sanos y 60 ojos de 43 pacientes con DM 2, y cuyo propósito era evaluar la repetitibilidad intrasesión de las mediciones de grosor coroideo obtenidas mediante SS-OCT en pacientes con DM 2 y en controles sanos. Dentro del grupo diabético, 7 pacientes no tenían retinopatía diabética, 13 tenían leve, 32 tenían moderada, 5 tenían grave y 3 tenían proliferativa. La mitad de los pacientes diabéticos tenía edema macular diabético. La repetitibilidad se analizó tras medir el grosor coroideo en tres exámenes diferentes que se habían realizado consecutivamente en una sola sesión, y además habían sido delineados automáticamente por el software interno. Sobre la línea horizontal de 12 mm, se midieron 11 posiciones con intervalos de 500 μm con el compás por parte del mismo examinador.

La edad media fue de 68.02±8.80 años en el grupo de sanos y 66.28±7.80 años en el de diabéticos (p=0.28). El grosor coroideo subfoveal en los sanos y en los diabéticos fue de 222.97±79.90 μm y 192.67±74.30 μm, respectivametne (p=0.013). Se calcularon el coeficiente de correlación intraclase, el coeficiente de variación y la variabilidad test-retest. Todos los coeficientes de correlación intraclase fueron mayores de 0.95 y 0.99, respectivamente. Los coeficientes de variación fueron menores de 4.4% y 1.8%, respectivamente. La variabilidad test-retest oscilaba entre 0.76 y 11.12 μm, y entre 0.64 y 6.29 μm, respectivamente. No se encontraron diferencias significativas en la repetitibilidad intrasesión de ninguna medición coroidea tanto en sujetos sanos como en diabéticos.

En conclusión, la SS-OCT tenía una excelente repetitibilidad intrasesión de las mediciones de grosor coroideo en individuos sanos y en pacientes con DM 2.

2. **Abadia B, Suñen I, Calvo P, Bartol F, Verdes G, Ferreras A. Choroidal thickness measured using swept-source optical coherence tomography is reduced in patients with type 2 diabetes. PLoS One. 2018 Feb 2;13(2):e0191977.**

Se trata de un estudio transversal que incluye 157 ojos de 94 pacientes con DM 2 y 71 ojos de 38 sujetos sanos. Su objetivo era comparar el grosor coroideo entre los diabéticos y los controles sanos ajustados por edad.

De entre los 157 ojos diabéticos, 48 tenían edema macular diabético. 49 ojos no tenían retinopatía diabética, 27 leve, 60 moderada, 14 grave y 7 proliferativa. En cada imagen de SS-OCT se realizaron 11 mediciones manuales de grosor coroideo. Una era la subfoveal, cinco nasales y cinco temporales, con intervalos de 500 μm entre ellas. Además de comparar el grosor coroideo entre los tres grupos de estudio, se llevó a cabo un análisis de correlación entre la duración de la diabetes, los niveles de HbA1c y el grosor coroideo. Se enmascararon las imágenes para que el examinador no pudiera identificar de qué paciente era cada corte.

La edad media fue de 67.60±8.10 años y no hubo diferencias en cuanto a edad, longitud axial ni tensión arterial entre los grupos ($p>0.05$). La duración media de la DM 2 fue de 16.6±9.5 años, mientras que la Hb1Ac media fue del 7.7±1.3%. En general, la coroides era significativamente más fina en los diabéticos. Los pacientes con edema macular diabético mostraban grosores coroideos reducidos en todas las mediciones, excepto en las posiciones a 2000 y 2500 μm nasales, en comparación con los sanos. Se halló una correlación moderada entre el grosor coroideo y los niveles de HbA1c en pacientes con edema ($r=0.342$, $p=0.017$ en la posición subfoveal). La duración de la diabetes no se correlacionó significativamente con el grosor coroideo. En ambos grupos, la coroides mostró un patrón similar: era más gruesa en la posición subfoveal, seguida de temporal y nasal. Estos resultados eran similares a otros estudios.[10–12]

En conclusión, las mediciones con SS-OCT revelan que la coroides está significativamente adelgazada en pacientes con DM 2, pacientes con retinopatía diabética moderada, y pacientes con edema macular diabético, que en sujetos sanos.

3. **Abadia B, Bartol-Puyal F, Calvo P, Verdes G, Isanta C, Pablo L. Mapping choroidal thickness in patients with type 2 diabetes. Can J Ophthalmol. 2019 Aug 9. pii: S0008-4182(19)30344-8**

Se trata de un estudio transversal cuyo objetivo era determinar y comparar los rasgos topográficos de grosor coroideo con SS-OCT entre pacientes con DM 2 y controles sanos ajustados por edad. Se analizaron 66 ojos de 33 individuos sanos y 192 ojos de 96 pacientes diabéticos. 36 ojos no tenían retinopatía diabética, 26 tenían leve, 25 moderada, 5 grave y 4 proliferativa. Ninguno de ellos presentaba edema macular diabético.

Se analizó un cubo macular de 6x6 mm con SS-CT, con segmentación y medición de espesor de coroides automáticos. El área escaneada se dividió en diferentes zonas según el grosor coroideo y se compararon entre los grupos las zonas equivalentes. Además se crearon mapas 3D para representar la coroides.

No se hallaron diferencias en edad ni longitud axial ($p>0.05$). La edad media fue de 66.83±3.71 años en el grupo sano y 67.94±7.93 años en el grupo diabético. En general, el grosor coroideo era significativamente más fino en los diabéticos ($p<0.05$). Fuera de la fóvea, el grosor coroideo medio era mayor en la hemirretina superior y disminuía hacia inferior, temporal y nasal, siendo mínimo en los puntos más distantes.

Estos resultados eran similares a los que afirmaban que el grosor coroideo es menor en pacientes diabéticos, pero era la primera vez que se mostraban mapas 3D exhaustivos originados a partir de datos obtenidos de SS-OCT con segmentación y mediciones automáticas.

En conclusión, el grosor coroideo sigue un patrón elipsoide tanto en ojos de diabéticos como no-diabéticos, con adelgazamiento difuso en el primero. Comprender estas diferencias es importante para futuros estudios que pretendan explicar la fisiopatología y la relación entre coroides y retinopatía diabética.

4. **Bartol-Puyal F, Isanta C, Ruiz-Moreno Ó, Abadía B, Calvo P, Pablo L. Distribution of Choroidal Thinning in High Myopia, Diabetes Mellitus, and Aging: A Swept-Source OCT Study. J Ophthalmol. 2019 Aug 15;2019:3567813.**

Se trata de un estudio transversal que comparaba el adelgazamiento coroideo macular entre jóvenes sanos, mayores sanos, jóvenes miopes magnos y pacientes con DM 2 usando la rejilla ETDRS y mapas 3D. El primer grupo de estudio incluía 102 ojos de 51 sujetos jóvenes sanos, el segundo incluía 60 ojos de 30 sujetos mayores sanos, el tercero se componía de 110 ojos de 55 pacientes con DM 2, y el cuarto estaba formado por 24 ojos de 12 pacientes jóvenes miopes magnos.

Los valores de grosor coroideo se obtuvieron en rejillas de 30x30 cubos de 200x200 μm cada cubo, que daba de forma automática la OCT, y se crearon mapas 3D para representar el grosor coroideo. Este también se midió en cada sector de la rejilla ETDRS. La edad media fue de 27.31±3.95, 66.41±7.54, 27.69±3.89 y 66.48±7.39 años en los cuatro grupos, respectivamente. El grosor coroideo no mostró ser uniforme, ya que las zonas superior y centrales eran más gruesas en todos los grupos. Todos los sectores ETDRS eran siempre más gruesos ($p<0.05$) en individuos jóvenes sanos que en los otros. Se encontró que el sector coroideo que más se adelgazaba era el inferior en el caso de la edad (disminución de 103.28 μm), el inferior-nasal en miopía magna (disminución de 86.19 μm) y el temporal en DM 2 (disminución de 55.57 μm).

La coroides de los jóvenes sanos se usó como referencia y se dividió en diferentes zonas según el grosor coroideo medio en cada cubo macular. Se delimitaron cinco zonas nasales y cinco temporales. Las comparaciones entre las zonas equivalentes revelaron que la coroides se adelgazaba más en aquellas zonas donde era más gruesa en los jóvenes sanos.

Las representaciones 3D mostraron diferentes patrones: un patrón “en cadena montañosa” en individuos jóvenes sanos, “en pico montañoso” en individuos mayores sanos, “en garganta invertida” en pacientes jóvenes miopes magnos, y “en colinas agrupadas” en pacientes mayores con DM 2. Algunos autores habían intentado realizar descripciones topográficas o mapas coroideos, pero fue la primera vez que se

creaba un mapa tan pormenorizado. Asimismo, era la primera vez que se definían diferentes patrones topográficos.

En conclusión, no todas las regiones coroideas se afectan de forma similar, dado que depende de la patología. Para una mejor comprensión y análisis más exhaustivo, los mapas 3D son una herramienta útil. Deberían llevarse a cabo más estudios que explicaran la fisiopatología de estos diferentes patrones coroideos.

## c) Résumé de la thèse (FR)

La DM 2 est une maladie avec de l'affectation multisystémique, qui peut être classifiée dans macro et microangiopathie. La première inclut la cardiopathie ischémique, l'accident cérébrovasculaire et l'artériopathie périphérique. La deuxième inclut la néphropathie, la polyneuropathie périphérique et la rétinopathie diabétique. Selon la classification internationale, on classifie la rétinopathie diabétique dans cinq stades : pas de rétinopathie, rétinopathie minime, modérée, sévère et proliférante. La rétinopathie minime, modérée et sévère sont classifiées comme rétinopathie diabétique non proliférante. Une autre manifestation additionnelle à la rétine est l'œdème maculaire diabétique, qui a normalement comme conséquence une acuité visuelle plus baise et qui est réversible quand traité en temps.

La tomographie de cohérence optique (OCT) est devenue très utile pour détecter l'œdème maculaire diabétique, ainsi que pour mesurer l'épaisseur rétinienne. Le développement de la swept-source OCT (SS-OCT) et la technologie EDI ont permis des analyses plus profondes et précises sur la choroïde. La version antérieure d'OCT était la OCT de domaine spectral (SD-OCT) et elle avait une résolution axiale plus petite en comparaison avec la SS-OCT, avec de la segmentation imprécise de la choroïde, à moins que le mode EDI fût habilité. La choroïde est formée principalement par des vaisseaux sanguins et elle emmène apport sanguin aux couches externes de la rétine. Pendant les dernières années, la choroïde a été exhaustivement examinée et on a fait le lien entre son épaisseur et plusieurs conditions physiologiques et maladies oculaires et systémiques. La plupart des études ont trouvé qu'elle est  plus maigre dans la DM 2. Cependant, c'est pas encore clair comment l'œdème maculaire diabétique affecte l'épaisseur choroïdienne. De la même manière, on a trouvé qu'elle suive un patron irrégulier mais jusqu'à présent on n'a pas réalisé plus de recherche qui établit sa topographie avec précision et comment elle change avec les différentes conditions et maladies.

Le thème principal des quatre articles qui donnent forme à cette thèse doctoral était l'étude de la choroïde et sa topographie avec SS-OCT chez des sujets et des patients diabétiques. Les objectifs étaient les suivants : vérifier la répétabilité intratest des mesures de l'épaisseur choroïdienne avec SS-OCT chez des sujets sains et des

patients avec DM 2 avec de la rétinopathie diabétique, comparer l'épaisseur choroïdienne entre des sujets sains et des patients avec DM 2, et analyser l'épaisseur choroïdienne dans toute la zone maculaire chez des patients diabétiques et chez des contrôles ajustés par l'âge.

Une étude transversale a été réalisée à l'Hôpital Universitaire Miguel Servet à Saragosse (Espagne) entre novembre 2015 et novembre 2017, avec un recrutement de plusieurs groupes d'étude. Les critères d'inclusion dans le premier groupe ont étés : des patients avec DM 2 entre 55 et 75 ans, avec une longitude axiale ≤ 26 mm, < 6 D de myopie et < 2 D de cylindre. En cas d'œdème maculaire diabétique, une épaisseur rétinienne minimum de 300 µm ont été requise. Les critères d'inclusion dans le deuxième groupe ont été les mêmes mais sans la présence de DM 2. Les critères d'inclusion pour le troisième groupe incluyaient des volontaires jeunes sains entre 18 et 35 ans avec une longitude axiale ≤ 26 mm, < 6 D de myopie et < 2 D de cylindre. Dans tous eux, les critères d'exclusion ont été : quelque pathologie oculaire, du traitement ou de la chirurgie ophtalmologique précédente, amblyopie, une autre race différente de la caucasique, de la grossesse ou post-partum, des maladies endocrines ou neurologiques, de l'histoire de cancer, du traitement systémique avec des corticoïdes, des médicaments immunosuppressives, des thérapies biologiques et du traitement précédent avec des médicaments potentiellement toxiques pour la rétine et/ou le nerve optique.

Tous les examens sur OCT ont été acquis à travers des pupilles dilatées à la même heure du jour et par le même examinateur expérimenté. Deux types d'analyses ont été réalisés : une ligne horizontale de 12 mm et un cube maculaire de 6x6 mm. Du premier type, 11 mesures manuelles de l'épaisseur choroïdienne ont été obtenues. Du deuxième type, les épaisseurs sur la grille ETDRS et sur un autre de 30x30 petits cubes ont été obtenues, à partir desquels des représentations en 2D et 3D ont été créés, et une nouvelle division choroïdienne ont été établie pour effectuer des comparaisons.

Ci-dessous est le résumé des quatre articles :

1. **Abadía B, Calvo P, Bartol-Puyal F, Verdes G, Suñén I, Ferreras, A. Repeatability of choroidal thickness measurements assessed with swept-source optical coherence tomography in healthy and diabetic individuals. Retina. 2019 Apr;39(4):786-793.**

Il s'agit d'une étude transversal qui inclut 50 yeux des 33 sujets sains et 60 yeux des 43 patients avec DM 2, et dont l'objectif était évaluer la répétabilité intrasession des mesures de l'épaisseur choroïdienne obtenues avec SS-OCT chez des patients avec DM 2 et chez des témoins sains. Au sein du groupe diabétique, 7 patients ne présentaient pas de la rétinopathie diabétique, 13 avaient une rétinopathie minime, 32 modérée, 5 sévère et 3 proliférante. La moitié des diabétiques avaient de l'œdème maculaire diabétique. La répétabilité a été analysée après avoir mesuré l'épaisseur choroïdienne sur trois examens différents qui s'avaient réalisés consécutivement dans une seule session, et en plus avaient été délinéés automatiquement par le software interne. Sur la ligne horizontale de 12 mm, 11 localisations avec des intervalles de 500 μm ont été mesurées avec le compas par le même examinateur.

L'âge moyen était de 68.02±8.80 ans chez le groupe des témoins, et de 66.28±7.80 ans chez les diabétiques (p=0.28). L'épaisseur choroïdienne subfovéale chez les sains et les diabétiques a été de 222.97±79.90 μm et 192.67±74.30 μm, respectivement (p=0.013). Le coefficient de corrélation intra-classe, le coefficient de variation et la variabilité test-retest ont été calculés. Tous les coefficients de corrélation intra-classe ont été plus de 0.95 et 0.99, respectivement. Les coefficients de variation one été moins de 4.4% et 1.8%, respectivement. La variabilité test-retest oscillait entre 0.76 et 11.12 μm, et entre 0.64 et 6.29 μm, respectivement. Aucune différence significative n'a pas été trouvée sur la répétabilité intrasession des mesures choroïdiennes chez des sujets sains comme chez des diabétiques.

En conclusions, la SS-OCT avait une excellente répétabilité intrasession des mesures de l'épaisseur choroïdienne chez des sujets sains et avec DM 2.

2. **Abadia B, Suñen I, Calvo P, Bartol F, Verdes G, Ferreras A. Choroidal thickness measured using swept-source optical coherence tomography is reduced in patients with type 2 diabetes. PLoS One. 2018 Feb 2;13(2):e0191977.**

Il s'agit d'une étude transversale qui inclut 157 yeux des 94 patients avec DM 2 et 71 yeux des 38 sujets sains. Son objectif était comparer l'épaisseur choroïdienne entre les diabétiques et les témoins sains ajustés de l'âge.

Parmi les 157 yeux diabétiques, 48 présentaient de l'œdème maculaire diabétique. 49 yeux n'avaient pas de la rétinopathie diabétique, 27 avaient une rétinopathie minime, 60 modérée, 14 sévère et 7 proliférante. Sur chaque image de SS-OCT, 11 mesures manuelles de l'épaisseur choroïdienne ont été réalisées. Une était subfovéale, cinq nasales et cinq temporales, avec des intervalles de 500 μm entre elles. En plus de comparer l'épaisseur choroïdienne entre les trois groupes d'étude, un analyse de corrélation entre la duration du diabète, les niveaux de HbA1c et l'épaisseur choroïdienne ont été exécutés. On a masqué les images afin que l'examinateur ne pût pas identifier à quel patient appartenait chaque coupe.

L'âge moyen était de 67.60±8.10 ans et il n'avait pas des différences quant à l'âge, la longitude axiale et la tension artérielle entre les groupes ($p>0.05$). La duration moyenne de la DM 2 était de 16.6±9.5 ans, tandis que la Hb1Ac moyenne était de 7.7±1.3%. En général, la choroïde était significativement plus maigre chez les diabétiques. Les patients avec de l'œdème maculaire diabétique montraient des épaisseurs choroïdiennes réduits dans toutes les mesures, sauf sur les positions à 2000 et 2500 μm nasales, en comparaison avec les sains. On a trouvé une corrélation modérée entre l'épaisseur choroïdienne et les niveaux de HbA1c chez les patients avec de l'œdème ($r=0.342$, $p=0.017$ sur la position subfovéale). La duration du diabète ne se corrélait pas significativement avec l'épaisseur choroïdienne. Dans les deux groupes, la choroïde montrait un patron similaire : elle était plus épaisse sur la localisation subfovéale, suivie par la temporale et la nasale. Ces résultats se ressemblaient à ces des autres études précédents.[10–12]

En conclusion, les mesures sur SS-OCT révèlent que la choroïde est significativement maigre chez les patients avec DM 2, des patients avec rétinopathie

diabétiques modérée et des patients avec de l'œdème maculaire diabétique, que chez des sujets sains.

3. **Abadia B, Bartol-Puyal F, Calvo P, Verdes G, Isanta C, Pablo L. Mapping choroidal thickness in patients with type 2 diabetes. Can J Ophthalmol. 2019 Aug 9. pii: S0008-4182(19)30344-8**

Il s'agit d'une étude transversal dont l'objectif était déterminer et comparer les caractéristiques topographiques de l'épaisseur choroïdienne sur SS-OCT entres des patients avec DM 2 et des témoins sains ajustés par l'âge. On a analysé 66 yeux de 33 sujets sains et 192 yeux de 96 patients diabétiques. 36 yeux ne présentaient pas de la rétinopathie diabétique, 26 présentaient une rétinopathie minime, 25 modérée, 5 sévère et 4 proliférante. Aucun d'eux n'avait pas de l'œdème maculaire diabétique.

Un cube maculaire de 6x6 mm sur SS-OCT a été analysé, avec de la segmentation et de la méditions de l'épaisseur choroïdienne automatiques. Ensuite, la zone analysée a été divisée en zones différentes selon l'épaisseur choroïdienne et on a comparé les zones équivalentes entre les groupes. En plus on a créé des cartes 3D pour représenter la choroïde.

On n'a pas trouvé des différences quant à l'âge ni la longitude axiale ($p>0.05$). L'âge moyen était de 66.83±3.71 ans chez les sains et 67.94±7.93 ans chez les diabétiques. En général, l'épaisseur choroïdienne était significativement plus maigre chez les diabétiques ($p<0.05$). Hors de la fóvea, l'épaisseur choroïdienne moyenne était plus grosse dans la demi-rétine supérieure et diminuait vers inférieur, temporal et nasal, avec le minimum dans les points les plus éloignés.

Ces résultats étaient similaires à ces qui déclaraient que l'épaisseur choroïdienne est plus petit chez des patients diabétiques, mais c'était la première fois qu'on montrait des cartes 3D exhaustives provenant des données obtenues à partir de la SS-OCT avec de la segmentation et mesures automatiques.

En conclusion, l'épaisseur choroïdienne suit un patron ellipsoïdal chez des yeux des diabétiques comme non-diabétiques, avec un amaigrissement diffus chez les premiers. Comprendre ces différences est important pour des études futures qui

auront l'intention d'expliquer la physiopathologie et la relation entre la choroïde et la rétinopathie diabétique.

4. **Bartol-Puyal F, Isanta C, Ruiz-Moreno Ó, Abadía B, Calvo P, Pablo L. Distribution of Choroidal Thinning in High Myopia, Diabetes Mellitus, and Aging: A Swept-Source OCT Study. J Ophthalmol. 2019 Aug 15;2019:3567813.**

Il s'agit d'une étude transversal qui comparait l'amaigrissement choroïdien maculaire entres des jeunes sains, des sujets âgés sains, des jeunes myopes fortes et des patients avec DM 2 utilisant la grille ETDRS et des cartes 3D. Le premier groupe d'étude incluait 102 yeux de 51 sujets sains, le deuxième incluait 60 yeux de 30 sujets âgés sains, le troisième se était composé de 110 yeux de 55 patients avec DM 2, et le quatrième était composait de 24 yeux de 12 patients avec de la myopie forte.

Les valeurs de l'épaisseur choroïdienne ont été obtenues sur des grilles de 30x30 cubes de 200x200 μm chacun, donnés de forme automatique par l'OCT, et après des cartes 3D ont été créées pour représenter l'épaisseur choroïdienne. Ces-ci ont été mesurées aussi dans tous les secteurs de la grille ETDRS. L'âge moyen était de 27.31±3.95, 66.41±7.54, 27.69±3.89 et 66.48±7.39 ans dans les quatre groupes, respectivement. L'épaisseur choroïdienne ne s'est pas montrée uniforme, puisque les zones supérieures et centrales étaient plus épaisses dans tous les groupes. Tous les secteurs ETDRS étaient toujours plus épaisses ($p<0.05$) chez des sujets jeunes sains que chez les autres. On a trouvé que le secteur choroïdien qui se maigrit le plus était l'inférieur en cas de l'âge (réduction de 103.28 μm), l'inférieur-nasal dans la myopie forte (réduction de 86.19 μm) et le temporal chez les diabétiques (réduction de 55.57 μm).

La choroïde des jeunes sains a été utilisée comme référence et s'est divisée en zones différentes selon l'épaisseur moyenne dans chaque cube maculaire. Cinq zones nasales et cinq temporales ont été définies. Les comparaisons entres les zones équivalentes ont révélé que la choroïde se maigrit plus dans ces zones où c'était plus épaisse chez les sujets sains.

Les représentations 3D montraient patrons différents : un patron « en chaîne de montagnes » chez des jeunes sains, « en sommet » chez des sujets sains âgés, « en gorge inversée » chez des jeunes avec de la myopie forte, et « en collines regroupées » chez des patients avec DM 2. Quelques auteurs avaient essayé de réaliser des descriptions topographiques ou cartes choroïdiennes, mais ça a été la première fois qu'on a créé une carte si détaillée. De la même manière, ça a été la première fois qu'on a défini des différents patrons topographiques.

Pour conclure, pas toutes les régions choroïdiennes ne se modifient de forme similaire, puisque ça dépend de la pathologie. Afin d'une meilleur compréhension et un analyse plus exhaustive, les cartes 3D sont un outil utile. Il faudrait faire plus d'études qui expliquent la physiopathologie de ces différents patrons choroïdiens.

## d) Zusammenfassung der Doktorarbeit (DE)

Der DM 2 ist eine Krankheit mit multisystemischen Störungen, die in Makro und Mikorangiopathie eingeteilt werden können. Die erste umfasst die ischämische Herzkrankheit, den Schlaganfall und die periphere arterielle Verschlusskrankheit. Die zweite umfasst die Nephropathie, periphere Polyneuropathie und diabetische Retinopathie. Nach der internationalen Einteilung, die diabetische Retinopathie teilt sich in fünf Stadion: keine Retinopathie, milde, mäßige, schwere und proliferative Retinopathie. Die milde, mäßige und schwere Retinopathie gehörten zu der nicht proliferativen diabetischen Retinopathie. Eine andere zusätzliche Manifestation in der Netzhaut ist das diabetische Makulaödem, das normalerweise schlechtere Sehschärfe

Die optische Kohärenztomografie (OCT) ist sich sehr nützlich erwiesen, um diabetisches Makulaödem aufzufinden, als auch zum die Netzhautdicke zu vermessen. Die Entwicklung der swept-source OCT (SS-OCT) und die Technologie EDI haben tiefe und präzise Analysen der Aderhaut ermöglicht. Die vorhergehende Version der OCT war die Spektral Domain OCT (SD-OCT) und die hatte eine kleinere axiale Auflösung im Vergleich zu der SS-OCT, mit ungenauer Segmentierung der Aderhaut, außer wenn der EDI Modus aktiviert wurde. Die Aderhaut besteht hauptsächlich aus Blutgefäßen und bringt sie Blutzufuhr in die äußeren Netzhautschichten. Die letzte Jahre lang wurde die Aderhaut gründlich untersucht und man hat ihre Dicke mit vielfältigen physiologischen Zuständen und Augen- und Systemischekrankheiten verbindet. Die Mehrzahl der Studien haben gefunden, dass die beim DM 2 verdünnt ist. Trotzdem, ist es noch nicht klar, wie das diabetische Makulaödem die Aderhaut beeinflusst. Ebenfalls hat man angeregt, dass die ein unregelmäßiges Muster befolgt aber zum Moment werden noch keine weitere Forschung duchgeführt, die ihre genaue Topographie beschreiben und die erklären, wie die Aderhautdicke mit den verschiedenen Zuständen und Krankheiten verändert.

Das Hauptthema der vier Artikeln, die diese Doktorarbeit bilden, war das Studien der Aderhaut und ihre Topografie mit SS-OCT in Gensunden und diabetischen Patienten. Das Ziel waren die folgenden: die intrasitzunge Wiederholbarkeit der Vermessungen der Aderhautdicke mit SS-OCT in Gensunden und Patienten mit DM 2 mit diabetischer Retinopathie festzustellen, die

Aderhautdicke zwischen Gesunden und Patienten mit DM 2 zu vergleichen, und die Aderhautdicke um die Makula zwischen Patienten mit DM 2 und gleichaltrigen Gesudnen zu analysieren.

Eine Querschnittstudie wurde zwischen November 2015 und November 2017 beim Universitätsklinikum Miguel Servet in Zaragoza (Spanien) durchgeführt, mit Rekrutierung von verschiedenen Studiengruppen. Die Einschlusskriterien für die erste Gruppe waren Patienten mit DM 2 zwischen 55 und 75 Jahren alt, mit einer axialen Augenlänge ≤ 26 mm, < 6 D von Myopie und < 2 D von Zylinder. Im Fall von diabetischem Makulaödem, wurde eine minimale Mindestnetzhautdicke von 300 µm gefordert. Die Einschlusskriterien für die zweite Gruppe waren gleich aber ohne DM 2. Die Einschlusskriterien für die dritte Gruppe umfassten gesunde junge Freiwilliger zwischen 18 und 35 Jahren alt mit einer axialen Augenlänge ≤ 26 mm, < 6 D von Myopie und < 2 D von Zylinder. Für alle die Gruppen waren die Einschlusskriterien: irgendeine Augenpathologie, vorige Behandlung oder Augenchirurgie, Amblyopie, nicht-kaukasische Rasse, Schwangerschaft oder Wochenbett, endokrine oder neurologische Erkrankungen, Krebsgeschichte, systemische Behandlung mit Kortikosteroiden, Immunsuppressiven, biologischen Therapien oder Arzneimitteln mit möglicher Netzhauts oder Sehnervstoxizität.

Alle die Untersuchungen mit OCT wurden um dieselbe Uhrzeit durch erweiterte Pupillen von demselben Untersucher aufgenommen. Zwei Arten von Analysen wurden aufgenommen: eine 12 mm horizontale Linie und ein 6x6mm makulärer Würfel Aufnahmfeld. Von der ersten, 11 Handmessungen der Aderhautdicke wurden aufgenommen. Von der zweiten, wurden die Aderhautdicke sowohl beim ETDRS-Gitter als auch bei einer anderen Gitter mit 30x30 kleinen Würfeln aufgenommen, von denen 2D und 3D Darstellungen geschaffen wurden. Eine neue Aderhautteilung wurde aufgestellt um Vergleichen auszuführen.

Hier unten steht die Zusammenfassung der vier Artikeln:

1. **Abadía B, Calvo P, Bartol-Puyal F, Verdes G, Suñén I, Ferreras, A. Repeatability of choroidal thickness measurements assessed with swept-source optical coherence tomography in healthy and diabetic individuals. Retina. 2019 Apr;39(4):786-793.**

Es handelt sich um eine Querschnittstudie, an der 50 Augen von 33 gesunden Personen und 60 Augen von 43 Patienen mit DM 2 teilnahmen. Ihre Objektiv war die intrasitzunge Wiederholbarkeit der Vermessungen der Aderhautdick mit SS-OCT in Patienten mit DM 2 und in gesunden Personen festzustellen. Innerhalb der diabetischen Gruppe, hatten 7 Patienen keine diabetische Retinopathie, 13 milde, 32 mäßige, 5 schwere und 3 proliferative Retinopathie. Die Hälfte der Patienten mit DM 2 wiesen diabetischem Makulaödem auf. Die Wiederholbarkeit wurde nach der Vermessung der Aderhautdicke in drei verschiedenen Untersuchungen analysiert, die nacheinander bei einer einzellen Sitzung durchgeführt worden waren, und außerdem waren die automatisch von innerer Software abgegrenzt worden. Auf der horizontaler 12mm-Linie wurden 11 Positionen mit 500µm-Zwischenraum mit dem Kompass von demselben Untersucher gemessen.

Das Duchschnittsalter betrug 68.02±8.80 Jahre bei den gesunden Patienten und 66.28±7.80 Jahre bei den Diabetikern (p=0.28). Die subfoveale Aderhautdicke in Gesunde und Diabetikern betrug 222.97±79.90 µm beziehungsweise 192.67±74.30 µm (p=0.013). Der Intraklassen-Korrelationskoeffizient, der Variationskoeffizient und die test-retest Variabilität wurden gerechnet. Alle die Intraklassen-Korrelationskoeffizienten waren höher als 0.95 beziehungsweise 0.99. Die Variationskoeffizienten waren kleiner als 4.4% beziehungsweise 1.8%. Die test-retest Variabilität schwankten zwischen 0.76 und 11.12 µm beziehungsweise 0.64 und 6.29 µm. Man hat keine signifikative Unterschiede bei der intrasitzungen Wiederholbarkeit von keinen Aderhautmessungen sowohl bei Gesunden als auch Diabetikern gefunden.

Abschließend hatte die SS-OCT eine ausgezeichnete intrasitzunge Wiederholbarkeit von der Aderhautmessungen bei gensunden Personen und Patienten mit DM 2.

2. **Abadia B, Suñen I, Calvo P, Bartol F, Verdes G, Ferreras A. Choroidal thickness measured using swept-source optical coherence tomography is reduced in patients with type 2 diabetes. PLoS One. 2018 Feb 2;13(2):e0191977.**

Es handelt sich um eine Querschnittstudie, die 157 Augen von 94 Patienten mit DM 2 aufnahm. Ihre Objektiv war die Aderhautdicke zwischen Diabetikern und gleichaltrigen Gesunden Personen zu vergleichen.

Innerhalb der 157 diabetischen Augen, wiesen 48 diabetischen Makulaödem auf. 49 hatten keine diabetische Retinopathie, 27 hatten milde, 60 mäßige, 14 schwere und 7 proliferative Retinopathie. Auf jedes OCT-Bild wurden 11 Handmessungen von Aderhautdicke durchgeführt. Eine war subfoveal, fünf nasal und fünf temporal, mit 500μm-Zwischenraum zwischen diesen Messungen. Außer dem Aderhautdickevergleich zwischen die drei Studiengruppe, wurde eine Korrelationsanalyse zwischen die Diabetesdauer, die HbA1c-Werte und die Aderhautdicke durchgeführt. Man hat die Bilder maskiert, sodass der Untersucher nicht identifizieren könnte zu welchem Patient gehörte jeder Schnitt.

Das Durchschnittsalter betrug 67.60±8.10 Jahre und es gab keine Unterschiede bezüglich des Alters, der axialen Augenlänge und des Blutdrucks zwischen den drei Gruppen ($p>0.05$). Die Durchschnittsdauer der Diabetes war 16.6±9.5 Jahre, während die durchschnittliche HbA1c-Werte war 7.7±1.3%. Ingesamt, die Aderhaut war signifikantlich dünner als in Diabetikern. Die Patienten mit diabetischem Makulaödem zeigten kleinere Aderhautdicke in allen den Messungen, außer der nasalen 2000- und 2500μm-Positionen, im Vergleich zu den Gesunden. Man hat eine mäßige Korrelation zwischen der Aderhautdicke und die HbA1c-Werte in Patienen mit Ödem gefunden ($r=0.342$, $p=0.017$ in subfovealer Position). Es gab keine signifikante Korrelation zwischen die Diabetesdauer und der Aderhautdicke. In beiden Gruppen zeigte die Aderhaut ein ähnliches Muster: die war dicker in subfovealer Position, gefolbt von temporaler und nasaler Positionen. Diese Ergebnisse waren ähnlich wie andere Studien.[10–12]

Abschließend entdecken die SS-OCT-Messungen, dass die Aderhaut signifikantlich dünner ist in Patienten mit DM 2, Patienten mit mäßiger diabetischen Retinopathie und Patienten mit diabetischem Makulaödem, als in gesunden Personen.

3. **Abadia B, Bartol-Puyal F, Calvo P, Verdes G, Isanta C, Pablo L. Mapping choroidal thickness in patients with type 2 diabetes. Can J Ophthalmol. 2019 Aug 9. pii: S0008-4182(19)30344-8**

Der Objektiv dieser Querschnittstudie war, die topografische Striche der Aderhautdicke mit SS-OCT zwischen Patienten mit DM 2 und gleichaltrigen Gesunden zu bestimmen und zu vergleichen. 66 Augen von 33 Gesunden und 192 Augen von 96 Diabetikern nahmen teil. 36 Augen hatten keine diabetische Retinopathie, 26 hatten milde, 25 mäßige, 5 schwere und 4 proliferative Retinopathie. Kein von ihnen wiesen Makulaödem auf.

Ein makulärer 6x6mm Würfel von SS-OCT wurde analysiert, nach automatischer Abgrenzung und Aderhautdicke-Vermessungen von dem inneren Software. Die gescannte Zone wurde in verschiedene kleineren Zonen nach der Aderhautdicke eingeteilt und die entsprechende Zonen wurden zwischen die Gruppe verglichen. 3D Karte wurden außerdem geschafft, um die Aderhaut darzustellen.

Es gab keine Verschiedene weder in Alter noch in axialer Augenlänge ($p>0.05$). Die Durchschnittsalter betrug 66.83±3.71 Jahre beim Gesunden und 67.94±7.93 Jahre bei Diabetikern. Die Aderhautdicke war ingesamt signifikantlich dünner bei Diabetikern ($p<0.05$). Außer der Fovea, die Durchschnittsaderhautdicke war größer in der oberer Netzhaut und die verkleinerte nach temporal und nasal. Die kleinste Dicke befand sich in den entferntesten Punkten.

Diese Ergebnisse waren ähnlich diesen, die behaupteten, dass die Aderhautdicke kleiner bei Diabetikern war. Trotzdem war dieses Mal das erste, dass vollständige 3D Karte gezeigt wurden, die aus SS-OCT Angaben mit automatischen Abgrenzung und Vermessungen hergestellt worden waren.

Abschließend folgt die Aderhautdicke ein ellipsoides Muster sowohl bei diabetischen Augen als auch nicht-diabetischen, mit einer allgemeinen Verdünnung

im Vorhergehend. Diese Unterschiede zu verstehen ist wichtig für zukünftige Studien, die die Pathophysiologie und die Verbindung zwichen Aderhaut und diabetischer Retinopathie erklären möchten.

4. **Bartol-Puyal F, Isanta C, Ruiz-Moreno Ó, Abadía B, Calvo P, Pablo L. Distribution of Choroidal Thinning in High Myopia, Diabetes Mellitus, and Aging: A Swept-Source OCT Study. J Ophthalmol. 2019 Aug 15;2019:3567813.**

Diese Querschnittstudie stellte die makuläre Aderhautverdünnung fest zwischen gesunden Jungen, gesunden Erwachsenen, Jungen mit höher Myopie und Patienten mit DM 2 im Gebrauch vom ETDRS-Gitter und 3D Karten. An die erste Studiengruppe nahmen 102 Augen von 51 gesunden Jungen teil, an die Zweite 60 Augen von 30 gesunden Erwachsenen, an die Dritte 110 Augen von 55 Erwachsenen Patienten mit DM 2 und an die Vierte 24 Augen von 12 Jungen mit höher Myopie.

Die Aderhautdickewerte wurden mittels 30x30-Würfel-Grillen von 200x200 μm jedem Grille erlanget, die die OCT automatisch stellte, und 3D Karte geschafft wurden, um die Aderhautdicke darzustellen. Die wurde auch in jedem ETDRS-Sektor gemessen. Das Durchschnittsalter war 27.31±3.95, 66.41±7.54, 27.69±3.89 und 66.48±7.39 Jahre beziehungsweise in den Studiengruppe. Die Aderhautdicke zeigte nicht gleichmäßig, weil die Obere und Zentrale dicker in allen die Gruppen waren. Alle die ETDRS-Sektoren waren immer dicker ($p<0.05$) in gesunden Jungen als in den anderen. Man hat gefunden, dass der Aderhautsektor, der am meisten verdünnte, der Unterer war im Fall von Alter (Verminderung von 103.28 μm), der Unterer-nasal im Fall von höher Myopie (Verminderung von 86.19 μm) und der Temporal in DM 2 (Vermindeurung von 55.57 μm).

Die Aderhaut der gesunden Jungen wurde als Bezug gedient und in verschiedene Zonen nach der Durchschnittsaderhautdicke bei jedem makulären Würfel eingeteilt. Fünf nasale und fünf temporale Zonen wurden abgegrenzt. Die Vergleiche zwischen entsprechenden Zonen entdeckten, dass die Aderhaut am mesiten in diesen Zonen verdünnte, wo die Aderhaut dicker war bei gesunden Jungen.

Die 3D Darstellungen zeigten verschiedene Muster: ein „Bergkette“ Muster bei gesuden Jungen, ein „Berggipfel“ Muster bei gesunden Erwachsenen, ein „umgekehrter Engpass“ Muster bei jungen höhen Myopen, und ein „zusammenstellte Hügel“ bei erwachsenen Diabetikern. Manche Autoren hatten schon früher versucht, topografische Beschreibungen oder Aderhautkarte durchzuführen, aber das war das erste Mal, eine so genaue Karte zu schaffen. Das war ebenso das erste Mal, dass verschiedene topografische Muster ausführlich beschreibt wurden.

Abschließend wurden die Aderhautregionen nicht ähnlich betroffen, da es an die Pathologie kommt. Um ein besseres Verstehen und eine vollständigere Analyse, werden die 3D Karte ein nützliches Werkzeug. Man sollte noch weiter forschen, um die Pathophysiologie dieser Aderhautmuster zu erklären.

# e) Resumen de la tesis (AR)

La DM 2 e una enfermedat con afectazión multisistémica, que puede cllasificar-se en macro i microangiopatía. La primera inclluye cardiopatía isquémica, azidén zelebrobasculá i enfermedat alterial periférica. La segunda inclluye nefropatía, polineuropatía periférica i retinopatía diabetica. Seguntes la cllasificazión internazional, la retinopatía diabetica se cllasifica en zinco escalóns: sin retinopatía, lixera, amoderada, grabe i proliferatiba. La retinopatía lixera, amoderada y grabe perteneixen al grupo de retinopatía diabetica no proliferatiba. Una atra manifestazión retiniana e el edema maculá diabetico, que normalmén suposa una pió agudeza bisual i e rebersiblle si se trata a tiempo.

La tomografía de coherenzia óptica (OCT) a resultau ser mui útil pa la detectar edema maculá diabetico, asinas como pa medir la grosaria retiniana. El desarrollo de la OCT swept-source (SS-OCT) i la tecnolochía EDI an permitiu analisis fundos i prezisos de la coroides. La bersión prebia d'OCT eba la OCT de dominio espectral (SD-OCT) i teniba menó resoluzión axial en comparanza con la SS-OCT, con segmentazión imprezisa de la coroides, a menos que s'actiba-se el modo EDI. La coroides está formada mayormén de benas sanguinas i lleba alporte sanguino a las capas externas de la retina. Durando los zagueros años, s'a examinau la coroides de forma esaustiba i s'a relazionau la suya grosaria con multiplles condizións fisiologicas, i enfermedaz oculás i sistematicas. La mayoría de los estudios ban trobar que'está enfllacada a la DM 2. Sin embargo, encara no está cllaro cómo afecta el edema maculá diabetico a la gordaria coroidea. Asinasmesmo, se ba proposar que sigue un patrón irregulá pero dica ara no s'an fei más inbestigazións que definan la suya topografía de forma prezisa i cómo baría con las diferéns condizións i enfermedaz.

El tema prenzipal de los quatro articllos qu'aconforman ista tesis dotoral ba ser l'estudio de la coroides i la suya topografía con SS-OCT a sanos i paziéns diabeticos. Los obchetibos ban ser los siguiéns: berificar la repetitibilidat intratest de las medizións de gordaria coroidea con SS-OCT a personas sanas i paziéns con DM 2 con retinopatía diabetica, comparar la gordaria coroidea entre sans i paziéns con DM 2, i analizar la gordaria coroidea per toda la mácula en paziéns diabeticos i controls sans achustaus per edat.

Se ba realizar un estudio trabersero a l'Espital Unibersitario Miguel Servet a Zaragoza (España) entre nobiembre de 2015 i nobiembre de 2017, con recllutamiento de barios grupos d'estudio. Los criterios d'incllusión pa'l primé grupo ban ser paziéns con DM 2 entre 55 i 75 años, con una largaria axial ≤ 26 mm, < 6 D de miopía i < 2 D de zilindro. En caso d'edema maculá diabetico, se ba requerir una gordaria retiniana minima de 300 µm. Los criterios d'incllusión pa'l segundo grupo ban ser los mesmos pero sin la presenzia de DM 2. Los criterios d'incllusión pa'l tercé grupo ban inclluir bolunarios chobes sanos entre 18 i 35 años con una largaría axial ≤ 26 mm, < 6 D de miopía i < 2 D de zilindro. A toz els, los criterios d'excllusión ban ser: cualquié patolochía ocular, tratamiento o ziruchía oftalmológica prebia, ambliopía, raza diferén de la caucásica, preño u puerperio, enfermedat endocrina u neurolóchica, istoria de cánzer, tratamiento sistémico con corticoides, inmunosupresores, terapias biológicas u melezinas potenzialmén tóxicas pa la retina u el nernio optico.

Toz los examens con OCT se ban alquirir per ninetas dilatadas a la mesma ora del día i pe'l mesmo técnico esperimentau. Se ban realizar dos tipos d'analisis: una llinia orizontal de 12 mm i un cubo maculá de 6x6 mm. Al primero, se ban obtenir 11 medizións manuals de gordaria coroidea. Al segundo, se ban obtenir las gordarias tanto a la reixeta ETDRS como a una atra de 30x30 cubos chicos, a partir de los cuales se ban crear representazións 2D i 3D, i se ba establleixer una nueba dibisión coroidea pa efectuar comparazións.

Deseguida e el resumen de los quatro articllos:

1. **Abadía B, Calvo P, Bartol-Puyal F, Verdes G, Suñén I, Ferreras, A. Repeatability of choroidal thickness measurements assessed with swept-source optical coherence tomography in healthy and diabetic individuals. Retina. 2019 Apr;39(4):786-793.**

Iste e un estudio trabersero que inclluye 50 uellos de 33 indibiduos sanos i 60 uellos de 43 paziéns con DM 2, i que su proposito eba ebaluar la repetitibilidat intrasesión de las medizións de gordaria obtenidas meyán SS-OCT a paziéns con DM 2 i a controls sanos. Dintro del grupo diabetico, 7 paziéns no teniban retinopatía diabetica, 13 teniban lixera, 32 amoderada, 5 grabe i 3 proliferatiba. La mitat de los paziéns diabeticos teniba edema maculá diabetico. La repetitibilidat se ba analisar tras medir la gordaria coroidea a tres examens diferéns que s'abeban fei consecutibamén a una sola sesión, i amás abeban siu deliniaus automaticamén p'el software interno. Sobre la línea de 12 mm, se ban medir 11 posizións con interbalos de 500 μm con el compás per parti del mesmo examinadó.

La edat meya ba ser de 68.02±8.80 años al grupo de sanos i 66.28±7.80 años al de diabeticos (p=0.28). La gordaria coroidea subfobeal a los sanos i a los diabeticos ba ser de 222.97±79.90 μm i 192.67±74.30 μm, respeutibamén (p=0.013). Se ban calcular el coefizién de correlazión intracllase, el coefizién de bariazión i la bariabilidat test-retest. Toz los coefiziéns de correlazión intracllase ban ser mayós de 0.95 i 0.99, respeutibamén. Los coefiziéns de bariazión ban ser menós de 4.4% i 1.8%, respeutibamén. La bariabilidat test-retest oszilaba entre 0.76 i 11.12 μm, i entre 0.64 i 6.29 μm, respeutibamén. No se ban trobar diferenzias significatibas a la repetibilidat intrasesión de nenguna medizión coroidea tanto a indibiduos sanos como a diabeticos.

En remazanza, la SS-OCT teniba una eszelén repetibilidat intrasesión de las medizións de gordaria coroidea a indibiduos sanos i a paziéns con DM 2.

2. **Abadia B, Suñen I, Calvo P, Bartol F, Verdes G, Ferreras A. Choroidal thickness measured using swept-source optical coherence tomography is reduced in patients with type 2 diabetes. PLoS One. 2018 Feb 2;13(2):e0191977.**

Iste e un estudio trabersero que incluye 157 uellos de 94 paziéns con DM 2 i 71 uellos de 38 indibiduos sanos. El suyo obchetibo eba acomparar la gordaria coroidea entre los diabeticos i los controls sanos achustaus per edat.

D'entre los 157 uellos diabeticos, 48 teniban edema maculá diabetico. 49 uellos no teniban retinopatía diabetica, 27 lixera, 60 amoderada, 14 grabe i 7 proliferatiba. A cada imachen de SS-OCT se ban realizá 11 medizións manuals de gordaria coroidea. Una eba la subfobeal, zinco nasals i zinco temporals, con interbalos de 500 μm entre ellas. Amás d'acomparar la gordaria coroidea entre los tres grupos d'estudio, se b afer un analisis de correlazión entre la durazión de la diabetes, los rans de HbA1c i la gordaria coroidea. Se ban enmarcarar las imachens pa qu'el examinadó no podese identificar de qué pazién eba cada tallo.

La edat meya ba ser de 67.60±8.10 años i no ba ny'aber diferenzias en cuanto a edat, largaria axial ni tensión alterial entre los grupos ($p>0.05$). La durazión meya de la DM 2 ba ser de 16.6±9.5 años, mientras que la Hb1Ac meya ba ser de 7.7±1.3%. En cheneral, la coroides eba significatibamén más fina a los diabeticos. Los paziéns con edema maculá diabetico amostraban gordarias coroideas reduzidas a todas las medizións, fueras de las posizións 2000 i 2500 μm nasals, en acomparanza con los sanos. Se ba trobar una correlazión amoderada entre la gordaria coroidea i los rans de HbA1c a paziéns con edema ($r=0.342$, $p=0.017$ a la posizión subfobeal). La durazión de la diabetes no se ba correlazionar significatibamén con la gordaria coroidea. A los dos grupos, la coroides ba amostrar un patrón similá: eba más rezia a la posizión subfobeal, seguida de temporal i nasal. Istos resultaus eban similás a atros estudios.[10–12]

En rematanza, las medizións con SS-OCT rebelan que la coroides está significatibamén enfllacada a paziéns con DM 2, paziéns con retinopatía diabetica amoderada, i paziéns con edema maculá diabetico, que a indibiduos sanos.

3. **Abadia B, Bartol-Puyal F, Calvo P, Verdes G, Isanta C, Pablo L. Mapping choroidal thickness in patients with type 2 diabetes. Can J Ophthalmol. 2019 Aug 9. pii: S0008-4182(19)30344-8**

Se trata d'un estudio trabersero que su obchetibo eba determinar i acomparar las trazas topográficas de gordaria coroidea con SS-OCT entre paziéns con DM 2 i controls sanos achustaus per edat. Se ban analizar 66 uellos de 33 indibiduos sanos i 192 uellos de 96 paziéns diabeticos. 36 uellos no teniban retinopatía diabetica, 26 teniban lixera, 25 amoderada, 5 grabe y 4 proliferatiba. Nenguno d'els presentaba edema maculá diabetico.

Se ba analizar un cubo maculá de 6x6 mm con SS-OCT, con segmentazión i medizión de gordaria de coroides automaticas. L'aria escaneada se ba dibidir en diferéns zonas seguntes la gordaria coroidea i se ban acomparar entre los grupos las zonas equibaléns. Amás se ban crear mapas 3D pa representar la coroides.

No se ban trobar diferenzias a edat ni largaría axial ($p>0.05$). La edat meya ba ser de 66.83±3.71 años al grupo sano i 67.94±7.93 años al grupo diabetico. En cheneral, la gordaria coroidea eba significatibamén más enfllacada a los diabeticos ($p<0.05$). Fuera de la fobea, la gordaria coroidea meya eba mayó a la hemirretina superió i minguaba enta inferió, temporal i nasal, sén minima a los puntos más llejanos.

Istos resultaus eban similás a los qu'afirmaban que la gordaria coroidea e menó a paziéns diabeticos, pero eba la primera begada que s'amostraban mapas 3D esaustibos orichinaus a partir de datos obtenius de SS-OCT con segmentazión i medizións automaticas.

En rematanza, la gordaria coroidea sigue un patrón elipsoide tanto a uellos de diabeticos como no-diabeticos, con enfllacamén difuso a la primera. Comprender istas diferenzias e importante pa estudios esbenideros que pretendan expllicar la fisiopatolochía i la relazión entre coroides i retinopatía diabetica.

4. **Bartol-Puyal F, Isanta C, Ruiz-Moreno Ó, Abadía B, Calvo P, Pablo L. Distribution of Choroidal Thinning in High Myopia, Diabetes Mellitus, and Aging: A Swept-Source OCT Study. J Ophthalmol. 2019 Aug 15;2019:3567813.**

Se trata d'un estudio trabersero qu'acomparaba l'enfllacamén coroideo maculá entre chobes sanos, mayós sanos, chobes miopes magnos i paziéns con DM 2 usán la reixeta ETDRS i mapas 3D. El primé grupo d'estudio incl luyiba 102 uellos de 51 chobes sanos, el segundo incl luyiba 60 uellos de 30 indibiduos mayós sanos, el terzero se comoniba de 110 uellos de 55 paziéns con DM 2, i el quarto estaba formau per 24 uellos de 12 paziéns chobes miopes magnos.

Las baluras de gordaria coroidea se ban obtenir a reixetas de 30x30 cubos de 200x200 μm cada cubo, que daba de forma automatica la OCT, i se ban crear mapas 3D pa representar la gordaria coroidea. Iste tamé se ba medir a cada sectó de la reixeta ETDRS. La edat meya ba ser de 27.31±3.95, 66.41±7.54, 27.69±3.89 i 66.48±7.39 años a los quatro grupos, respeutibamén. La gordaria coroidea no ba mostrar ser uniforme, ya que las zonas superió i zentrals eban más rezias a toz los grupos. Toz los sectós ETDRS eban siempre más rezios ($p<0.05$) a indibiduos chobes sanos qu'a los atros. Se ba trobar qu'el sectó coroideo que más s'enfllacaba eba l'inferió al caso de la edat (mingua de 103.28 μm), el inferió-nasal a miopía magna (mingua de 86.19 μm) i el temporal a DM 2 (mingua de 55.57 μm).

La coroides de los chobes sanos se ba usar como referenzia i se ba dibidir en zonas diferéns seguntes la gordaria coroidea meya a cada cubo maculá. Se ban delimitar zinco zonas nasals i zinco temporals. Las comparanzas entre las zonas equibaléns ban rebelar que la coroides s'enfllacaba más a aquelas zonas ane eba más rezia a los chobes sanos.

Las representazións 3D amostraron patróns diferéns: un patrón "en cadena montanyosa" a indibuduos chobes sanos, "en pico montanyoso" a indibiduos mayós sanos, "en garganchón tornau" a paziéns chobes miopes magnos, i "en pueyos agrupaus" a paziéns mayós con DM 2. Bellos autos abeban mirau de realizar descripzións u mapas coroideos, pero ba ser la primera begada que se creaba un mapa

tan pormenorizau. Asinasmesmo, eba la primera begada que se definiban diferéns patróns topográficos.

En rematanza, no todas las rechións coroideas s'afectan de forma similá, dau que depende de la patolochía. Pa una milló comprensión i analisis más esaustibos, los mapas 3D son una ferramienta útil. Deberían realizar-se más estudios que explicasen la fisiopatolochía d'istos diferéns patróns coroideos.

# 5) Introduction

## a) Diabetes mellitus type 2

T2D is a systemic disease with a multisystemic affection. It is the most common type of diabetes and it is characterized by chronic hyperglycaemia. According to the American Diabetes Association, it may be diagnosed with the presence of any of the following criteria: Haemoglobin A1C ≥ 6.5%, fasting plasma glucose ≥126mg/dl (7.0 mmol/l), a 2-hour plasma glucose level ≥ 200 mg/dl (11.1 mmol/l) during a 75-g oral glucose tolerance test or a random plasma glucose level ≥ 200 mg/dl (11.1 mmol/l) in a patient with classic symptoms of hyperglycaemia or hyperglycemic crisis.[13,14]

The risk of developing depends on risk factors; some of them are not preventable such as gender, age over 40 years, ethnicity or family history, but some other are such as eating, overweight, sedentary lifestyle, smoking or alcohol. There are other conditions contributing to its severity such as high blood pressure, hyperlipidaemia, disturbed sleep, some mental health conditions, the polycystic ovary syndrome or gestational diabetes.[15]

Its prevalence in developed countries has been increasing for the last decades.[15] In 2011-2012 between 12 and 14% of adults in the United States of America were diagnosed as T2D patients, in contrast to a 9.8% in 1988-1994.[16] If this trend continues, it should be expected to be one of the most prevalent diseases in developed countries.

Peripheral resistance to insulin features in its pathogenesis and leads to a maintained hyperglycaemia, what has implications such as: production of glycosylation end products, mitochondrial stress, activation of the aldose reductase and the glycolytic pathway, and higher levels of diacylgycerol, as a result of the activation of the metabolic pathways increasing polyol.[17] Sorbitol is increased and it implies a potential osmotic damage.[18] Other metabolic pathways are increased and have implications on the vascular system, such as the protein kinase pathway,[19] the

upregulation of vascular endothelial growth factor (VEGF),[19] generation of advanced glycation endproducts,[20] chronic oxidative damage[21] or increased activation of the renin angiotensin system.[22] As consequences, cell dysfunction and apoptosis occur in endothelial cells, pericytes and podocytes, which together with increased inflammation factors eventually lead to an increased vascular permeability, vascular occlusion, inflammation and angiogenesis.[23] Hence, multisystemic affection is due to this vascular dysfunction and it can be divided into macro and microangiopathy, depending on vessels' calibre. The former encompasses ischemic cardiopathy, cerebrovascular accident and peripheral artery disease. The latter include nephropathy and DR.

Diabetes may have other ophthalmological implications such as higher risk of primary open-angle glaucoma,[24] cataracts,[25] diabetic corneal neuropathy, dry eye syndrome, Meibomian gland dysfunction,[26,27] diabetic papillopathy[28] or palsies of the third, fourth or sixth cranial nerves.[29] Cataracts are more 2-5 times more frequent in diabetic patients than in non-diabetic and they appear as well at a younger age.[23] Generally, diabetes is a risk factor for all types of cataracts, but especially for posterior cortical and posterior subcapsular cataracts.[25] Diabetic corneal neuropathy comprises the loss of corneal nerves, what leads to a reduced neurotrophic support and results in accelerated loss and reduced proliferation of epithelial cells. Complications on anterior pole may have some consequences on corneal and cataracts surgery, and in the use of contact lenses. Diabetic papillopathy is a self-limited entity which is identified by unilateral or bilateral optic disk swelling associated with minimal or even no dysfunction.[23] Diabetes is a common cause of binocular diplopia, which is due to microvascular neuropathy in cranial nerves, and it usually recovers spontaneously in five months.[30]

## b) Diabetic retinopathy

One of the leading causes of blindness among the working population is DR. Approximately the 35% of an estimated 415 million people with DM worldwide will develop DR.[31] By the year 2040, its prevalence is expected to rise to an estimated 642 million.[32] It is a microangiopathy affecting small retinal vessels and there is a strong relationship between DR and chronic hyperglycemia.[33,34]

Based on the international clinical DR disease severity scale,[1] five steps have been defined.[2] The first one includes those patients with no DR. The second step comprises those with only retinal microaneurysms, and it is called 'mild NPDR'. The third is named 'moderate NPDR' and it consists of those patients with at least one of the following retinal lesions: intraretinal haemorrhages, cotton wool spots, hard exudates or venous beading. 'Severe NPDR' is the fourth step and it is defined by at least one of the following criteria: more than 20 intraretinal haemorrhages in the four quadrants, 2 or more venous beadings or one intraretinal microvascular abnormality (IRMA). The last step is the 'PDR' and it is featured by the presence of retinal neovascularization. Neovessels may appear next to the papilla (papillary neovessels), elsewhere in the retina, in the iris (rubeosis) or in the irido-corneal angle. Lesions such as vitreous haemorrhage or preretinal haemorrhage imply that the patient may be developing PDR without prior knowledge. If not treated, neovessels on the retina may eventually lead to a tractional retinal detachment, which has a poorer prognosis than most of rhegmatogenous retinal detachments and higher risk of vitreoretinal proliferation. Rubeosis usually precedes neovessels in irido-corneal angle and therefore they ought to aware us of the high risk of developing neovascular glaucoma. However, not always do they appear in this sequence. In some occasions, neovessels in irido-corneal angle are prior to those on the iris or on the retina, and that is why gonioscopy should be performed in patients with high risk of PDR. Panretinal photocoagulation with Argon laser is reserved as a treatment for PDR,[35] although recent research has revealed that treatment with anti-VEGF injections in non-inferior to panretinal photocoagulation at least through two years.[36]

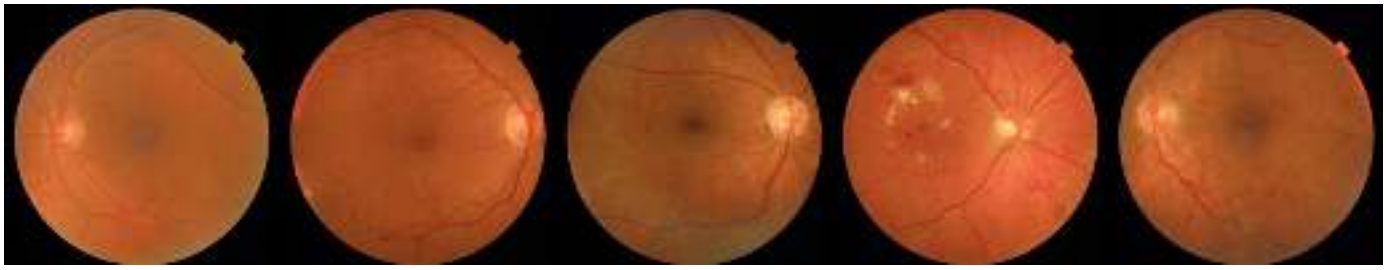

**Figure 1. The five steps of DR from left to right.**

Patients with DR should regularly undergo ophthalmological examinations in order to prevent complications due to PDR. The higher the severity of their lesions, the more often ophthalmological examinations should be performed. Additionally, high HbA1c levels are a risk factor for developing higher stages of DR,[37] that is why those patients should have their diabetes better controlled.

Apart from the DR severity scale, DME may be present, usually classified as 'subfoveal' or 'extra-foveal' DME. This is one of the main causes of visual loss in diabetic patients, which is reversible if correctly treated and in time. It is the result of microvascular changes secondary to maintained hyperglycaemia and other metabolic pathways such as polyol pathway, advanced glycation endproducts pathway, protein kinase C pathway and hexosamine pathway.[38] They lead to endothelial dysfunction and hyperpermeable retinal capillaries, with increased exudation of serum and high levels of inflammatory cytokines.[39] According to the American Diabetes Association,[1] patients may be classified into 'absent DME' or 'present DME'.[2] The latter is featured by some retinal thickening and/or hard exudates in posterior pole. These patients may be further classified into three stages: mild, moderate and severe DME. In the former those patients with some retinal thickening and/or hard exudates in posterior pole but distant from macula are included. The moderate DME is defined by retinal thickening and/or hard exudates approaching the centre of the macula but not involving it. The last stage is for those patients with retinal thickening and/or hard exudates involving the centre of the macula.[1] Different types of classifications have been proposed for DME, mainly based on OCT findings.[40] One of the main classifications has been that of Cunha-Vaz et al,[41] who established three phenotypes of patients with DR according to the risk of developing DME. It may not be a simple issue, but in general it has been accepted to classify it after the main underlying pathophysiological mechanism: vasogenic, inflammatory or a combination of both. Some findings on OCT scans have been related to one or another type. On the whole they may help clinicians to choose the most adequate treatment option. Other findings on OCT such as epiretinal traction have been associated with DME, which does not seem to have an influence on the pathophysiological underpinnings of the oedema. Epiretinal membranes are rather related to the systemic and ophthalmological inflammation that occurs in diabetic patients.

The presence of DME does not always require to be treated. It depends on factors such as VA impairment or oedema location. In case of centre-involving DME, there are two first-line treatment options for DME: intravitreal anti-VEGF agents and dexamethasone intravitreal implant. However, there are other second or third-line treatment options such as: laser photocoagulation, vitrectomy and intravitreal fluocinolone implant.[42]

## c) Optical coherence tomography

New technological devices have been being used in ophthalmology in general to get objective measurements, which can be compared with reference values. These have been very useful particularly in patients with DME, because of the possibility of evaluating response to treatment.[3] Hence, the OCT has been playing a key role.

The OCT is a non-invasive imaging technique which uses a low-coherent near-infrared light which is emitted by a superluminescent diode, and light waves are reflected by the internal microstructures within biological tissues due to their differing optical indices. The echo time delay of reflected light waves is determined by an interferometer, and the intensity of the reflected light waves is translated into an intensity map and encoded using a grey scale.[43] The interference patterns construct an axial A-scan, and multiple A-scans from adjacent points reconstruct a cross-sectional image of the target tissue, known as B-scan.[44] Time-domain OCT (TD-OCT) was the first version whose implementation was spread throughout ophthalmologists worldwide. Light echoes are detected sequentially by the step-movement of a reference mirror. It has an axial resolution of 8-10μm and performs 400 A-scans per second.[45] The following version was the SD-OCT, which uses a wavelength of 840nm and an interferometer with a high-speed spectrometer, what enables a higher image resolution (around 5-10μm) and a scan rate of 20 000-80 000 A-scans per second.[46] The last generation of OCT is the SS-OCT, which uses a longer wavelength (1050nm) and provides a resolution of 3-5μm and scan rate of 100 000 A-scans per second and a deeper penetration in the choroid.[3] One of the most important advantages of this last version is the capability of visualizing the whole choroid with high resolution, although it was already possible with the SD-OCT when the EDI technology was activated.

## d) Choroid

The choroid is the ocular layer between retina and sclera mainly made up of blood vessels, which proceed from the posterior ciliary arteries. Not only does it carry blood supply up to the outer plexiform layer of the retina, it also plays an important role in thermoregulation, control of intraocular pressure (IOP) and drainage of acqueous humor. It is mainly composed of blood vessels but there is some stroma including connective tissue, fibroblasts, smooth muscle cells, melanocytes, mastocytes, macrophages, lymphocytes, nerves and extracellular fluid.[47] It has been divided into different layers: Bruch's membrane, choriocapillaris, medium-vessel or Sattler's layer, large-vessel or Haller's layer and suprachoroid.

## e) Current situation and relationship between the four published articles

With the development of EDI technology and SS-OCT, choroid has been thoroughly analysed. It was not possible to make accurate measurements of its thickness using previous OCT such as SD-OCT without EDI or TD-OCT. For the last years, CT has been being measured and it has been found to vary with age,[48–50] AL,[7,8,51,52] day time[53–55] and race.[56] A choroidal thinning has been found in pathologies such as myopia[9] and DM,[4–6] and a relevant thickening has been found in the pachychoroid spectrum, which includes the polypoidal choroidal vasculopathy.[57]

Although multiple authors have proven that CT decreases in DM, but its pathophysiological role in DME is not clear indeed.[58] Some found a thickening,[59] some others found a thinning[10,60,61] and some others no change.[11,12,62] Furthermore, CT has not been associated with functional or anatomical outcomes.[63]

Whereas the relationship between CT and those ocular pathologies has been playing a major role for some years, its topography has not. Some authors analysed the whole choroid and not only a few slides, finding an irregular or asymmetrical pattern.[7–9] In summary, no concrete topographic pattern has been found either in healthy individuals or in T2D patients, since most of the studies perform horizontal lineal analyses of the choroid.

# 6) Hypothesis and Objectives

## a) Hypothesis

CT is reduced in T2D diabetic individuals with DR compared to healthy subjects. The choroidal thinning is related to T2D, regardless that age implies choroidal thinning itself.

## b) Objectives

1) To assess the intrasession repeatability of CT measurements with SS-OCT in healthy individuals and in T2D patients with DR.
2) To compare CT between healthy subjects and T2D patients with different stages of DR, with and without DME.
3) To determine and compare the topographic features of CT between T2D patients and age-matched healthy controls.
4) To evaluate the relationship between macular CT and HbA1c levels and duration of diabetes.
5) To compare CT in the macular region between young healthy, aged healthy and T2D individuals.

# 7) Methods

A cross-sectional study was performed at the Miguel Servet University Hospital in Zaragoza (Spain) between November 2015 and November 2017. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (Clinical Research Ethics Committee of Aragón, CEICA). Patients were informed about the study and signed the informed consent.

## a) Inclusion and exclusion criteria

Different study groups were included in this study. The first one included those T2D patients between 55 and 75 years old with or without DR. Patients were diagnosed according to the criteria of the American Diabetes Association and they were required to have no anti-glutamic acid decarboxylase antibodies. Their AL had to be ≤ 26 mm, < 6 D of myopia and < 2 D of cylinder. Tor the DME subgroup, a minimum central RT of 300 μm was required.

The second study group enrolled healthy individuals between 55 and 75 years old. Inclusion criteria were the same as those for the diabetic group but without T2D. Healthy individuals' medical records were examined in order to verify that none of them had either any systemic illnesses or were under systemic treatment. HbA1c and fasting glycaemic levels were measured as verification.

The third study group included young healthy volunteers between 18 and 35 years old. The other inclusion criteria were the same as those for the senior healthy group.

For all of them, exclusion criteria were: any ocular pathology, previous ophthalmological treatment or surgery, amblyopia, a race different from Caucasian, pregnancy and puerperium, endocrine disease, neurological disease, cancer history, systemic treatment with corticosteroids, immunosuppressive drugs, biologic therapies and previous treatment with potentially toxic drugs to the retina and/or optic nerve. In case of opacities of the optical media interfering with the OCT quality (signal/noise ratio <40/100), they were excluded, too.

| Criteria | | Study group | | | |
|---|---|---|---|---|---|
| | | T2D | DME | Aged healthy | Young healthy |
| Age | 55-75 years old | ✓ | ✓ | ✓ | ✗ |
| | 36-54 years old | ✗ | ✗ | ✗ | ✗ |
| | 18-35 years old | ✗ | ✗ | ✗ | ✓ |
| | 0-34 years old | ✗ | ✗ | ✗ | ✗ |
| Diseases | T2D | ✓ | ✓ | ✗ | ✗ |
| | Other endocrine | ✗ | ✗ | ✗ | ✗ |
| | Neurological | ✗ | ✗ | ✗ | ✗ |
| | Cancer history | ✗ | ✗ | ✗ | ✗ |
| Treatment | Corticosteroids | ✗ | ✗ | ✗ | ✗ |
| | Immunosuppressive | ✗ | ✗ | ✗ | ✗ |
| | Biologics | ✗ | ✗ | ✗ | ✗ |
| | Other previous with potential ophthalmological toxicity | ✗ | ✗ | ✗ | ✗ |
| Other conditions | Caucasian race | ✓ | ✓ | ✓ | ✓ |
| | Other race | ✗ | ✗ | ✗ | ✗ |
| | Pregnancy | ✗ | ✗ | ✗ | ✗ |
| | Puerperium | ✗ | ✗ | ✗ | ✗ |
| Ocular conditions | Amblyopia | ✗ | ✗ | ✗ | ✗ |
| | DR | 0 | ✓ | ✗ | ✗ |
| | DME | ✗ | ✓ | ✗ | ✗ |
| | Myopic fundus | ✗ | ✗ | ✗ | ✗ |
| | Other ocular pathology | ✗ | ✗ | ✗ | ✗ |
| | Previous treatment | ✗ | ✗ | ✗ | ✗ |
| | Pseudophakia | 0 | 0 | 0 | ✗ |
| | Other previous surgery | ✗ | ✗ | ✗ | ✗ |
| | <6 D of myopia | ✓ | ✓ | ✓ | ✓ |
| | ≥6 D of myopia | ✗ | ✗ | ✗ | ✗ |
| | <26 mm of AL | ✓ | ✓ | ✓ | ✓ |
| | ≥26 mm of AL | ✗ | ✗ | ✗ | ✗ |
| | <2 D of cylinder | ✓ | ✓ | ✓ | ✓ |
| | ≥2 D of cylinder | ✗ | ✗ | ✗ | ✗ |
| OCT | Signal/noise ratio < 40 | ✓ | ✓ | ✓ | ✓ |
| | Signal/noise ratio > 40 | ✗ | ✗ | ✗ | ✗ |
| | Central RT<300 µm | ✓ | ✗ | ✓ | ✓ |
| | Central RT≥300 µm | ✗ | ✓ | ✗ | ✗ |
| | Artifacts | ✗ | ✗ | ✗ | ✗ |

✓ = required criterion
✗ = exclusion criterion
0 = neither required, nor exclusion criterion

## b) Examination protocol

All patients underwent a deep ophthalmological examination which included clinical history, best corrected visual acuity (BCVA), refraction, slit-lamp examination, IOP with Goldmann applanation tonometry, optical biometry (IOLMaster 500, Carl Zeiss Meditec, Jena, Germany), indirect funduscopy and SS-OCT Triton Deep Range Image (Topcon Corporation, Tokyo, Japan).

The following data were recorded for T2D patients: duration of diabetes and mean HbA1c in the last year.

Topical tropicamide 1% and phenylephrine 2.5% were used for mydriasis.

### i. SS-OCT

The SS-OCT used in the study was the Deep Range Imaging (DRI) Triton (software version 1.1.4, Topcon Corporation, Tokyo, Japan). Its repeatability and reliability have been proved in healthy patients[64,65] and in choroid-thickness thinning pathologies.[66] It gives similar measurements to the Zeiss Cirrus HD-OCT[67] (Carl Zeiss) although results should not be interchangeable.[64] It has been stated that automatic measurements reduce variability,[68] though there is still little possibility of scan artifacts.[69]

**Figure 2. DRI Triton (from www.topcon-medical.eu)**

All OCT scans were acquired through dilated pupils at the same day time –between 4:00 and 7:00 pm– and by an experienced technician and under low mesopic lighting conditions. Two types of analyses were performed in all patients: a

horizontal 12-mm line and a macular 6x6 mm 3D cube, both centered on fovea and using eye-tracking. They were performed three times but only the best examination was selected for the analysis. Scans with low quality (<40/100), motion artifacts or decentration were discarded. The choroidal segmentation was automatically performed using the on-board device software called Topcon Advanced Boundary Segmentation (TABS). In case of segmentation errors, manual corrections of individual scans were performed to fit the choroidal boundaries (from the outer edge of the hyper-reflective retinal pigment epithelial line to the inner edge of the sclera). Patients underwent three consecutive SS-OCT scans in a single session. Between scans, patients sat back away from the device and rested at least for 2 minutes. Two weeks later, patients were re-examined using the same OCT protocols, and by the same operator and conditions.

In case of horizontal 12-mm lines, CT measurements were manually obtained at 11 positions using a caliper: five nasal (N1, N2, N3, N4 and N5) and five temporal measurements (T1, T2, T3, T4 and T5) to the fovea at 500-μm intervals along the subfoveal measurement. Before these measurements, a masking was performed so that the operator could not recognize patients.

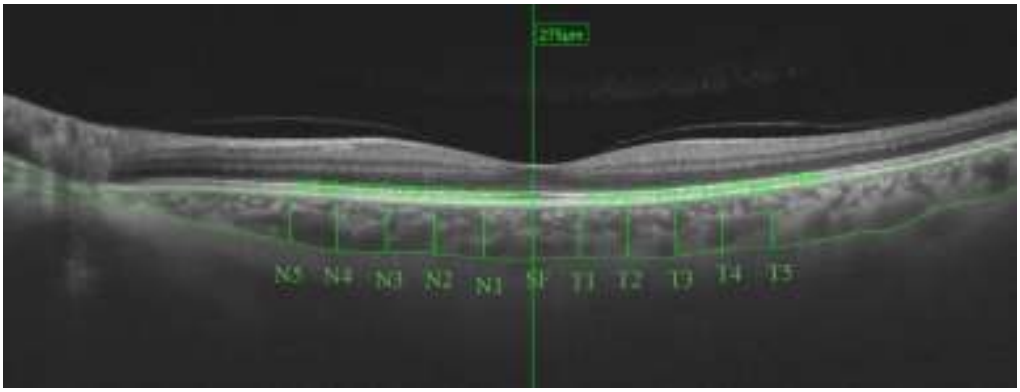


**Figure 3. Example of horizontal line scan with 11 manual measurements.**

In macular 6x6 mm cubes, CT was obtained in two different ways: in every of the nine ETDRS grids and in every of the 900 little cubes which form the full cube. This type of acquisition consists of a grid of 30x30 little cubes of 200x200 μm. For comparability, left-eye outcomes were converted into a right-eye format; in other words, nasal and temporal CT values were exchanged in left eyes, but not superior

and inferior values or right-eye values. All the analyses, considerations and figures from now on refer to the right-eye format.

## ii. New choroidal division

Besides the classic ETDRS grid, a new choroidal division was created. In the control group, the choroid was divided into different zones according to the mean CT of each cube, and five zones were established. This division was later applied to the other study groups; that is, no new zones were demarcated, but the choroidal division obtained from the healthy group was applied to the other study groups so that CT values in every zone comprised exactly the same choroidal cubes. Mean CT of equivalent zones were compared between groups.

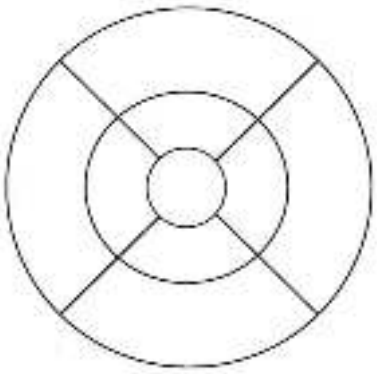

**Figure 4. ETDRS grid division.**

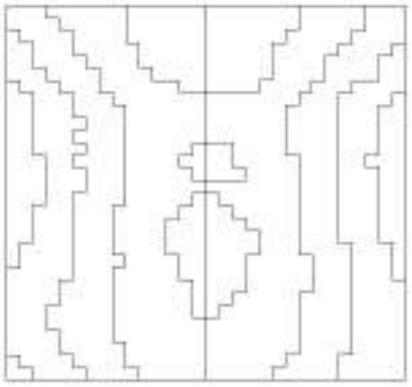

**Figure 5. New choroidal division.**

## iii. 2D and 3D choroidal maps

Using the mean CT of the 900 cubes obtained with the macular 6x6 mm macular cubes, 2D and 3D representations were plotted using Microsoft Word 14.0 (Word 2010, Microsoft Corporation, Redmond, WA, USA) for the former, and Microsoft Excel 14.0 (Excel 2010, Microsoft Corporation) for the latter. These images are intended to be a representation of real CT in such a way that choroidal topography is easily identifiable and differences between groups are easier to distinguish. Metric units on the vertical plane do not match the horizontal ones.

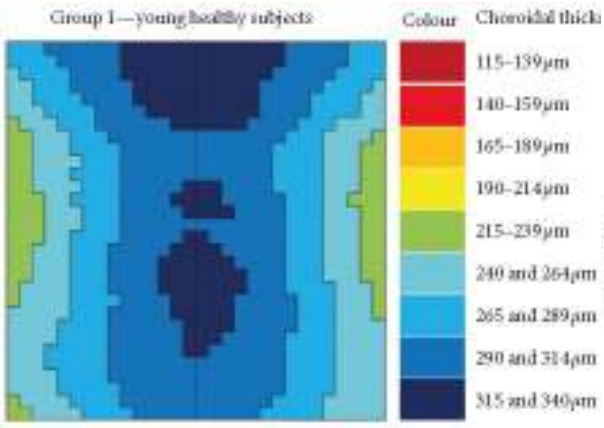


**Figure 6. 2D representation of CT in young healthy subjects.**

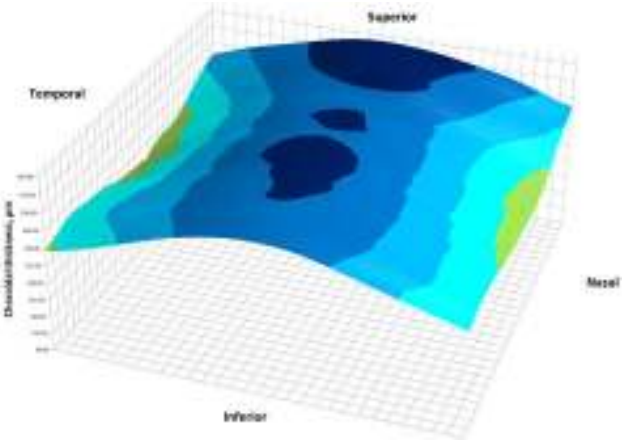


**Figure 7. 3D representation of CT in young healthy subjects.**

## c) Statistical analysis

Statistical analyses were performed using IBM SPSS (version 23.0; IBM Corporation, Somers, NY, USA) and MedCalc (version 12, MedCalc Software, Mariakerke, Belgium) statistical softwares. First, normality was verified by the Kolmogorov-Smirnov test. If normal, a two-tailed Student's or an ANOVA test was used, and Scheffe test for post-hoc analysis. If not, a Mann-Whitney U or a Kruskall-Wallis test was used. Differences between percentages and qualitative measurements were assessed by the $\chi^2$ test. Pearson correlations were calculated, because all the correlated variables followed a normal distribution. For all analyses, $p<0.05$ was considered as statistically significant.

For the repeatability analysis, the ICC, COV and test-retest variability were calculated for each CT measurement. The COV were calculated as the standard deviation (SD) divided by the average of the measured values expressed as a percentage. The test-retest variability in CT was calculated as twice the SD of the three repeated measurements for each CT variable.

# 8) Publications Making up the Thesis / Results & Discussion

# REPEATABILITY OF CHOROIDAL THICKNESS MEASUREMENTS ASSESSED WITH SWEPT-SOURCE OPTICAL COHERENCE TOMOGRAPHY IN HEALTHY AND DIABETIC INDIVIDUALS

BEATRIZ ABADÍA, MD, PhD,* PILAR CALVO, MD, PhD,*† FRANCISCO BARTOL-PUYAL, MD,* GUAYENTE VERDES, MD, PhD,‡ INÉS SUÑÉN, MD,† ANTONIO FERRERAS, MD, PhD*†

**Purpose:** To assess the intrasession repeatability of choroidal thickness measurements obtained using swept-source optical coherence tomography in Type 2 diabetic (T2D) patients and healthy controls.

**Methods:** This was a single-center, prospective, observational, cross-sectional study with consecutive inclusion of 33 healthy subjects and 43 T2D patients. Subjects underwent three consecutive swept-source optical coherence tomography scans in a single session. After automatic delineation of the choroid, subfoveal choroidal thickness, and thickness at 500-μm intervals up to 2,500 μm nasal and temporal from the fovea were measured using the software caliper by the same operator. Intraclass correlation coefficients (ICCs), coefficients of variation, and test-retest variability were calculated.

**Results:** Mean subfoveal choroidal thickness in healthy subjects and in T2D patients was 229.97 ± 79.9 and 192.67 ± 74.3 μm, respectively ($P = 0.013$). All intrasession intraclass correlation coefficients were higher than 0.95 and 0.99, respectively. Coefficients of variations were less than 4.4% and 1.8%, respectively. Test-retest variability ranged from 0.76 μm to 11.12 μm and 0.64 μm to 6.29 μm, respectively. No significant differences were found in the intrasession repeatability of any choroidal measurement between healthy subjects and T2D patients.

**Conclusion:** Swept-source optical coherence tomography provided excellent intrasession repeatability of choroidal thickness measurements in healthy subjects and T2D patients.

**RETINA** 0:1–8, 2017

Optical coherence tomography (OCT) has rapidly evolved since its development in the early 1990s, with ongoing improvements allowing for a better understanding of ocular structures such as the optic nerve, retina, and choroid.[1] Continuous improvement has been made to the scanning speed, sensitivity, and depth for generating high-resolution cross-sectional imaging of OCT, providing the opportunity to explore this vascular tissue in better detail. Enhanced depth imaging (EDI) spectral domain (SD) OCT system[2–4] and more recently the incorporation of technology for deep range image swept-source (SS) OCT has permitted a more precise study of the choroid.[5] Swept-source optical coherence tomography uses a longer-wavelength light source than SD-OCT, which allows deeper penetration in the choroid than EDI SD-OCT and provides better layer segmentation of the sclerochoroid interface, without affecting resolution in the retina.[6,7] Moreover, the automatic segmentation software of SS-OCT makes the measurements more accurate and reproducible.[8] Although Adhi et al[9] reported no differences in macular choroidal thickness measurements

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None of the authors has any financial/conflicting interests to disclose.

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between SS- and EDI SD-OCT, Tan et al[10] found that manual segmentation of SD-OCT may differ by more than 50 $\mu$m compared with the automated segmentation of SS-OCT.

The better visualization has led to more intensive investigations of this vascular structure that seems to have a significant role in different retinal pathologies.[11] Diabetic retinopathy (DR) is a neurovascular disease with a high prevalence and high socioeconomic impact. Recent studies revealed associations between an abnormal choroidal thickness and diabetes.[12–18] Evaluating choroidal changes may help clinicians to make better therapeutic decisions and to monitor the effect of treatments. For example, recent studies in patients with wet age-related macular degeneration and diabetes reported that choroidal thickness may predict the response to antiangiogenic agents.[19,20] Assessment of the accuracy of the measurements to compare them over time and differentiate true anatomic changes from the actual variability of the measurements is thus critical. Although other studies have evaluated the choroidal thickness SS-OCT's reproducibility in healthy eyes,[21–25] eyes of diabetic patients have not been evaluated. The purpose of this study was to evaluate the repeatability of choroidal thickness measurements using SS-OCT in healthy individuals and in patients with Type 2 diabetes (T2D).

## Material and Methods

The Clinical Research Ethics Committee of Aragón (CEICA) approved the study protocol, which adhered to the tenets of the Declaration of Helsinki. This study was performed in a retrospective observational cross-sectional manner. All individuals from December 2015 to July 2016 who met the inclusion criteria and provided written informed consent were consecutively recruited for the study. Healthy patients were selected from healthy volunteers and study-naive patients with T2D were recruited from the Retina Unit of Miguel Servet University Hospital at Zaragoza (Spain).

Subjects were eligible if they were adults with a refractive error of less than 6 spherical diopters and/or 2 diopters cylinder, axial length ≤26 mm, and euthyroid. Exclusion criteria included opacity of the optical media that could interfere with the quality of the OCT (signal/noise ratio <70/100), preexisting retinal, choroidal, or optic nerve pathology, previous ocular treatment with laser (focal or panretinal photocoagulation) or intravitreal agents, inflammatory diseases or active or recent infection (ocular and/or systemic), systemic treatment with corticosteroids, immunosuppressive drugs or biologic therapies, pregnancy, and puerperium.

A full ophthalmologic examination was performed in all patients including clinical history, best-corrected visual acuity (BCVA, decimal scale), examination of the anterior segment using a slit-lamp, Goldmann applanation tonometry, and ophthalmoscopy of the posterior segment. Optical biometry (IOLMaster 500, Carl Zeiss Meditec AG, Jena, Germany) was used to measure axial length. In addition, a fasting blood sample was obtained from an arm vein to determine plasma glucose levels.

### *Diabetic Retinopathy Grading*

Naive T2D patients were diagnosed based on the criteria of the American Diabetes Association,[26] and all were negative for anti-glutamic acid decarboxylase antibody. This group was divided according to the degree of DR into five subgroups based on the Diabetic Retinopathy Severity Scale criteria[27]: no DR, mild nonproliferative DR (NPDR), moderate NPDR, severe NPDR, and proliferative DR. Diabetic macular edema was assessed by clinical examination and SS-OCT imaging.

### *Choroidal Thickness Measurements Using Swept-Source Optical Coherence Tomography*

Each SS-OCT (Topcon 3D deep range imaging OCT Triton [plus]; Topcon Corporation, Tokyo, Japan) scan comprised a 12-mm horizontal line scan protocol centered between the optic disc and the fovea with 1,024 A-scans for each 96 B-scan. The images were obtained by an experienced technician after pupil dilation with tropicamide 1% and phenylephrine 2.5% and performed at the same time of day in all patients (between 4:00 PM and 7:00 PM). Scan acquisition was realized with low ambient light looking at the internal fixation point to obtain the best alignment. Subjects underwent three consecutive SS-OCT scans in a single session. Between scans, patients sat back away from the device and rested at least for 2 minutes. The on-board segmentation algorithm (Topcon Advanced Boundary Segmentation; TABS) was used to automatically segment the choroidal layer from the outer edge of the hyper-reflective retinal pigment epithelial line to the inner edge of the sclera. After automatic delineation of the choroid on the B-scan, 11 thickness measurements were manually obtained using a caliper: 5 measurements nasal (N1, N2, N3, N4, and N5) and temporal (T1, T2, T3, T4, and T5) to the fovea were obtained at 500-$\mu$m intervals along with the subfoveal (SF) measurement (Figures 1 and 2). Each location was measured by the same operator within 2 weeks. The operator was masked to the patients' identity and clinical history. Automated segmentation errors of choroidal layers were defined as

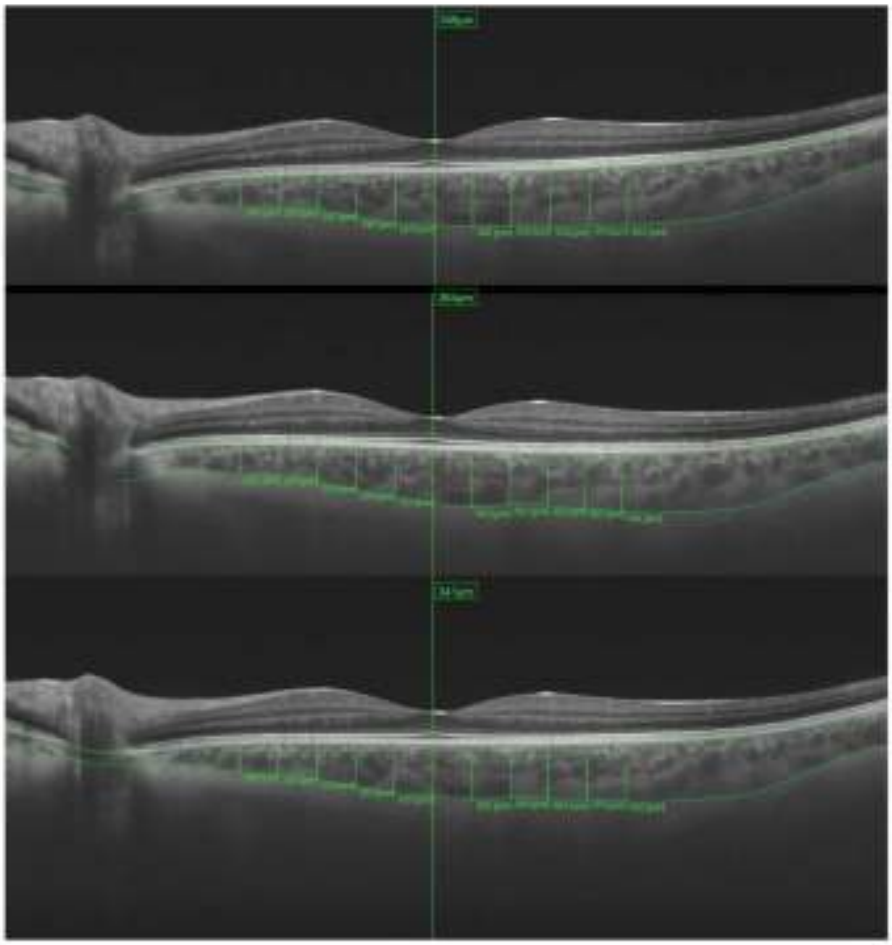

Fig. 1. Choroidal measurements obtained on the 3 different captured scans at SF level, and at 500-μm intervals up to 2,500 μm nasal and temporal from the fovea in a healthy individual.

instances in which the software determined choroidal boundaries that clearly deviated from the true anatomical boundaries. The automated segmentation errors were manually corrected by the same experienced observer. Scans with a lower quality (<70/100) were discarded.

*Statistical Analysis*

Statistical analyses were performed using IBM SPSS (version 23.0; IBM Corporation, Somers, NY) statistical software. All the variables followed a normal distribution as verified by the Kolmogorov–Smirnov test. For description of the clinical characteristics of the groups, the mean and standard deviation were used. The intraclass correlation coefficient (ICC), coefficient of variation (COV), and test-retest variability (TRTV) were calculated for each choroidal thickness.

Intraclass correlation coefficient is a statistic that condenses the reproducibility of a parameter for a given group of subjects. A large ICC suggests small fluctuations among repeated measurements in the same individual. The ICC value can range from 0 to a maximum of 1.

Coefficients of variation were calculated as the standard deviation divided by the average of the measured values expressed as a percentage. Test-retest variability in choroidal thickness was calculated as two times the standard deviation of the three repeated measurements for each choroidal thickness variable.

Differences between quantitative parameters were tested by Student's *t* test, and qualitative variables were compared by the chi-square test. The mean of the three scans was used for comparison of the choroidal measurements. For all analyses, $P < 0.05$ was considered statistically significant.

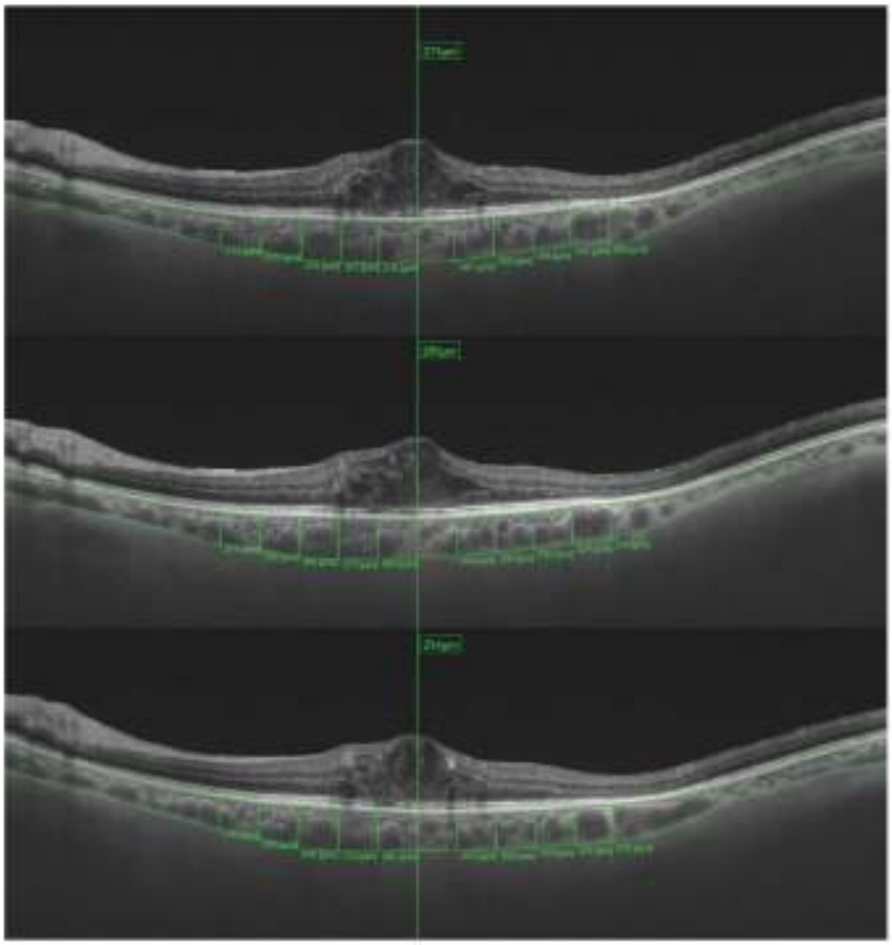

**Fig. 2.** Choroidal measurements obtained on the 3 different captured scans at SF level, and at 500-μm intervals up to 2,500 μm nasal and temporal from the fovea in a diabetic patient with diabetic macular edema.

## Results

Overall, 110 eyes of 76 Caucasian individuals were included in this prospective study. All participants completed the study. The healthy group comprised 50 eyes of 33 patients, and the T2D group included 60 eyes of 43 patients: 7 eyes without DR, 13 eyes with mild NPDR, 32 eyes with moderate NPDR, 5 eyes with severe NPDR, and 3 eyes with proliferative DR. Diabetic macular edema was diagnosed in 30 eyes (50%). Mean patient age in the healthy and T2D groups was 68.02 ± 8.8 and 66.28 ± 7.8 years, respectively (Table 1). Overall, no statistically significant differences were detected between healthy controls and the T2D group regarding age, intraocular pressure, quality of scan, accuracy of automatic layer segmentation, or laterality. The groups differed significantly regarding sex, BCVA, and choroidal thickness in SF, N1, T1, T2, T3, T4, and T5 measurements.

Table 2 shows ICC and 95% confidence interval (CI), COV, and TRTV in the whole sample. All ICCs were higher than 0.98 ($P < 0.001$) with a 95% CI close to 1 in all positions. Coefficient of variation was <2% for all choroidal measurements, and the maximum variability (TRTV) observed was 6.78 μm in the N5 position.

In the healthy group, ICCs were excellent (>0.95; $P < 0.001$) for all choroidal measurements (Table 3). The SF choroidal thickness had the highest ICC (1; 95% CI 1–1; $P < 0.001$) and the N5 choroidal thickness exhibited the lowest ICC (0.965; 95% CI 0.944–0.979; $P < 0.001$). All COVs were under 4.5%, with the highest value (4.38%) in the N5 choroidal measurement and the lowest (0.20%) in the SF choroidal measurement. Test-retest variability ranged from 0.76 μm to 11.12 μm. The lowest value corresponded to the SF measurement and the highest to the N5 position.

Table 1. Clinical Characteristics in Healthy Subjects and Type 2 Diabetic Patients

| | Healthy Subjects | T2D Patients | *P* |
|---|---|---|---|
| Age (years) | 58.02 ± 8.8 | 66.28 ± 7.8 | 0.28* |
| BCVA (Snellen) | 0.88 ± 0.2 | 0.69 ± 0.3 | **<0.001*** |
| IOP (mmHg) | 16.06 ± 2.4 | 16.85 ± 3.6 | 0.17* |
| Plasma glucose (mg/dL) | 94.64 ± 12.5 | 143.07 ± 45.8 | **<0.001*** |
| Quality scan | 94.34 ± 4.4 | 93.13 ± 5.2 | 0.20* |
| Choroidal thickness SF (μm) | 229.97 ± 79.9 | 192.67 ± 74.3 | **0.013*** |
| Choroidal thickness N1 (μm) | 228.83 ± 81.4 | 191.43 ± 75.3 | **0.014*** |
| Choroidal thickness N2 (μm) | 218.11 ± 79.6 | 189.04 ± 78.1 | 0.06* |
| Choroidal thickness N3 (μm) | 197.92 ± 81.1 | 171.04 ± 75.6 | 0.08* |
| Choroidal thickness N4 (μm) | 173.56 ± 81.7 | 149.74 ± 70.0 | 0.10* |
| Choroidal thickness N5 (μm) | 150.00 ± 75.4 | 129.42 ± 67.2 | 0.13* |
| Choroidal thickness T1 (μm) | 225.08 ± 73.0 | 189.51 ± 67.4 | **0.009*** |
| Choroidal thickness T2 (μm) | 222.95 ± 72.4 | 188.61 ± 68.7 | **0.012*** |
| Choroidal thickness T3 (μm) | 223.53 ± 71.5 | 187.78 ± 68.3 | **0.009*** |
| Choroidal thickness T4 (μm) | 218.19 ± 69.5 | 180.37 ± 63.0 | **0.003*** |
| Choroidal thickness T5 (μm) | 213.23 ± 69.3 | 173.94 ± 63.1 | **0.002*** |
| Female-male (%) | 39-11 (78%–22%) | 21-39 (35%–65%) | **<0.001†** |
| Right/left (%) | 26-24 (52%) | 31-29 (51.7%) | 0.97† |
| Accurate segmentation | 45-5 (90%) | 50-10 (80%) | 0.31† |
| n | 50 | 60 | |

Choroidal thicknesses and quality scan are expressed as the mean of the three scans. Inaccurate segmentation was considered when the three scans had automated segmentation errors. Significant differences are highlighted in bold print. Data are expressed in mean ± SD, except sex, laterality, accuracy of layer segmentation, and number of cases.

*Student's *t* test.

†Chi-square test.

BCVA, best-corrected visual acuity; IOP, intraocular pressure; n, number of cases; N1, nasal 500 μm from fovea; N2, nasal 1,000 μm from the fovea; N3, nasal 1,500 μm from the fovea; N4, nasal 2,000 μm from the fovea; N5, nasal 2,500 μm from the fovea; T1, temporal 500 μm from the fovea; T2, temporal 1,000 μm from the fovea; T3, temporal 1,500 μm from the fovea; T4, temporal 2,000 μm from the fovea; T5, temporal 2,500 μm from the fovea.

Intrasession repeatability of all choroidal thickness measurements in the T2D group is shown in Table 4. Intraclass correlation coefficients ranged from 0.981 (N2) to 1 (SF; $P < 0.001$). Coefficients of variation ranged from 0.17% (SF) to 1.79% (N2), and TRTV ranged from 0.64 μm (SF) to 6.29 μm (N2).

No significant difference ($P > 0.05$) was found in the intratest repeatability of any choroidal measurement between healthy controls and T2D patients.

## Discussion

In recent years, investigations have begun to focus on the role played by the choroid in DR.[15] This increase in interest is related to the development of improvements in OCT, because of technology such as EDI, and more recently to SS-OCT. These advances have brought faster scanning speeds and a reduction in artefacts that allow for better visualization of this

Table 2. Intrasession Repeatability of Choroidal Thicknesses in the Whole Sample

| | ICC | ICC, 95% Lower Bound | ICC, 95% Upper Bound | *P* | COV ± SD (%) | TRTV ± SD (μm) |
|---|---|---|---|---|---|---|
| SF | 1 | 1 | 1 | <0.001 | 0.18 ± 0.3 | 0.69 ± 1.2 |
| N1 | 0.995 | 0.993 | 0.996 | <0.001 | 0.96 ± 3.0 | 3.50 ± 11.2 |
| N2 | 0.984 | 0.978 | 0.988 | <0.001 | 1.79 ± 5.1 | 6.40 ± 19.6 |
| N3 | 0.995 | 0.993 | 0.996 | <0.001 | 1.39 ± 3.2 | 4.54 ± 10.6 |
| N4 | 0.995 | 0.993 | 0.996 | <0.001 | 1.45 ± 3.7 | 4.10 ± 10.5 |
| N5 | 0.982 | 0.975 | 0.987 | <0.001 | 2.75 ± 7.6 | 6.78 ± 18.3 |
| T1 | 0.999 | 0.999 | 0.999 | <0.001 | 0.76 ± 1.2 | 2.65 ± 3.7 |
| T2 | 0.985 | 0.979 | 0.989 | <0.001 | 1.21 ± 3.6 | 5.39 ± 17.1 |
| T3 | 0.994 | 0.992 | 0.996 | <0.001 | 1.12 ± 3.9 | 3.73 ± 10.3 |
| T4 | 0.987 | 0.983 | 0.991 | <0.001 | 1.51 ± 4.6 | 5.29 ± 14.6 |
| T5 | 0.985 | 0.980 | 0.996 | <0.001 | 1.43 ± 5.8 | 4.65 ± 16.1 |

N1, nasal 500 μm from the fovea; N2, nasal 1,000 μm from the fovea; N3, nasal 1,500 μm from the fovea; N4, nasal 2,000 μm from the fovea; N5, nasal 2,500 μm from the fovea; SD, standard deviation; T1, temporal 500 μm from the fovea; T2, temporal 1,000 μm from the fovea; T3, temporal 1,500 μm from the fovea; T4, temporal 2,000 μm from the fovea; T5, temporal 2,500 μm from the fovea.

Table 3. Intrasession Repeatability of Choroidal Thicknesses in Healthy Subjects

| | ICC | ICC, 95% Lower Bound | ICC, 95% Upper Bound | P | COV ± SD (%) | TRTV ± SD (μm) |
|---|---|---|---|---|---|---|
| SF | 1 | 1 | 1 | <0.001 | 0.20 ± 0.4 | 0.76 ± 1.3 |
| N1 | 0.999 | 0.999 | 1 | <0.001 | 0.72 ± 1.0 | 2.89 ± 2.9 |
| N2 | 0.986 | 0.977 | 0.991 | <0.001 | 1.80 ± 4.9 | 6.53 ± 18.2 |
| N3 | 0.990 | 0.985 | 0.994 | <0.001 | 2.01 ± 4.6 | 6.85 ± 15.2 |
| N4 | 0.991 | 0.985 | 0.994 | <0.001 | 2.16 ± 5.3 | 6.25 ± 15.2 |
| N5 | 0.965 | 0.944 | 0.979 | <0.001 | 4.38 ± 11.0 | 11.12 ± 26.4 |
| T1 | 0.998 | 0.957 | 0.999 | <0.001 | 0.97 ± 1.6 | 3.40 ± 4.7 |
| T2 | 0.968 | 0.950 | 0.981 | <0.001 | 1.88 ± 5.2 | 8.74 ± 24.8 |
| T3 | 0.988 | 0.981 | 0.993 | <0.001 | 1.47 ± 5.7 | 4.78 ± 14.9 |
| T4 | 0.974 | 0.959 | 0.984 | <0.001 | 2.29 ± 6.7 | 8.07 ± 21.1 |
| T5 | 0.970 | 0.952 | 0.982 | <0.001 | 2.30 ± 8.8 | 7.81 ± 23.5 |

N1, nasal 500 μm from the fovea; N2, nasal 1,000 μm from the fovea; N3, nasal 1,500 μm from the fovea; N4, nasal 2000 μm from the fovea; N5, nasal 2,500 μm from the fovea; SD, standard deviation; T1, temporal 500 μm from the fovea; T2, temporal 1,000 μm from the fovea; T3, temporal 1,500 μm from the fovea; T4, temporal 2,000 μm from the fovea; T5, temporal 2,500 μm from the fovea.

structure and therefore a better understanding of this vascular tissue.[11]

Knowledge of the behavior of the choroid in healthy subjects will elucidate the changes of the choroid in diabetic patients. Previous studies reported that the choroid undergoes significant changes throughout the day, with age and with axial length, in healthy individuals.[28–32] In diabetic patients, choroid thickness seems to decrease,[13–17] although other authors have reported the opposite finding (thicker choroid in diabetic patients).[12] Panphotocoagulation and antiangiogenic treatment may decrease choroidal thickness over the long-term[12,33–35] and choroidal thickness may predict the response to antiangiogenic treatment, where a greater thickness predicts a better anatomic and functional result after the injection.[20]

Overall, T2D patients presented with a thinner choroid than healthy subjects. In both groups, measurements revealed a similar pattern: the choroid was thickest in the SF location, followed by temporal and nasal measurements close to the SF area. The choroid was thinner in the temporal and nasal measurements far away from the SF area, and thinnest in the nasal choroid near the optic disc. Our results agree with previous reports by Regatieri et al, Querques et al, and Esmaeelpour et al that diabetic patients have a thinner choroid.[14–16]

Variability of measurements for any test may be critical for accurate diagnosis, follow-up, and assessment of the response to treatment. Repeatability of choroidal measurements can improve our understanding of the detection, progression, and response to treatment of DR, where the choroid may have an important role. To interpret these changes in choroidal thickness it is crucial to understand the test variability. We found that choroidal measurements acquired with SS-OCT had low variability (high ICCs and low COVs) for healthy and diabetic eyes.

To the best of our knowledge, this study is the first to report the intratest repeatability of 11 choroidal measurements with SS-OCT in a large population of healthy and diabetic patients. The results of

Table 4. Intrasession Repeatability of Choroidal Thicknesses in T2D Patients

| | ICC | ICC, 95% Lower Bound | ICC, 95% Upper Bound | P | COV ± SD (%) | TRTV ± SD (μm) |
|---|---|---|---|---|---|---|
| SF | 1 | 1 | 1 | <0.001 | 0.17 ± 0.3 | 0.64 ± 1.2 |
| N1 | 0.990 | 0.984 | 0.993 | <0.001 | 1.17 ± 3.0 | 4.02 ± 15.0 |
| N2 | 0.981 | 0.972 | 0.988 | <0.001 | 1.79 ± 5.4 | 6.29 ± 20.9 |
| N3 | 0.999 | 0.999 | 1 | <0.001 | 0.86 ± 1.0 | 2.62 ± 2.9 |
| N4 | 0.999 | 0.999 | 1 | <0.001 | 0.85 ± 1.0 | 2.30 ± 2.4 |
| N5 | 0.999 | 0.998 | 0.999 | <0.001 | 1.39 ± 1.5 | 3.17 ± 3.6 |
| T1 | 0.999 | 0.999 | 1 | <0.001 | 0.59 ± 0.7 | 2.03 ± 2.3 |
| T2 | 0.999 | 0.998 | 0.999 | <0.001 | 0.66 ± 0.8 | 2.60 ± 3.5 |
| T3 | 0.999 | 0.998 | 0.999 | <0.001 | 0.84 ± 1.1 | 2.85 ± 3.4 |
| T4 | 0.999 | 0.998 | 0.999 | <0.001 | 0.86 ± 1.0 | 2.98 ± 3.3 |
| T5 | 0.999 | 0.999 | 1 | <0.001 | 0.71 ± 0.9 | 2.01 ± 2.2 |

N1, nasal 500 μm from the fovea; N2, nasal 1,000 μm from the fovea; N3, nasal 1,500 μm from fovea; N4, nasal 2,000 μm from the fovea; N5, nasal 2,500 μm from the fovea; SD, standard deviation; T1, temporal 500 μm from the fovea; T2, temporal 1,000 μm from the fovea; T3, temporal 1,500 μm from the fovea; T4, temporal 2,000 μm from the fovea; T5, temporal 2,500 μm from the fovea.

intraobserver repeatability were excellent. We obtained ICCs values close to one in all choroidal locations in the whole sample and in both healthy and diabetic groups.

In the healthy group, choroidal thickness at N5 (2,500 $\mu$m from the fovea) exhibited the worst repeatability values. This may be due to the presence of the optic nerve in the nasal zone, which could make measuring more difficult, and also to the decrease in choroidal thickness peripherally. In T2D patients, choroidal thickness at N2 (1,000 $\mu$m from the fovea) showed the worst repeatability values. Although no significant differences were found in the intratest repeatability between healthy controls and T2D patients, diabetics tended to have better repeatability values than healthy controls. This could be due to the thinner choroidal thicknesses in diabetics, which would decrease the range of change of the same variable.

Previous studies evaluated the reproducibility of choroidal thickness measurements using SD-OCT, especially in healthy and young populations[21–25,36,37]; few of these studies, however, were based on SS-OCT technology.[38,39] Shao et al[25] studied the intraobserver reproducibility of 21 healthy eyes (mean age, 63.1 ± 10.6 years) with EDI SD-OCT. They scanned 10 times with 1-minute breaks between each examination. They found an ICC of 1 ($P < 0.001$) and a mean COV of 0.85 ± 1.48%. Mansuri et al[39] studied intraobserver reproducibility with SS-OCT in 54 eyes of 27 healthy subjects (mean age, 36.6 ± 10.4 years) with 4 different scanning protocols, one of which was the same as ours, a 12-mm horizontal line centered on the fovea in undilated patients. Each scan protocol was repeated three times consecutively on the same visit, similar to our study, and the ICC was 0.93 (95% CI: 0.91–0.95). Sim et al[37] studied reproducibility in a cohort of 51 eyes of 51 patients with T2D (mean age: 60.1 ± 13.6 years) using SD-OCT, a manual segmentation made by 2 different graders, and calculation of mean choroidal thicknesses within Early Treatment Diabetic Retinopathy Study (ETDRS) areas. They found an ICC of 0.97 (95% CI: 0.94–0.99). Our results confirmed the low variability of choroidal thickness measurements acquired with SD-OCT and SS-OCT.

A strength of our study is that this was a prospective study of 11 choroidal measurements with SS-OCT in a large sample, including healthy and T2D patients. Another strength was that we used automatic detection and segmentation software to delineate choroidal structures, which theoretically allows for a more accurate and objective analysis, although errors of segmentation had to be manually corrected in 10% to 20% of images. A limitation of this study was that we did not perform vertical or radial scans and, consequently, our results are based only on the horizontal axis measurements. Another limitation is that the T2D group was characterized by different stages of DR, which limits any conclusion on choroidal differences between the two groups. In addition, clinicians should take into account that only good-quality scans were included in the statistical analysis, which might have influenced the upper and lower limits, as real-world practice includes patients with cataracts, poor fixation, and larger refractive errors. Further studies using SS-OCT are needed to elucidate the differences in choroidal thickness between diabetic and healthy eyes.

In conclusion, intrasession repeatability of choroidal thickness measurements in healthy and T2D patients obtained with SS-OCT was excellent. Clinicians must take into account the repeatability of every parameter to differentiate normal variability from significant clinical changes.

**Key words:** choroid, choroidal thickness, diabetic retinopathy, repeatability, swept-source OCT.

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PLOS ONE

RESEARCH ARTICLE

# Choroidal thickness measured using swept-source optical coherence tomography is reduced in patients with type 2 diabetes

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## Abstract

### Objective

To compare choroidal thickness between patients with type 2 diabetes (T2D) and healthy controls measured using swept-source optical coherence tomography (SS-OCT).

### Methods

The sample comprised 157 eyes of 94 T2D patients, 48 eyes of which had diabetic macular edema (DME), and 71 normal eyes of 38 healthy patients. Subfoveal (SF) choroidal thickness, and choroidal thickness at 500-μm intervals up to 2500 μm nasal and temporal from the fovea were measured using the SS-OCT. Choroidal thicknesses were compared between groups using Student's t-test. Additionally, Pearson correlations were calculated between diabetes duration, glycosylated hemoglobin (HbA1c) levels, and choroidal thickness.

### Results

Mean diabetes duration was 16.6±9.5 years, while mean glycosylated hemoglobin was 7.7 ±1.3%. Overall, the choroid was significantly thinner in T2D patients. Individuals with DME had reduced choroidal thickness in all measurements, except at 2000 and 2500-μm nasal positions, compared to healthy controls. There was a moderate correlation between choroidal thickness and HbA1c levels in DME patients (SF: $r = 0.342$; $p = 0.017$). Diabetes duration did not correlate significantly with choroidal thickness.

### Conclusion

SS-OCT measurements revealed that the choroid was significantly thinner in T2D patients, moderate non-proliferative diabetic retinopathy patients, and DME patients than in healthy individuals. Further studies are needed to clarify the effect of diabetes on this layer and the relationship between choroidal thickness and DME.

## Introduction

Diabetes mellitus (DM) is chronic disease affecting 415 million people worldwide, and the prevalence is expected to rise to an estimated 642 million by the year 2040 [1]. The choroidal layer supplies blood to the outer layers of the retina and may play a key role in the pathophysiologic mechanism of diabetic retinopathy (DR). The most consequential changes of the choroid mainly affect the choriocapillaris layer, but may also extend to larger vessels located in the outer choroidal layers [2,3]. The choroid seems to play a role in different retinal pathologies [4]. A better understanding of the morphology and function of this vascular structure could facilitate the management of DR [5]. Recent studies regarding neovascular age-related macular degeneration and diabetes reported that choroidal thickness may predict the response to anti-angiogenic agents [5,6]. Consequently, the assessment of choroidal changes may help to better make therapeutic decisions and to improve treatment follow-up.

Before the introduction of swept-source optical coherence tomography (SS-OCT) in clinical practice, choroidal thickness was evaluated by enhanced-depth imaging spectral domain (SD)-OCT [7–10]. Nevertheless, SS-OCT allows for faster scanning speed and its longer wavelength enables deeper penetration in the choroid to reveal more details and a clearer sclerochoroidal interface [11–13]. Consequently, the higher contrast of the images acquired with SS-OCT may lead to a better layer segmentation and more accurate measurements.

The purpose of the present study was to prospectively analyze the choroidal thickness measured by SS-OCT in patients with type 2 diabetes (T2D) having different degrees of DR with or without diabetic macular edema (DME) and compare them to age-matched healthy controls.

## Materials and methods

### Patient eligibility

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Aragón (CEICA). Study-naïve patients with T2D were recruited from the Retina Unit of Miguel Servet University Hospital at Zaragoza (Spain) and control patients were selected from among healthy volunteers. All white individuals from December 2015 to July 2016 who met the inclusion criteria were consecutively pre-enrolled. Five patients with T2D did not provide informed consent, and were excluded from further analysis.

Participants were eligible if they were older than 18 years of age, with a refractive error of less than 6 spherical diopters and/or 2 diopters cylinder, axial length (AL) $\leq$26 mm, and euthyroid. Exclusion criteria included opacity of the optical media that could interfere with the quality of the OCT (signal/noise ratio <70/100), previous treatment with focal laser photocoagulation, panretinal photocoagulation, intravitreal anti-vascular endothelial growth factor or steroid injections, previous treatment with potentially toxic drugs to the retina and/or optic nerve, eye diseases that could affect retinal or choroidal anatomy, inflammatory diseases or active or recent infection (ocular and/or systemic), systemic treatment with corticosteroids, immunosuppressive drugs or biologic therapies, pregnancy, and puerperium.

Participants underwent full ophthalmologic examination: clinical history, including duration of diabetes in T2D patients; best-corrected visual acuity (BCVA, decimal scale), biomicroscopy of the anterior segment using a slit lamp, Goldmann applanation tonometry, and ophthalmoscopy of the posterior segment, and AL measured using optical biometry (IOL Master Zeiss; Jena, Germany). In all participants, glycosylated hemoglobin (HbA1c) was also measured.

### Diabetic retinopathy grading

Study-naïve patients with T2D were diagnosed based on the criteria of the American Diabetes Association and all were negative for anti-glutamic acid decarboxylase antibody. This group was divided into five subgroups depending on the degree of DR according to the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria [14]: no DR, mild non-proliferative DR (NPDR), moderate NPDR, severe NPDR, and proliferative DR (PDR). DME was assessed by clinical examination and SS-OCT imaging.

### Choroidal thickness measurements using SS-OCT

Each SS-OCT (3D deep range imaging [DRI] OCT Triton [plus], Topcon Corporation, Tokyo, Japan) scan comprised a horizontal line of 12 mm centered on the fovea and was obtained by an experienced technician. OCT scans were performed at the same time in all patients: between 4:00 pm and 7:00 pm. The choroidal layer was automatically segmented using the proprietary algorithm from the outer edge of the hyper-reflective retinal pigment epithelial line to the inner edge of the sclera. DRI SS-OCT Triton images were directly visualized by an independent observer to detect automated segmentation errors of the choroidal layer. After automatic delineation of the choroid, thickness measurements were obtained manually at 11 positions using a caliper: five measurements nasal (N1, N2, N3, N4, and N5) and temporal (T1, T2, T3, T4, and T5) to the fovea were taken at 500-μm intervals along with the subfoveal (SF) measurement (Fig 1). Automatic segmentation errors were recorded and corrected manually. Scans with a lower quality (<70/100) were discarded (S1 Database).

### Statistical analysis

Statistical analyses were performed using IBM SPSS (version 23.0; IBM Corporation, Somers, NY, USA) and MedCalc (version 12; MedCalc Software, Mariakerke, Belgium) statistical software. A sample size calculation estimated that 45 eyes would be necessary for a type 1 error rate of 0.05 and a power of 80% to detect a mean difference of 10%, assuming that mean choroidal thickness was 260.8±60.9 μm (analysis performed with MedCalc software version 12; Mariakerke, Belgium) [15]. All the variables followed a normal distribution as verified by the Kolmogorov-Smirnov test. Student's t-test or ANOVA (Scheffe test for post-hoc analysis) were used to compare choroidal thicknesses between groups. Differences between percentages were assessed by the chi-square test. Additionally, Pearson correlations were calculated between diabetes duration, HbA1c levels, and choroidal thickness. For all analyses, $p<0.05$ was considered statistically significant.

## Results

### Demographics and clinical characteristics

A total of 228 eyes of 132 patients were included in the study (50.9% women, 50.9% right eyes, mean age 67.6±8.1 years, range 49–86 years). Mean HbA1c was 5.6±0.3% in the healthy group and 7.7±1.3% in the T2D patients. Mean DM duration in T2D patients was 16.6±9.5 years. Mean OCT scan quality was 93.9/100±4.4, while an automatic and accurate segmentation was achieved in 82.9% of cases. The healthy group included 71 eyes and the T2D group comprised 157 eyes (48 eyes had DME). Based on the DR severity scale, the T2D group had 49 eyes without DR, 27 eyes with mild NPDR, 60 eyes with moderate NPDR, 14 eyes with severe NPDR, and 7 with PDR. The characteristics of each group are summarized in Table 1.

Overall, the groups did not differ significantly ($p>0.05$) in age, spherical equivalent, axial length or intraocular pressure. The difference in BCVA (decimal) was statistically significant

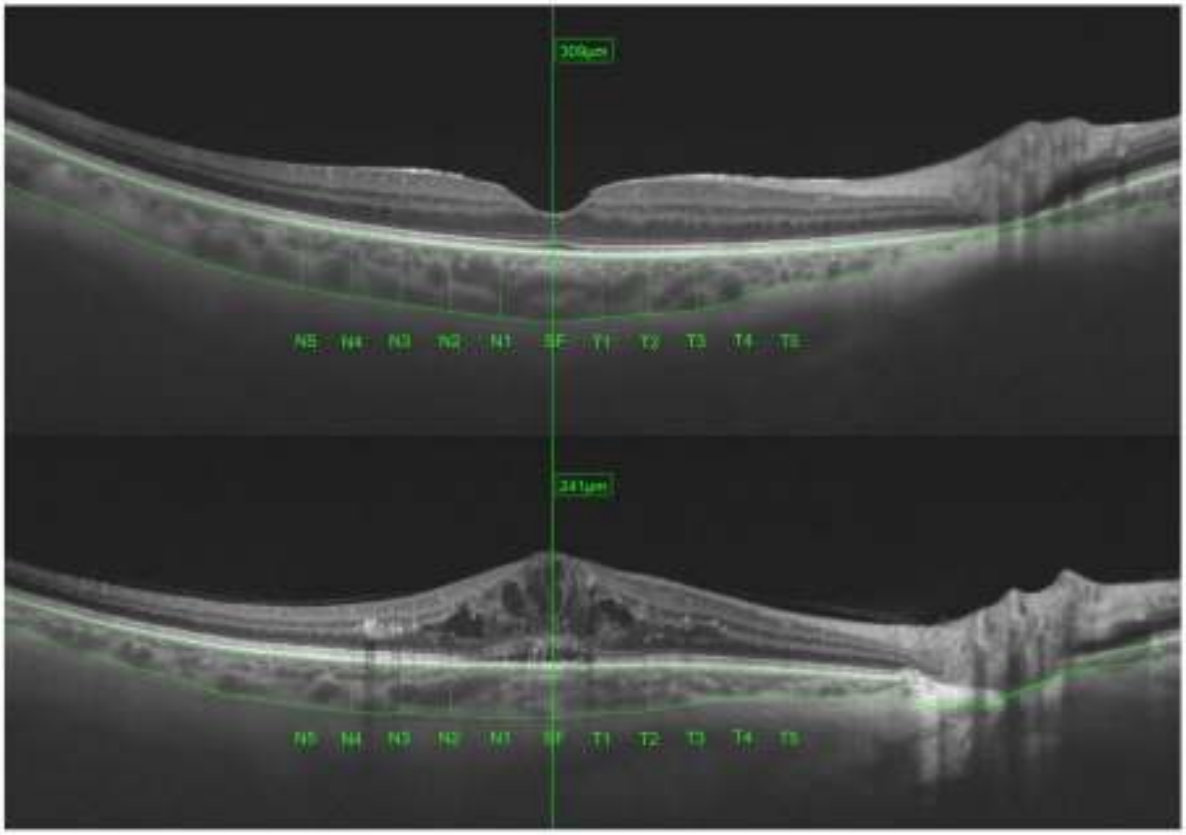


**Fig 1. Choroidal measurements at subfoveal, nasal (N1, N2, N3, N4, and N5), and temporal (T1, T2, T3, T4, and T5) locations.** Measurements were acquired at 500-μm intervals up to 2500 μm nasal and temporal to the fovea. SS-OCT images of representative cases from a healthy participant (top image) and a DME patient (bottom image).

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between the healthy group and the moderate, severe, and PDR groups (ANOVA, $p<0.001$); between the T2D without DR and the moderate, severe, and PDR groups (ANOVA, $p = 0.004$, $p = 0.001$, $p = 0.01$, respectively); and between the mild and severe NPDR groups (ANOVA, $p = 0.019$). Triglycerides were lower in the healthy group than in the T2D groups, except the PDR group, while high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol was higher in the healthy group compared with the T2D groups (ANOVA for HDL cholesterol: $p<0.001$ for all comparisons, except between the healthy and PDR groups [$p = 0.003$]; ANOVA for LDL cholesterol: $p<0.001$, except between the healthy and severe NPDR and PDR groups, $p = 0.004$ and $p = 0.007$, respectively). Systolic pressure was lower in the healthy and T2D without DR groups than in the moderate and sever NPDR groups ($p<0.009$), while diastolic pressure was similar between the groups.

The HbA1c levels and disease duration between the different T2D groups did not differ significantly. The scan quality was significantly lower ($p = 0.006$) in the PDR group compared with the healthy group and between the T2D without DR and PDR groups ($p = 0.012$). The accuracy of the automatic segmentation did not differ significantly between the healthy

**Table 1. Characteristics of the study sample.** Age, BCVA, IOP, Spherical equivalent, Axial length, DM duration, HbA1c, Triglycerides, HDL cholesterol, LDL cholesterol, Systolic pressure, Diastolic pressure, and Scan quality are expressed as mean ± standard deviation.

| | Healthy | No DR | Mild NPDR | Moderate NPDR | Severe NPDR | PDR |
|---|---|---|---|---|---|---|
| Age (y) | 68 ± 8.4 | 66.2 ± 8.9 | 68.5 ± 7.0 | 68.3 ± 7.5 | 68.9 ± 8 | 59.8 ± 5.1 |
| BCVA (decimal) | 0.8 ± 0.1 | 0.8 ± 0.1 | 0.7 ± 0.2 | 0.6 ± 0.2 | 0.5 ± 0.2 | 0.5 ± 0.1 |
| BCVA (logMAR) | 0.06 ± 0.1 | 0.08 ± 0.1 | 0.14 ± 0.2 | 0.18 ± 0.2 | 0.33 ± 0.3 | 0.27 ± 0.1 |
| IOP (mmHg) | 16 ± 2.3 | 17.2 ± 3.3 | 15.9 ± 3.2 | 16.9 ± 3.2 | 17 ± 2.3 | 16.8 ± 3.0 |
| Spherical equivalent (diopters) | -0.9 ± 2.2 | -0.3 ± 1.7 | -0.2 ± 1.7 | -0.2 ± 0.7 | -0.6 ± 2.2 | -0.4 ± 1.0 |
| Axial length (mm) | 23.9 ± 1.4 | 23.7 ± 0.7 | 23.3 ± 1.1 | 23.0 ± 0.7 | 23.2 ± 0.5 | 23.1 ± 0.6 |
| DM duration (y) | | 13.3 ± 9.8 | 15.4 ± 10.2 | 17.7 ± 9.1 | 13.5 ± 6.1 | 18.3 ± 16.1 |
| HbA1c (%) | 5.7 ± 0.3 | 7.4 ± 1.8 | 7.6 ± 1.6 | 7.7 ± 1.4 | 7.9 ± 0.7 | 8.1 ± 0.5 |
| Triglycerides (mg/dl) | 92.7 ± 40.9 | 144.3 ± 49.2 | 156.8 ± 73.8 | 153.1 ± 18.9 | 165.7 ± 75.2 | 122.6 ± 28.9 |
| HDL cholesterol (mg/dl) | 65.1 ± 16.0 | 48.1 ± 10.9 | 44.9 ± 10.5 | 43.4 ± 9.6 | 40.0 ± 5.5 | 42.6 ± 7.1 |
| LDL cholesterol (mg/dl) | 139.5 ± 24.2 | 103.6 ± 29.6 | 86.8 ± 31.1 | 87.8 ± 32.5 | 101.0 ± 25.4 | 122.6 ± 28.9 |
| Systolic pressure (mmHg) | 135.4 ± 14.4 | 136.1 ± 16.6 | 142.7 ± 15.6 | 153.1 ± 18.9 | 158.6 ± 25.2 | 153.7 ± 21.9 |
| Diastolic pressure (mmHg) | 77.4 ± 6.8 | 79.8 ± 9.6 | 77.8 ± 11.4 | 80.1 ± 11.8 | 78.7 ± 8.6 | 76.7 ± 6.4 |
| Scan quality | 95 ± 9.9 | 94.8 ± 4.1 | 91.8 ± 4.4 | 93.5 ± 4.6 | 94.7 ± 2.6 | 88.1 ± 5.9 |
| Segmentation accuracy (%) | 87.3 | 75.5 | 88.9 | 81.7 | 85.7 | 71.4 |
| DME (No. eyes) | | | 4 | 29 | 10 | 5 |
| Smoker / non-smoker (No. eyes) | 4 / 67 | 14 / 35 | 9 / 18 | 13 / 47 | 1 / 13 | 3 / 4 |
| No (eyes) | 71 | 49 | 27 | 60 | 14 | 7 |

DR: Diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; y: years; BCVA: best-corrected visual acuity; IOP: intraocular pressure; DM: diabetes mellitus; HbA1c: glycosylated haemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; DME: diabetic macular edema; No: number.

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controls and T2D patients or the healthy controls and the DME group (p = 0.47 and p = 0.36, respectively).

## Choroidal thickness measurements

In 10 of the 11 choroidal measurements (SF, T1, T2, T3, T4, T5, N1, N2, N3, and N4), significant differences ($p<0.05$) were detected between the healthy and T2D groups (Table 2).

**Table 2. Choroidal thickness measurements in healthy participants and diabetic patients.**

| | Healthy | | T2D group | | |
|---|---|---|---|---|---|
| | Mean (μm) | SD | Mean (μm) | SD | p |
| SF | 228.1 | 78.8 | 189.4 | 68.9 | <0.001* |
| N1 | 225.6 | 81.1 | 186.9 | 70.0 | <0.001* |
| N2 | 213.8 | 82.5 | 177.8 | 72.3 | 0.001* |
| N3 | 194.6 | 86.6 | 164.1 | 75.5 | 0.007* |
| N4 | 168.8 | 85.0 | 146.5 | 71.0 | 0.04* |
| N5 | 146.7 | 79.5 | 129.7 | 68.1 | 0.10 |
| T1 | 225.5 | 74.1 | 187.4 | 66.7 | <0.001* |
| T2 | 221.2 | 72.0 | 185.3 | 66.2 | <0.001* |
| T3 | 219.3 | 72.3 | 179.8 | 64.5 | <0.001* |
| T4 | 214.6 | 68.3 | 174 | 62.8 | <0.001* |
| T5 | 211.2 | 67.5 | 170.6 | 62.9 | <0.001* |

T2D: Type 2 diabetes; SD: standard deviation; SF: subfoveal; N: nasal position; T: temporal position.
*t test ($p<0.05$)

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Overall, T2D patients presented with a thinner choroid than healthy participants (mean SF thickness was 228.1±78.8 μm in healthy controls and 189.4±68.9 μm in T2D patients; $p<0.001$). In both groups, measurements revealed a similar pattern: the choroid was thickest in the SF location, followed by temporal and nasal measurements close to the SF area (T1, T2, N1, and N2). The choroid was thinner in the temporal and nasal measurements far away from the SF area (T3, T4, T5, and N3) and the thinnest measurements were in the nasal choroid near the optic disc (N4 and N5).

Table 3 shows the mean choroidal thickness (and standard deviation) of each of the 11 measurements obtained in control group and each group of T2D patients. No differences ($p>0.05$) were detected between the healthy group and the no DR, mild NPDR, severe NPDR, or PDR groups, respectively. In 8 of 11 choroidal measurements (SF, N1, N2, T1, T2, T3, T4, and T5), significant differences ($p<0.05$) were detected between the moderate NDPR and healthy groups. Mean SF thickness was 228.1±78.8 μm in healthy controls and 173.7±68.4 μm in moderate NPDR patients ($p = 0.003$).

Within the T2D group, we detected no differences ($p>0.05$) in the choroidal thickness between DME and non-DME patients. When comparing healthy and DME patients (Table 4), however, significant differences ($p<0.05$) were detected in 9 of 11 measurements (SF, N1, N2, N3, T1, T2, T3, T4, and T5). Mean SF thickness was 228.1±78.8 μm in healthy controls and 183.5±72.9 μm in DME patients ($p = 0.002$).

In the total sample, HbA1c correlated with SF ($r = -0.138$; $p = 0.039$) and N1 ($r = -0.146$; $p = 0.029$) choroidal thickness. DM duration had mild correlations with choroidal thickness at SF ($r = -0.173$; $p = 0.030$), N3 ($r = -0.160$; $p = 0.046$), N4 ($r = -0.168$; $p = 0.036$), N5 ($r = -0.164$; $p = 0.041$), T1 ($r = -0.165$; $p = 0.040$), T2 ($r = -0.166$; $p = 0.039$).

In the DME group, mean HbA1c was 7.6±1.1% and DM duration was 14.9±8.6 years. There was a moderate correlation between choroidal thickness in all measurements and HbA1c levels (SF: $r = 0.342$; $p = 0.017$). The strongest correlation was observed for choroidal thickness at N5 ($r = 0.436$; $p<0.001$). No significant correlation was detected between choroidal thickness and DM duration in DME patients.

**Table 3. Choroidal thickness measurements in healthy participants and each T2D group.**

| | Healthy | | No DR | | Mild NPDR | | Moderate NPDR | | Severe NPDR | | PDR | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean (μm) | SD | Mean (μm) | SD | Mean (μm) | SD | Mean (μm) | SD | Mean (μm) | SD | Mean (μm) | SD |
| SF | 228.1 | 78.8 | 191.1 | 72.7 | 210.2 | 73.1 | 173.7* | 68.4 | 210.7 | 47.2 | 188.8 | 42.4 |
| N1 | 225.6 | 81.1 | 186.9 | 73.6 | 210.2 | 78.4 | 173.8* | 68.6 | 202.3 | 50.6 | 179.8 | 29.4 |
| N2 | 213.8 | 82.5 | 174.5 | 74.9 | 199.6 | 81.7 | 168.3* | 72.3 | 191.6 | 53.2 | 170.3 | 30.9 |
| N3 | 194.6 | 86.6 | 160.7 | 71.3 | 189.6 | 93.1 | 153.2 | 69.8 | 175.9 | 56.8 | 160.8 | 44.4 |
| N4 | 168.8 | 85.0 | 145.5 | 65.1 | 167.2 | 93.9 | 136.3 | 68.8 | 155.3 | 56.1 | 143.3 | 50.7 |
| N5 | 146.7 | 79.3 | 130.9 | 61.5 | 144.7 | 89.8 | 123.5 | 68.9 | 128.7 | 50.1 | 118.0 | 39.4 |
| T1 | 225.3 | 74.1 | 188.1 | 66.4 | 205.4 | 63.1 | 174.0* | 69.0 | 210.5 | 37.4 | 182.0 | 43.9 |
| T2 | 221.2 | 72.0 | 181.4 | 66.9 | 200.2 | 57.4 | 175.3* | 72.6 | 213.1 | 52.6 | 185.4 | 48.6 |
| T3 | 219.3 | 72.3 | 175.3 | 64.7 | 198.3 | 58.8 | 170.2* | 68.9 | 203.7 | 47.5 | 174.1 | 65.3 |
| T4 | 214.6 | 68.3 | 170.9 | 64.7 | 184.1 | 61.6 | 167.5* | 66.6 | 198.1 | 43.9 | 164.1 | 50.0 |
| T5 | 211.2 | 67.5 | 169.5 | 67.2 | 176.1 | 61.1 | 164.1* | 65.5 | 189.4 | 44.5 | 176 | 52.3 |

T2D: Type 2 diabetic SD: standard deviation; SF: subfoveal; N: nasal position; T: temporal position.

*ANOVA, $p<0.05$ (statistical difference compared to healthy group).

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**Table 4. Choroidal thickness measurements in healthy participants and DME patients.**

| | Healthy | | DME patients | | |
|---|---|---|---|---|---|
| | Mean (μm) | SD | Mean (μm) | SD | p |
| SF | 228.1 | 78.8 | 183.5 | 72.9 | 0.002* |
| N1 | 225.6 | 81.1 | 179.4 | 72.5 | 0.002* |
| N2 | 213.8 | 82.5 | 174.6 | 74.4 | 0.009* |
| N3 | 194.6 | 86.6 | 160.2 | 72.5 | 0.025* |
| N4 | 168.8 | 85.0 | 141.5 | 67.6 | 0.065 |
| N5 | 146.7 | 79.3 | 122.0 | 64.1 | 0.075 |
| T1 | 225.5 | 74.1 | 184.5 | 68.9 | 0.003* |
| T2 | 221.2 | 72.0 | 188.1 | 69.4 | 0.014* |
| T3 | 219.3 | 72.3 | 181.1 | 68.3 | 0.005* |
| T4 | 214.6 | 68.5 | 173.7 | 62.7 | 0.001* |
| T5 | 211.2 | 67.5 | 167.1 | 60.2 | <0.001* |

DME: diabetic macular edema; SD: standard deviation; SF: subfoveal; N: nasal position; T: temporal position.
*t test ($p<0.05$)

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## Discussion

SS-OCT uses a longer-wavelength light source than spectral domain OCT, which allows deeper penetration in the choroid than enhanced-depth imaging (EDI) spectral domain OCT and provides more accurate segmentation of the sclero-choroid interface [12,16]. To the best of our knowledge, this is the first study using SS-OCT to measure choroidal thickness in the SF area and at five different nasal and temporal choroidal points in study-naïve T2D patients with different stages of DR presenting with or without DME compared with healthy participants.

Our findings revealed significant thinning in the SF, temporal, and nasal choroidal regions between healthy participants and T2D patients, between healthy participants and moderate NPDR patients, and between healthy participants and DME patients. Ruiz-Medrano et al. demonstrated that choroidal thickness decreases 10–15 μm with each decade of age [15]. In our study, the sample included elderly participants with a mean age of 67.6 years and the groups were well balanced with respect to age. Moreover, diurnal variations in choroidal thickness have been described (maximum peak at morning and progressive decrease throughout the day), with a mean difference of 33.7 μm [3,16–18]. To avoid fluctuations due to time of day, all SS-OCT scans were performed between 4:00 pm and 7:00 pm. Selection criteria included a spherical equivalent ≤6 D and/or cylinder ≤2 D, and an AL ≤26 mm because choroid thickness is associated with AL [19–21].

SF, temporal and nasal choroidal thicknesses were reduced in T2D patients compared to healthy controls. The differences were larger in the SF and temporal regions than in the nasal regions. Differences were observed in 10 of 11 choroidal measurements (5 temporal measurements, SF, and 4 nasal measurements). We detected no significant differences at 2500 μm nasal from the fovea (N5). This may be because the nasal choroid is thinnest near the optic disc, whereas the thickness increases nearer to the fovea [22,23]. Furthermore, we observed mild inverse correlations between HbA1c and central choroidal thicknesses (SF and N1) in the whole population. Though, in the DME group moderate correlations were found between choroidal thickness in all measurements and HbA1c levels. Thus, in DME patients, the increased retinal thickness was related to the increased choroidal thickness. It is likely that in T2D patients with DME, the inflammation contributes to increase both, the retinal and choroidal thicknesses.

Regatieri et al. studied choroidal thickness at the same 11 points using SD-OCT [23]. They included 11 NPDR, 18 DME, and 20 treated PDR patients, and found no significant difference between healthy (24 eyes) and NPDR patients. Although the choroid thickness tended to be lower in the NPDR group than in the healthy group in their study, the sample was too small to detect a significant difference. Their obtained values and the observed pattern in healthy controls are very similar to our results; i.e., the choroid was thicker in the SF region and in temporal and nasal areas near the fovea, and thinner further away from the fovea. The choroid thickness was thinnest nasally near the optic disc.

Querques et al. measured choroidal thickness using SD-OCT [24]. They observed that mean SF choroidal thickness and choroidal thickness at 1.5 mm and 3 mm temporal, nasal, superior, and inferior to the fovea were significantly reduced in NPDR patients without DME compared to the control group. In contrast to our findings, they also found significant differences in the choroidal thickness between T2D patients and the control group near the optic disc. Notably, the mean thickness values in their healthy group were surprisingly greater (for example SF thickness, 309.8±58.5 μm) than in our study (SF thickness, 228.1±78.8 μm) even though both samples were of similar age. Differences in the OCT device used, the retrospective nature of their study, or differences in the AL are likely responsible for these large differences.

Regarding choroidal thickness stratified by ETDRS grading, significant differences were detected in 8 of 11 choroidal measurements between the moderate NPDR and healthy groups (5 temporal measurements, SF, and 2 nasal measurements nearest to the fovea). The thickness pattern was similar in each sub-group and the values were thinner than in the healthy group, but no significant differences were detected among no DR, mild, and severe NPDR, and PDR groups, which may be due to the small number of eyes in these sub-groups compared to that in the moderate NPDR group, which included 60 eyes.

Kim et al. evaluated SF and choroidal thickness at 1500 μm superior, inferior, nasal, and temporal to the fovea [22]. In contrast to previous reports, they found that SF choroidal thickness in PDR was thicker than that in eyes with no DR, or with mild/moderate and severe NPDR. Compared with healthy controls, however, SF and temporal, nasal, superior, and inferior choroidal thickness were slightly decreased in T2D eyes with no DR or with earlier stage NPDR (mild/moderate), although the differences were not statistically significant.

Esmaeelpour et al. evaluated choroidal thickness in 63 T2D eyes [25]. Their choroidal maps showed that SF choroidal thickness was smaller in NDPR patients than in healthy controls. Consistent with our findings, they found a decrease in SF choroidal thickness between a no-DR group, T2D patients with a microaneurysm, and T2D patients with exudates compared to healthy controls. In our study, significant differences were found in 9 of 11 measurements of the choroid (5 temporal, SF, and 3 nasal measurements) in DME patients (48 eyes), showing a thinner choroidal thickness than healthy controls. In accordance with our findings, Regatieri et al. reported the same significant differences at the same locations in the choroid between DME and healthy patients [23]. Querques et al. also reported a reduced choroidal thickness at the SF and at 1.5-mm and 3-mm nasal, temporal, superior, and inferior in DME patients compared to healthy controls [24]. Esmaeelpour et al. [25] and Adhi et al. [26] also found that the SF choroid was thinner in DME patients compared with healthy eyes. Contrary to these results, Kim et al. found that SF choroidal thickness was related to increased severity of DR (from no DR to proliferative DR) and with the presence of DME, particularly in those eyes with serous retinal detachment [22]. Nevertheless, it remains unclear whether the greater choroidal thickness could be related to local inflammation or if this discrepancy is due to differences in study design and patient profiles.

In our study, we detected no significant differences in HbA1c levels in the T2D groups, but there was a moderate correlation between choroidal thickness and HbA1c levels in DME

patients (SF r = 0.342, p = 0.017). In contrast to our findings, Kim et al. found a significant difference in the HbA1c levels between DR groups [22]. They also found a significant correlation between HbA1c and SF choroidal thickness (r = 0.252, p<0.05).

The strengths of this study include the large sample size with study-naive T2D elderly patients, grading retinopathy, and the use of SS-OCT with several measurements at different points in the choroid. The main limitations are the relatively small sample size for the severe and proliferative T2D groups and the lack of totally automatic segmentation software. Manual corrections were made to avoid mis-segmentations, making the technique semi-automatic.

The relationship between DR and diabetic choroidopathy is not clearly defined in the literature [5]. The choroidal layer supplies oxygen and nutrients to the outer retina. Any change or damage with thinning to this tissue may affect the overlying retina, causing hypoxia and leading to the appearance of DR lesions or the progression of existing retinopathy. However, whether the thinning of the choroid is prior to the appearance of DR lesions or if the DR lesions are associated with the reduction of the choroidal thickness remains unknown. Therefore, expanding our knowledge of the pathophysiologic mechanisms involved in DR, including those affecting the choroid, may help clinicians to better understand the course of the disease and optimize the management of DR based on tailored interventions.

In conclusion, choroidal thickness was significantly reduced in T2D patients compared to age-matched controls. Further studies are needed to clarify the effect of diabetes on the choroid and the overlying retina.

## Supporting information

**S1 Database. Database for choroidal measurements.**
(XLSX)

## Author Contributions

**Conceptualization:** Pilar Calvo, Antonio Ferreras.

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**Validation:** Antonio Ferreras.

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**Writing – review & editing:** Pilar Calvo, Antonio Ferreras.

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# Mapping choroidal thickness in patients with type 2 diabetes

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## ABSTRACT •

**Design:** Cross-sectional study.

**Participants:** 96 T2D patients and 33 healthy individuals aged above 18 years and with an axial length (AL) lower than 26 mm were included.

**Objective:** To determine and compare topographic features of the choroidal thickness (CT) between patients with type 2 diabetes (T2D) and age-matched healthy controls based on swept source-optical coherence tomography (SS-OCT).

**Methods:** A macular 6 × 6 mm cube, comprising 900 200 × 200 μm cubes, was scanned with SS-OCT. The choroid was automatically segmented using the segmentation algorithm. Three-dimensional maps were created to represent the choroid. The scanned area was divided into different zones based on CT, and equivalent zones were compared between groups.

**Results:** Mean age (standard deviation) in the control group was 66.83 (7.3) years, and that of the T2D group was 67.94 (7.9) years ($p = 0.48$). Both groups were similar regarding AL and spherical equivalent. Overall, CT was significantly thinner in the T2D group; it was 203.78 (53.40) in healthy individuals and 169.98 (63.22) in T2D patients ($p = 0.01$). Outside the fovea, the mean CT was thicker in the superior hemiretina and decreased inferiorly, temporally, and nasally, with minimum thickness in the most distant points from the fovea.

**Conclusions:** Choroidal thickness follows an ellipsoid pattern in both nondiabetic and diabetic eyes, with diabetic eyes showing thinner measurements diffusely. Understanding these differences is important for future studies aimed at understanding the pathophysiological underpinnings of diabetic retinopathy.

Diabetic retinopathy (DR) is one of the leading causes of blindness among the working population. Of an estimated 415 million people with diabetes mellitus worldwide, approximately 35% develop DR.[1] By the year 2040, the prevalence is expected to rise to an estimated 642 million.[2] Although diabetic microangiopathy mainly affects the kidney and retina, other microvasculature, such as the choroidal vessels, may also be impaired.[3]

The choroid has several functions: its vasculature is the major supply for the outer retina, and impaired oxygen flow from the choroid to the retina may be a key pathophysiologic mechanism of DR. Changes to the choroid mainly affect the choriocapillaris, although larger vessels in Sattler's and Haller's layers may be involved too.[3] Thermoregulation, adjustment of the position of the retina, and secretion of growth factors are other functions of the choroid.[4]

Before the introduction of swept source-optical coherence tomography (SS-OCT), choroidal thickness (CT) used to be evaluated with enhanced-depth imaging (EDI) spectral domain (SD)-OCT.[5–8] SD-OCT, however, mostly includes manual measurements of the choroidal layer, but only in a few locations. Because the choroidal layer is one of the most highly vascularized tissues of the body, we believe that speculating on the relationship between changes in CT and DR based solely on a few choroidal measurements may not adequately reveal whole and real dimensions of this complex tissue.

The purpose of the present study was to measure a wide area of the choroid using SS-OCT technology and evaluate the automatic segmentation software analysis of a 6 × 6 mm cube-grid centred on the macula. This article was written according to the 9 items of the advised protocol for oct study terminology and elements recommendations,[9] which have been developed to outline core information that should be provided when reporting quantitative optical coherence tomography (OCT) studies. To the best of our knowledge, this is the first study aimed at developing a detailed map of macular CT based on objective measurements, and to compare the choroidal topography between healthy subjects and subjects with type 2 diabetes (T2D).

## Materials and Methods

### Sample Selection

The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (Clinical Research Ethics Committee of Aragón; CEICA). From December 2015 to July 2016, all individuals of white European ancestry who met the inclusion criteria and provided informed written consent were consecutively and prospectively enrolled. Treatment-naïve patients with T2D were prospectively recruited from the Retina Unit of Miguel Servet University Hospital in Zaragoza (Spain). The control group was selected from among healthy volunteers.

Inclusion criteria for both diabetic and healthy individuals were euthyroidism, age above 18 years, refractive error less than 6 spherical dioptres and 2 dioptres cylinder, and axial



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length (AL) equal or lower than 26 mm. Exclusion criteria included optical media opacities interfering with the quality of the OCT (minimal signal/noise ratio of 40/100), previous treatment with retinal laser photocoagulation, intravitreal antivascular endothelial growth factor or steroid injections and drugs potentially toxic to the retina and/or optic nerve, ophthalmological diseases with potential retinal or choroidal anatomic alterations, inflammatory diseases or active or recent infection (ocular or systemic), systemic treatment with corticosteroids, immunosuppressive drugs or biologic therapies, and pregnancy or puerperium. Healthy individuals' medical records were examined to verify that all of them had no systemic illnesses.

T2D patients were diagnosed based on the criteria of the American Diabetes Association. All of them had no antiglutamic acid decarboxylase antibodies.

### Study Protocol

Participants underwent a comprehensive ophthalmologic examination: clinical history, best-corrected visual acuity (best-corrected visual acuity in decimal scale), biomicroscopy of the anterior segment using a slit lamp, Goldmann applanation tonometry, ophthalmoscopy of the posterior segment, and AL measured using optical biometry (IOL Master 700; Carl Zeiss Meditec, Jena, Germany).

A macular 6 × 6 mm 3-dimensional (3D) scan with eye tracking was obtained using the Deep Range Imaging (DRI) OCT Triton (software version 1.1.4, Topcon Corp, Tokyo, Japan) through dilated pupils. The subjects were seated and properly positioned. An experienced technician performed all of the OCT scans at the same time of day for all patients: between 4:00 PM and 7:00 PM under scotopic lighting conditions. The choroidal layer was automatically segmented from the outer edge of the hyper-reflective retinal pigment epithelial line to the inner edge of the sclera, using the internal segmentation algorithm. A grid of 30 × 30 cubes centred on the fovea was generated to automatically measure the CT. This grid comprised 900 200 × 200 μm cubes. SS-OCT images were revised by an independent observer to detect automated segmentation errors of the choroidal layer. Scans with a lower quality (<40/100) and those with motion artefact, involuntary saccade, or overt misalignment of decentration were discarded. Only one eye per subject was randomly included. Left eyes were converted to a right eye format; in other words, nasal and temporal CT values were exchanged in left eyes, but not superior and inferior values or right-eye values. From this moment on, all the analyses, considerations, and figures will refer to the right-eye format.

In the control group, the choroid was divided into different zones according to the mean CT of each cube. Zone 1 included cubes with a CT less than 155 μm; zone 2, between 155 and 179 μm; zone 3, between 180 and 204 μm; zone 4, between 205 and 230 μm; and zone 5, >230 μm (Fig. 1). The mean CT of equivalent zones was then compared between groups (Fig. 2). This division into 5 zones was later applied to the T2D group; that is, no new zones were demarcated, but the choroidal division obtained from the healthy group was applied to the T2D so that CT values in every zone comprised exactly the same choroidal cubes.

Mean thickness of the 900 cubes was plotted into a 3D image to represent CT in healthy subjects and individuals with diabetes using Microsoft Excel 14.0 (Excel 2010, Microsoft Corp, Redmond, WA).

### Statistical Analysis

Statistical analyses were performed using IBM SPSS (version 23.0; IBM Corp, Somers, NY) statistical software. All the variables followed a normal distribution as verified by the Kolmogorov-Smirnov test. A 2-tailed Student's $t$ test was used to compare the CT between groups. Differences between percentages were assessed by the $\chi^2$ test. For all analyses, $p < 0.05$ was considered statistically significant.

## Results

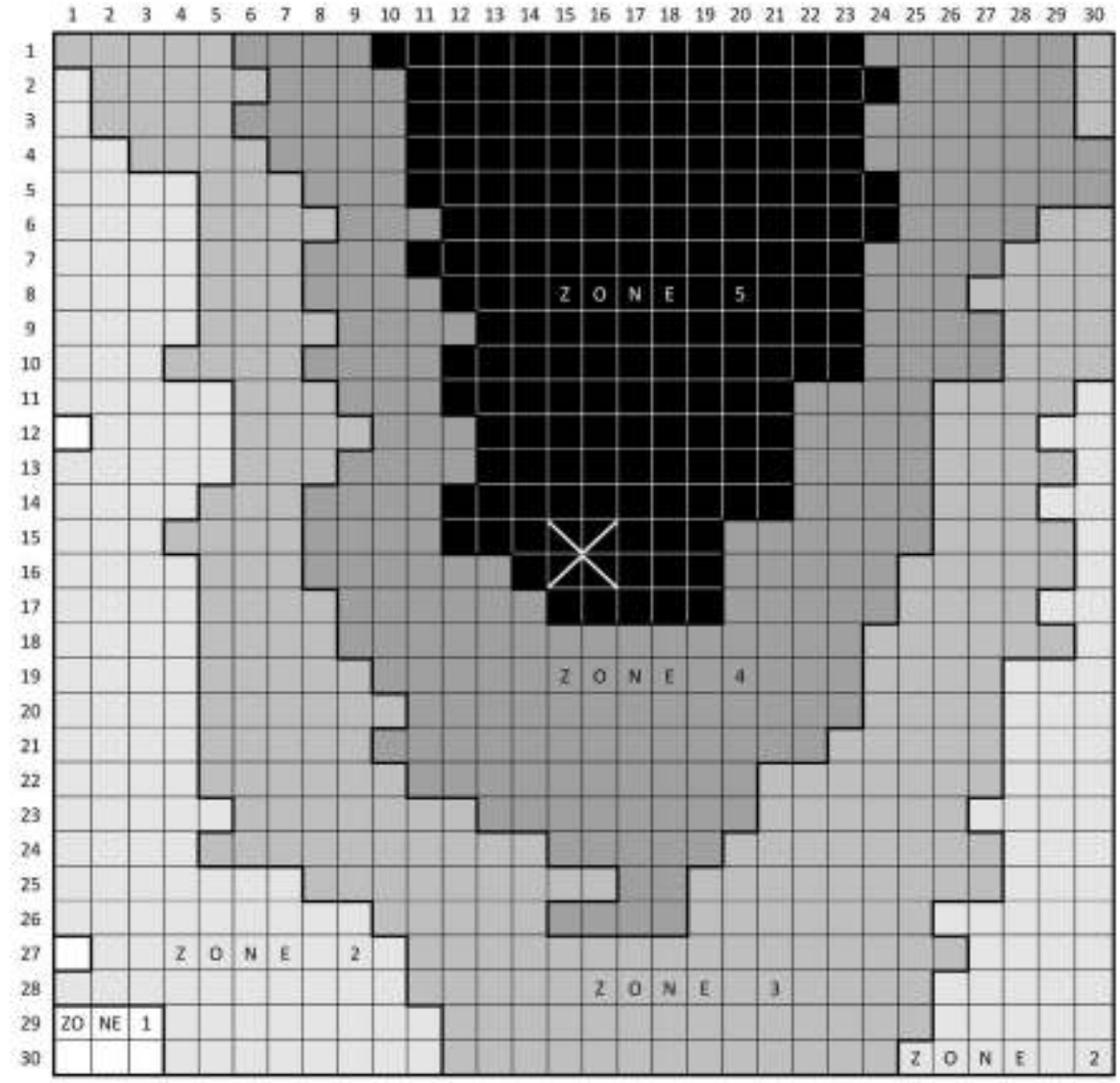
### Demographics and Clinical Characteristics

For this study 152 patients were screened, but only 129 eyes of 129 subjects were finally enrolled. Nine patients were discarded because of the presence of diabetic macular edema, 4 had glaucoma, and 10 had an OCT scanning quality too poor to be correctly segmented. The control group included 33 eyes (25 women) and the T2D group included 96 eyes (34 women). Based on the international clinical DR disease severity scale, the T2D group comprised 36 eyes without DR, 26 eyes with mild nonproliferative (NP) DR, 25 eyes with moderate NPDR, 5 eyes with severe NPDR, and 4 with proliferative DR. None of the T2D patients had diabetic macular edema. The clinical characteristics for each group are compared in Table 1. Age, intraocular pressure, AL, and spherical equivalent did not differ significantly between groups. Mean CT was 203.78 (53.40) in healthy individuals and 169.98 (63.22) in T2D patients ($p = 0.01$).

### Choroidal Measurements

In the control group, zone 1 comprised 8 cubes of the choroidal grid; zone 2, 194 cubes; zone 3, 279 cubes; zone 4, 233 cubes; and zone 5, 186 cubes (Fig. 1). Mean CT was compared between the control and T2D groups (Table 2). CT was thinner in the T2D group for all zones, except zone 1, compared with the control group. Due to the low number of patients with high degrees of DR, no analysis between DR degrees was conducted.

Regression analyses were performed between diabetes duration and the 5 choroidal zones, and between mean HbA1c the last year and the 5 choroidal zones. There were no correlations between them. The $p$ values for the former analysis were 0.23, 0.16, 0.14, 0.18, and 0.44 for zones 1, 2,




| | | |
|---|---|---|
| Zone 1 | | Mean choroidal thickness: <155 µm |
| Zone 2 | | Mean choroidal thickness: 155-179µm |
| Zone 3 | | Mean choroidal thickness: 180-204 µm |
| Zone 4 | | Mean choroidal thickness: 204-230 µm |
| Zone 5 | | Mean choroidal thickness: >230 µm |
| 'X' shows the fovea location. | | |

**Fig. 1—Map of the choroidal zones in the control group. The mean thickness of the 900 cubes was divided into different zones according to the mean choroidal thickness of the cube.**

3, 4, and 5, respectively, and 0.85, 0.99, 0.79, 0.64, and 0.46 for zones 1–5, respectively, for the latter regression analysis.

### Choroidal Maps

A color-coded map of the healthy control and T2D groups was created according to the CT. Red represents an area of CT <155 µm, orange 155–179 µm, yellow 180–204 µm, green 205–230 µm, and blue >230 µm (Fig. 2). Furthermore, a topographic 3D model was plotted for easier comparison of the control and T2D groups (Fig. 3). The T2D choroidal map showed large regions (28.3% of the 900 cubes) of decreased CT (<155 µm) compared with the control group (0.9%; $p = 0.002$). CT between 155 and 179 µm

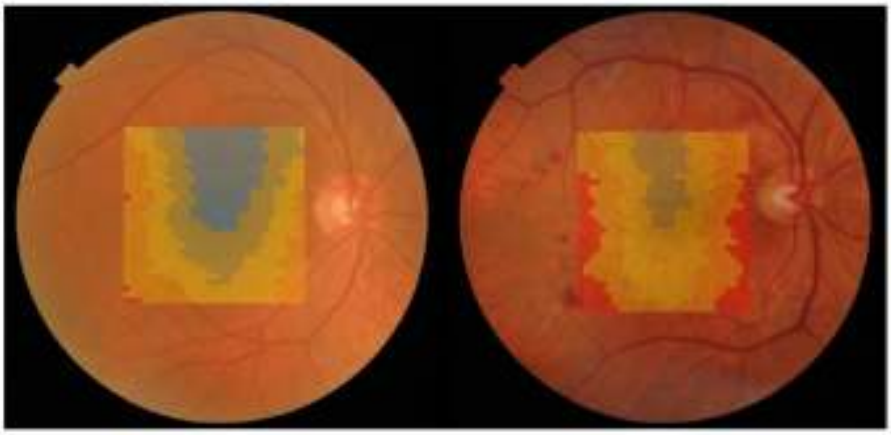


**Fig. 2—The map was first divided into 5 colour areas: red represents an area of choroidal thickness <155 μm, orange 155–180 μm, yellow 181–205 μm, green 206–230 μm, and blue >230 μm. Next, we compared the percentage of each area between groups. Left image: Photomontage of the choroidal thickness map of the control group. Right image: Photomontage of the choroidal thickness map on the T2D group.**

represented 21.6% and 37.4% of the 900 cubes in the control and T2D groups, respectively ($p = 0.14$); CT at the 180–204 μm interval represented 31.0% and 31.8% ($p = 0.89$), and that at the 205–230 μm interval represented 25.9% and 2.4% ($p < 0.001$), respectively. The T2D choroidal map showed no regions thicker than 230 μm compared with the control group (20.7%; $p < 0.001$).

The CT pattern was similar in the control and T2D groups. The thickest areas were located superocentral to the fovea, exhibiting an ellipsoid shape. Surrounding this area, progressive thinning was observed, with the same concentric ellipsoid shape. The thinnest values were detected at the most peripheral inferior, temporal, and nasal edges (Fig. 3).

**Table 1—Clinical characteristics of the studied sample**

| | Control Group | | T2D Group | | p* |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age (years) | 66.83 | 7.31 | 67.94 | 7.93 | 0.48 |
| BCVA (Snellen) | 0.87 (20/25) | 0.16 | 0.79 (20/30) | 0.22 | 0.02 |
| IOP (mm Hg) | 16.27 | 2.50 | 16.81 | 3.15 | 0.37 |
| AL (mm) | 23.92 | 1.69 | 23.33 | 0.93 | 0.27 |
| Spherical equivalent (D) | −0.60 | 2.71 | 0.96 | 1.92 | 0.08 |
| Duration of diabetes (years) | NA | | 15.98 | 14.39 | NA |
| HbA1c (%) | NA | | 7.66 | 1.27 | NA |
| N | 33 | | 96 | | |

*Student's *t* test.T2D, type 2 diabetes; SD, standard deviation; BCVA, best-corrected visual acuity; IOP, intraocular pressure; AL, axial length; D, dioptres; N, number of cases; NA, not applicable.

**Table 2—Comparison of the mean choroidal thickness of the 5 zones between both groups**

| | Healthy Group | | T2D Group | | p* |
|---|---|---|---|---|---|
| | Mean (μm) | SD | Mean (μm) | SD | |
| Zone 1 | 149.53 | 49.70 | 141.90 | 65.42 | 0.54 |
| Zone 2 | 162.60 | 51.68 | 138.81 | 60.26 | 0.04 |
| Zone 3 | 167.40 | 56.56 | 155.86 | 65.00 | 0.01 |
| Zone 4 | 211.54 | 58.29 | 172.87 | 66.21 | <0.001 |
| Zone 5 | 237.81 | 64.61 | 193.37 | 66.70 | <0.001 |

*Student's *t* test.T2D, type 2 diabetes; SD, standard deviation.

## Discussion

The purpose of this study was to determine and compare topographic features of the CT between T2D patients and age-matched controls. We found a CT pattern that was the same in both groups. Thicker areas were located superocentral to the fovea, and a progressive thinning surrounding this area was observed with an ellipsoid shape. T2D patients exhibited significantly more choroidal thinning compared with the control group.

The percentage of men and women differed between groups. Sex, however, should not have affected the validity of our results, as Ruiz-Medrano et al[10] reported no differences in CT related to sex. They also demonstrated that CT decreases 10–15 μm with each decade of age. In our study, both groups were similar in age.

In previous studies, manual choroidal segmentation was used to measure CT.[11–15] This method seems less accurate than automatic layer segmentation and could be too complicated and time-consuming to apply in clinical practice. Michalewski et al[11] evaluated CT in 122 healthy eyes using manual and automatic measurements with SS-OCT. Consistent with our results, in healthy controls the choroid was thicker in the subfoveal and superior areas, and thinner in the nasal area. They found also that the thickest outer superior CT was thicker than the inner superior. This is easily understandable with the choroidal maps we have created (Fig. 1). The CT values they obtained are similar to ours: higher than 220 μm in superior zones, and around 200 μm in the others.

Querques et al[15] retrospectively measured the subfoveal CT and at 1.5 and 3 mm temporal, nasal, superior, and inferior from the fovea using EDI SD-OCT. They included 21 eyes without DR, 21 NPDR patients without diabetic macular edema, and 21 patients with diabetic macular edema. In agreement with our findings, they found significant choroidal thinning in the diabetic patients. They also reported a thicker

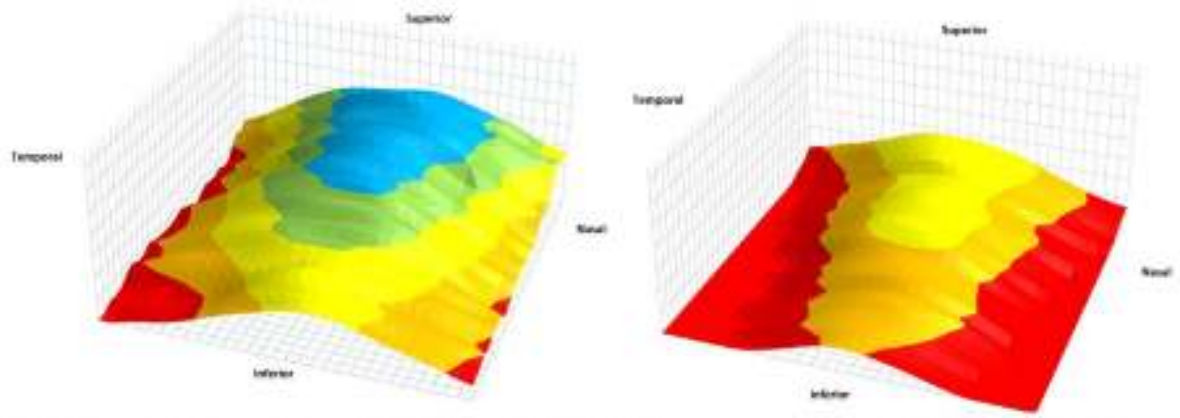



**Fig. 3—Topographic 3D map of the control (left side) and T2D (right side) groups generated according to the choroidal thickness.**

choroid superior to the fovea and progressive reduction at the inferior, temporal, and nasal locations.

Kim et al[14] conducted a retrospective study including 235 eyes to assess subfoveal and CT 1500 μm superior, inferior, nasal, and temporal to the fovea using EDI SD-OCT. Compared with healthy controls, subfoveal, temporal, nasal, superior, and inferior CT tended to be thinner in T2D eyes without DR or with mild or moderate NPDR. In the healthy group, the thickest choroidal measurements were found in the subfoveal and superior areas, followed by inferior, temporal, and nasal locations.

Esmaeelpour et al[15] mapped CT in 63 T2D eyes using high-speed 3D OCT imaging at 1060 nm. They found that the subfoveal CT was thinner in NPDR patients than in healthy controls. In their choroidal maps based on manual segmentation, the thickest values tended to locate superocentral to the fovea, surrounded by progressive choroidal thinning in both healthy and T2D eyes.

All those discussed studies aimed to describe the CT not only on a linear plane, but also over the whole macular surface. However, as already highlighted, manual measurements were only performed on some OCT slides. The first and only study providing CT maps is that of Esmaeelpour et al, who describe a method to create these maps, with valuable outcomes. As stated in the description: "for image processing and manual measurement of pixel distances in choroid and retina, ImageJ software was used."[15] In our study, we did not use any manual measurements or segmentation, as that was all automatic. Furthermore, the 900 CT values we obtained for every analysed eye and later used for creating 2D and 3D maps had been automatically given by the software of the OCT.

No clear relationship between DR and diabetic choroidopathy has been defined in the literature so far.[16] The choroid supplies oxygen and nutrients to the outer retina. Any change or damage leading to the thinning of this tissue may cause hypoxia and affect the overlying retina. Factors other than diabetes mellitus that play a role in the pathogenesis of DR, such as smoking, high blood pressure, and dyslipidaemia, may have contributed to the choroidal thinning observed in this study.

We found no correlation between these 5 choroidal zones and the duration of diabetes, nor with the mean level of HbA1c the last year. This is similar to other previous studies, in which no correlation has been found between the duration of diabetes and CT.[17–20] Endo et al state that despite not correlated, choroidal structure changes.[17] However, some others have found them correlated.[21] As for the relationship between CT and the degree of DR, different authors have found them correlated.[21,22] A possible explanation could be that the duration of diabetes is correlated to DR severity to a certain extent, and so it is possible to find CT and diabetes duration correlated.

The strengths of this study include the prospective design, study-naïve T2D patients, and SS-OCT automatic measurements performed in the afternoon in all patients. Some diurnal variations in CT have been described, having a maximum peak at morning and a progressive decrease throughout the day, with a mean difference of 33.7 μm.[4,23–25] To avoid them, all SS-OCT scans were performed in the afternoon between 4:00 PM and 7:00 PM. Previous studies suggested that CT is stable during this time period, having a lower thickness than that at noon and higher than that in the evening.[24,25] As CT is associated with AL,[11,12,26] we only included for this study patients with an AL ≤26 mm spherical and a spherical equivalent ≤6 D and/or cylinder ≤2 D.

The DRI OCT Triton is an SS-OCT whose repeatability and reproducibility in diabetic patients with and without macular edema have already been proved.[20,27] In case of diabetic macular edema, reproducibility seems to be lower, but this was an exclusion criterion in our study. Moreover, thickness maps seem easier to read and interpret than isolated manual measurements, particularly for comparisons between healthy and T2D eyes.

The main limitation of this study was that T2D patients were not analysed depending on the grade of DR. It could

be interesting to investigate if the choroidal topography is related to diabetes severity. We included only participants with transparent ocular media and limited refractive errors. Accordingly, our maps should be validated in populations with different clinical characteristics.

## Conclusions

Choroid shows an ellipsoid pattern in both nondiabetic and diabetic eyes, as displayed through choroidal maps, which may represent a useful tool for a rapid choroidal assessment. Topographically, the thickness of the choroid in diabetic patients decreases diffusely. Understanding these differences is important for future studies aimed at understanding the pathophysiological underpinnings of diabetic retinopathy.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2019.06.009.

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The authors have no proprietary or commercial interest in any materials discussed in this article.

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*Research Article*

# Distribution of Choroidal Thinning in High Myopia, Diabetes Mellitus, and Aging: A Swept-Source OCT Study

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*Purpose.* To compare the macular choroidal thinning between young healthy, aged healthy, young high myopic, and aged type 2 diabetic (T2D) patients using the Early Treatment Diabetic Retinopathy Study (ETDRS) grid and three-dimensional (3D) maps. *Methods.* A prospective study including 102 eyes of 51 healthy young subjects, 60 eyes of 30 healthy aged subjects, 24 eyes of 12 high myopic patients, and 110 eyes of 55 T2D patients. Choroidal thickness (CT) was examined with swept-source optical coherence tomography Triton DRI (Topcon Corporation, Tokyo, Japan). The choroid was automatically segmented using the software algorithm, and mean CT values of a 6 × 6 mm macular cube were exported. 3D maps were created to represent CT, and its values were compared using the ETDRS grid. *Results.* Mean age was 37.31 ± 3.95, 66.41 ± 7.54, 27.69 ± 3.89, and 66.48 ± 7.59 years in young healthy, aged healthy, young high myopic, and T2D patients, respectively. CT was not shown to be uniform, as superior and central zones were thicker. All ETDRS sectors were always thicker ($p < 0.05$) in young healthy individuals than in the others. It was found that the choroidal sector which got thinner was inferior in case of age (109.28 *μ*m decrease), inferior-nasal in high myopia (166.19 *μ*m decrease), and temporal in T2D (55.57 *μ*m decrease). In addition, the choroid got thinner in those regions where it was thicker in healthy subjects. *Conclusions.* 3D maps allow a further comprehension of choroidal changes. The choroidal pattern in young healthy individuals resembles a mountain range; with age, a mountain peak; in high myopia, an inverted gorge; and in aged T2D, gathered hills. Not all choroidal regions are affected in a similar way, as it depends on the pathology. The thicker the zone is in healthy subjects, the thinner it becomes with any pathology.

## 1. Introduction

With the advent of optical coherence tomography (OCT) technology, the choroid has been precisely visualized for the past few years. It has been proved to play an important role in different retinal disorders such as myopia, central serous chorioretinopathy, and age-related macular degeneration. Quantitative assessment of the choroid has allowed new research findings to differentiate normal from pathological processes within the choroid. It is known that choroidal thickness (CT) varies with age [1–3], axial length (AL) [4–7], day time [8–10], and race [11]. A choroidal thinning has been found in pathologies such as myopia [12] and diabetes mellitus [13–15], and a relevant thickening has been found in the pachychoroid spectrum, which includes the polypoidal choroidal vasculopathy [16].

Swept-source OCT (SS-OCT) is the last generation of OCT, and it uses a laser source of a longer wavelength (1050 nm) which penetrates deeper in the retinal and choroidal tissues than conventional laser sources used in previous spectral domain OCT devices [17].

SS-OCT provides retinal and choroidal macular thickness geographically displayed as a false color topographic map, and it is numerically reported as averages in each of the nine regions defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) [11]. The ETDRS grid includes a

central disc of 500 μm of diameter (foveal region) and an inner and an outer ring, each one was divided into four quadrants, with a diameter of 3000 μm and 6000 μm, respectively. This grid is used for quantitative evaluations of either retinal or choroidal thickness.

This study aimed to evaluate the distribution of choroidal thinning in high myopia, diabetes mellitus, and aging using the classic ETDRS grid from SS-OCT and a new different mapping.

## 2. Methods

*2.1. Sample Selection.* Over a 2 year duration (from November 2015 to November 2017), we performed a cross-sectional SS-OCT study on four different groups of patients: young healthy subjects (group 1), senior healthy subjects (group 2), young high-myopic patients (group 3), and patients with type 2 diabetes mellitus (T2D) (group 4). All patients underwent a complete ophthalmic evaluation at the Miguel Servet University Hospital in Zaragoza, Spain. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (Clinical Research Ethics Committee of Aragón (CEICA)).

Exclusion criteria were a race different from Caucasian, any ocular pathology or previous treatment, amblyopia, endocrine or neurological diseases, cancer history, corticosteroids, and immunosuppressive drugs.

Group 1 included young healthy volunteers between 18 and 35 years old and with an AL ≤ 25 mm. Group 2 included senior healthy volunteers between 55 and 75 years old and with an AL ≤ 25 mm. Group 3 included young healthy patients between 18 and 35 years old but with an AL ≥ 26 mm. Group 4 included T2D patients between 55 and 75 years old, with mild or moderate diabetic retinopathy (DR), without macular oedema and without any previous ophthalmological treatment. Healthy individuals' medical records were examined in order to verify that all of them had no systemic illnesses. T2D patients were diagnosed after the criteria of the American Diabetes Association, and all of them were negative for anti-glutamic acid decarboxylase antibodies.

*2.2. Study Protocol.* Patients underwent a deep ophthalmological examination which included best-corrected visual acuity (BCVA), refraction, slit-lamp examination, intraocular pressure (IOP) with Goldmann applanation tonometry, optical biometry (IOLMaster 500, Carl Zeiss Meditec, Jena, Germany), indirect funduscopy, and SS-OCT Triton Deep Range Image (Topcon Corporation, Tokyo, Japan).

SS-OCT scans were acquired through dilated pupils at the same day time and by an experienced technician. A macular 6 × 6 mm three dimensional (3D) cube centered on the fovea was analysed three times, but only the best examination was selected for the analysis. Scans with low quality (<40/100), motion artifacts, or decentration were discarded. The choroidal segmentation was automatically performed using the on-board device software. In case of segmentation errors, manual corrections of individual A-scans were performed to fit the choroidal boundaries (from the outer edge of the hyper reflective retinal pigment epithelial line to the inner edge of the sclera).

In every OCT image, the ETDRS grid was centered on the fovea, and measurements of the nine choroidal subfields were obtained and compared between groups.

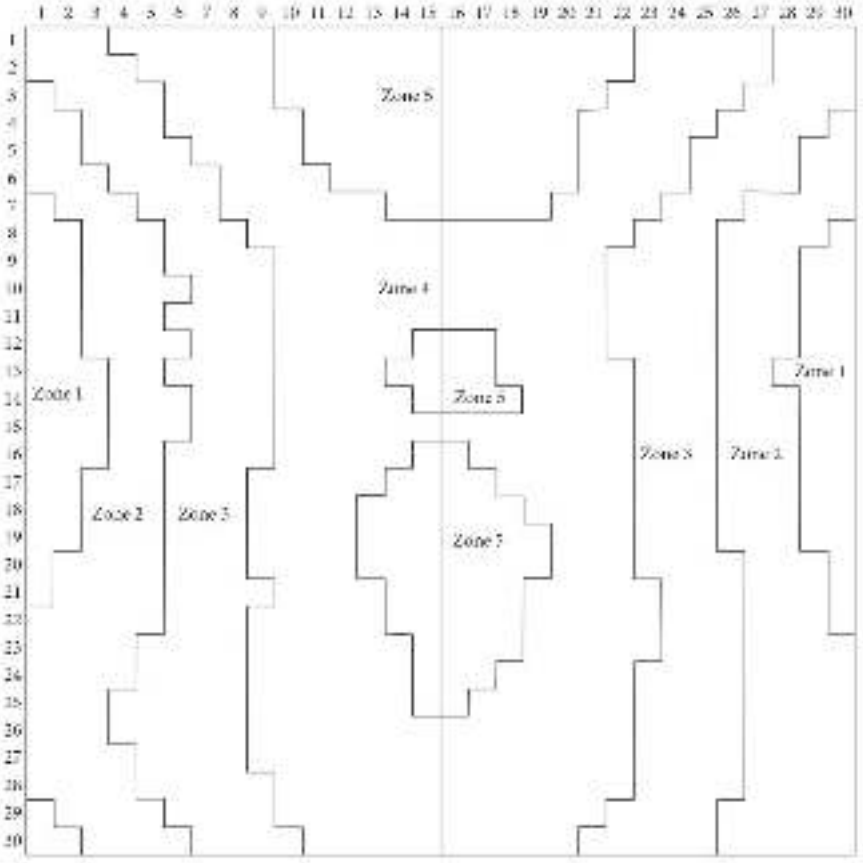
Besides the classic ETDRS grid, a fovea-centered map composed of 30 × 30 cubes was generated with automatic measurements of CT. This map comprised 900 200 × 200 μm cubes. Mean CT in every cube was exported and analysed. The left eyes were converted into the right eye format.

As a reference, young healthy subjects' choroid (group 1) was divided into different zones according to the mean CT in every macular cube (Figure 1). Zone 1 included those macular points with a CT between 215 and 239 μm, zone 2 between 240 and 264 μm, zone 3 between 265 and 290 μm, zone 4 between 290 and 314 μm, and zone 5 between 315 and 340 μm. The 5 zones were then divided into nasal and temporal, obtaining a total of 10 measurements. The mean CT of equivalent zones was calculated and compared between groups.

The two-dimensional (2D) maps of the four study groups were created with Microsoft Word (Microsoft Corporation), and Microsoft Excel (Microsoft Corporation) was used for the three dimensional (3D) maps.

*2.3. Statistical Analysis.* Statistical analyses were performed using IBM SPSS (version 23.0; IBM Corporation, Somers, NY, USA) statistical software. All variables followed a normal distribution as verified by the Kolmogorov-Smirnov test. A two tailed Student's $t$ test was used to compare CT between groups using both the classic ETDRS grid (9 regions) and the new choroidal distribution (10 regions). In case of comparisons involving group 3, a Mann Whitney $U$ test was performed due to the insufficient number of cases. For all analyses, $p < 0.05$ was considered as statistically significant.

*2.4. Demographics.* We enrolled 102 eyes of 51 healthy young subjects (group 1), 60 eyes of 30 healthy aged subjects (group 2), 24 eyes of 12 high-myopic patients (group 3), and 110 eyes of 55 aged patients with diabetes mellitus type 2 (group 4) with mild or moderate diabetic retinopathy and without macular oedema. Mean age outcomes in the four study groups are displayed in Table 1. There were no differences between mean ages of groups 1 (young healthy) and 3 (young myopic) ($p = 0.79$) and between groups 2 (aged healthy) and 4 (aged diabetic) ($p = 0.09$). There were no differences between the best-corrected visual acuity between groups 1 and 3 ($p = 0.97$), but there were between groups 2 and 4 ($p < 0.001$). There were no differences regarding intraocular pressure between groups 1 and 3 ($p = 0.83$), between 2 and 4 ($p = 0.14$), and between 1 and 2 ($p = 0.08$). There were differences in AL between groups 1 and 3 ($p < 0.001$), but




| | |
|---|---|
| Zone 1 | Choroidal thickness: 215–239 μm |
| Zone 2 | Choroidal thickness: 240–264 μm |
| Zone 3 | Choroidal thickness: 265–289 μm |
| Zone 4 | Choroidal thickness: 290–314 μm |
| Zone 5 | Choroidal thickness: 315–340 μm |

Figure 1: Choroidal zones in group 1 (young healthy individuals).

Table 1: Demographic and general ophthalmological factors.

| | Group 1 (young healthy) | Group 2 (senior healthy) | Group 3 (young high myopic) | Group 4 (senior T2 DM) |
|---|---|---|---|---|
| Age (years) | 27.31 ± 3.95 | 66.11 ± 7.51 | 27.69 ± 5.89 | 66.58 ± 7.59 |
| BCVA (decimal scale) | 0.99 ± 0.07 | 0.88 ± 0.13 | 0.99 ± 0.03 | 0.75 ± 0.25 |
| IOP (mmHg) | 16.07 ± 2.38 | 16.09 ± 2.56 | 16.81 ± 3.01 | 16.76 ± 2.96 |
| AL (mm) | 23.68 ± 0.73 | 23.87 ± 1.39 | 25.83 ± 0.79 | 25.21 ± 0.92 |
| Number of eyes (patients) | 102 (51) | 60 (30) | 24 (12) | 110 (55) |

BCVA = best-corrected visual acuity; IOP = intraocular pressure; AL = axial length.

there were not between groups 1 and 2 ($p = 0.33$) and between groups 2 and 4 ($p = 0.17$).

## 3. Results

3.1. *Choroidal Measurements.* Average CT values are displayed in Table 2. When evaluating choroid with the ETDRS grid, the thickest choroid was found in the inner temporal (317.65 ± 72.30 μm), inner superior (240.35 ± 62.92 μm), outer superior (247.78 ± 61.79 μm), and inner superior (191.68 ± 76.31 μm) sectors in groups 1, 2, 3, and 4, respectively. When evaluating choroid with the new choroidal division, the thickest choroid was found in zone 5 nasal (320.93 ± 67.90 μm), zone 5 temporal (286.51 ± 60.98 μm), zone 5 temporal (250.50 ± 56.96 μm), and zone 5 temporal (189.76 ± 66.24 μm) in groups 1, 2, 3, and 4, respectively.

Table 2: Choroidal thickness using the ETDRS grid

| ETDRS sector | Young healthy (group 1) | | Aged healthy (group 2) | | Young myopic (group 3) | | Aged diabetic (group 4) | |
|---|---|---|---|---|---|---|---|---|
| | Mean (μm) | SD | Mean (um) | SD | Mean (μm) | SD | Mean (um) | SD |
| Center | 315.73 | 37.13 | 237.75 | 68.57 | 239.80 | 60.30 | 186.24 | 69.56 |
| Inner temporal | 317.65 | 72.30 | 231.30 | 62.62 | 246.10 | 60.85 | 175.73 | 67.17 |
| Inner superior | 309.11 | 68.58 | 240.35 | 62.92 | 240.79 | 60.04 | 191.68 | 76.31 |
| Inner nasal | 285.95 | 70.71 | 218.63 | 70.19 | 201.57 | 59.60 | 173.62 | 75.05 |
| Inner inferior | 317.22 | 73.91 | 238.31 | 65.44 | 231.05 | 62.15 | 174.61 | 68.20 |
| Outer temporal | 300.65 | 70.89 | 212.30 | 56.27 | 240.79 | 58.47 | 160.24 | 58.58 |
| Outer superior | 312.02 | 67.68 | 225.10 | 63.92 | 242.78 | 61.79 | 183.53 | 68.34 |
| Outer nasal | 224.93 | 68.67 | 168.28 | 70.70 | 150.75 | 51.19 | 137.06 | 71.78 |
| Outer inferior | 308.42 | 74.12 | 199.13 | 62.81 | 228.59 | 56.20 | 160.28 | 62.21 |
| *Sector of the new division* | | | | | | | | |
| Zone 1 nasal | 234.71 | 93.06 | 168.33 | 73.10 | 175.31 | 77.57 | 137.57 | 71.43 |
| Zone 1 temporal | 232.19 | 80.77 | 170.32 | 66.48 | 184.45 | 79.29 | 137.93 | 62.21 |
| Zone 2 nasal | 255.35 | 87.33 | 178.05 | 66.33 | 189.50 | 69.62 | 142.66 | 64.57 |
| Zone 2 temporal | 253.88 | 75.41 | 181.00 | 63.64 | 196.54 | 70.98 | 141.28 | 58.14 |
| Zone 3 nasal | 279.29 | 70.04 | 196.30 | 62.86 | 206.77 | 64.19 | 154.80 | 64.39 |
| Zone 3 temporal | 277.77 | 71.42 | 198.19 | 62.05 | 214.47 | 62.26 | 155.73 | 60.61 |
| Zone 4 nasal | 304.85 | 71.80 | 217.06 | 59.71 | 229.41 | 57.96 | 173.11 | 64.49 |
| Zone 4 temporal | 303.68 | 66.63 | 218.29 | 60.37 | 235.26 | 58.23 | 174.23 | 62.30 |
| Zone 5 nasal | 320.93 | 67.90 | 234.10 | 59.93 | 246.21 | 58.39 | 185.62 | 66.61 |
| Zone 5 temporal | 320.92 | 67.37 | 236.51 | 60.36 | 250.50 | 58.96 | 189.78 | 66.24 |

Table 3: Choroidal thickness comparison between groups.

| ETDRS region | Groups 1-2 | | Groups 1-3 | | Groups 2-4 | |
|---|---|---|---|---|---|---|
| | CT reduction (μm) | $p$ | CT reduction (μm) | $p$ | CT reduction (μm) | $p$ |
| Center | 77.98 | <0.001 | 76.73 | <0.001 | 51.52 | <0.001 |
| Inner temporal | 86.36 | <0.001 | 71.54 | <0.001 | 55.57 | <0.001 |
| Inner superior | 68.77 | <0.001 | 68.32 | <0.001 | 48.66 | <0.001 |
| Inner nasal | 67.30 | <0.001 | 84.38 | <0.001 | 44.81 | <0.001 |
| Inner inferior | 97.80 | <0.001 | 86.19 | <0.001 | 44.70 | <0.001 |
| Outer temporal | 87.83 | <0.001 | 52.93 | <0.001 | 52.36 | <0.001 |
| Outer superior | 76.58 | <0.001 | 64.25 | <0.001 | 49.91 | <0.001 |
| Outer nasal | 55.25 | <0.001 | 73.80 | <0.001 | 32.22 | <0.001 |
| Outer inferior | 103.28 | <0.001 | 73.83 | <0.001 | 38.85 | <0.001 |
| *Sector of the new division* | | | | | | |
| Zone 1 nasal | 63.38 | <0.001 | 58.40 | <0.001 | 31.76 | <0.001 |
| Zone 1 temporal | 61.88 | <0.001 | 47.76 | <0.001 | 32.38 | <0.001 |
| Zone 2 nasal | 77.27 | <0.001 | 65.83 | <0.001 | 35.39 | <0.001 |
| Zone 2 temporal | 72.89 | <0.001 | 57.34 | <0.001 | 39.72 | <0.001 |
| Zone 3 nasal | 82.99 | <0.001 | 72.52 | <0.001 | 41.69 | <0.001 |
| Zone 3 temporal | 79.57 | <0.001 | 63.29 | <0.001 | 42.47 | <0.001 |
| Zone 4 nasal | 87.83 | <0.001 | 75.44 | <0.001 | 44.89 | <0.001 |
| Zone 4 temporal | 85.39 | <0.001 | 68.42 | <0.001 | 44.05 | <0.001 |
| Zone 5 nasal | 86.83 | <0.001 | 74.71 | <0.001 | 48.48 | <0.001 |
| Zone 5 temporal | 84.46 | <0.001 | 70.42 | <0.001 | 46.76 | <0.001 |

Table 3 shows the CT comparison between groups using ETDRS and the new division. CT was always significantly thicker ($p < 0.01$) in group 1 (young healthy) than in groups 2 and 3. Group 2 (aged healthy) always showed to have a thicker choroid ($p < 0.02$) than group 4 (aged diabetic). $p$ values are shown in Table 3 too.

For a better understanding, Figure 2 shows a visual representation of the thinning using the ETDRS grid. In this figure, the darker, the more the choroid gets thinned.

*3.2. Choroidal Maps Using the New Choroidal Division.* Figure 3 shows a colored 2D representation of CT in the four study groups. Black lines were drawn following the results in group 1 (young healthy) to allow an easier comparison. Figure 4 shows a 3D representation of CT in the four study groups. It does not represent the real choroidal shape, as it is just a mathematical representation of its thickness on a flat surface. Nevertheless, the combination of these 2D and 3D maps allows better and easier understanding and visual comparison.

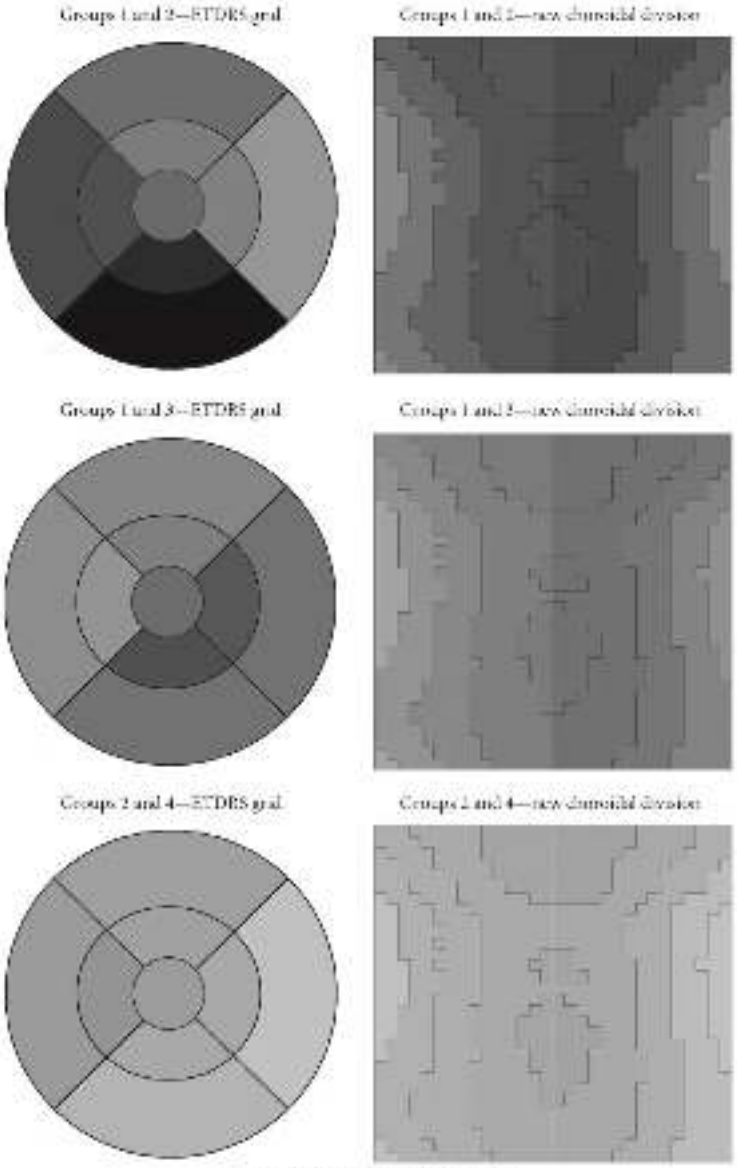



Figure 2: Mean choroidal thinning.

The thickest choroidal region was always superocentral to the fovea, showing a kind of ellipsoid shape. In young healthy individuals (group 1), it resembled a mountain range with its peaks and the valleys at both sides. In case of the other groups, the choroid tended to be flatter and the pattern was not always preserved. The aged healthy group (number 2) showed a higher reduction of CT in the inferior side, resulting in a choroidal pattern which resembled a single mountain peak. Something different happened with the young myopic patients (group 3), whose CT pattern stayed similar to the young healthy patients (group 1) but with a remarkable choroidal thinning on nasal and temporal sides. It resembled an inverted gorge. Finally, aged diabetic patients (group 4) showed to have the flattest choroid and its pattern was close to aged healthy patients' one (group 2), but instead of mountain peak, it was more similar to gathered hills.

## 4. Discussion

A thin choroid has been associated with ocular and systemic disorders, and sometimes can be useful in the differential diagnostic of some pathologies, such as between age-related macular degeneration and polypoidal choroidal vasculopathy

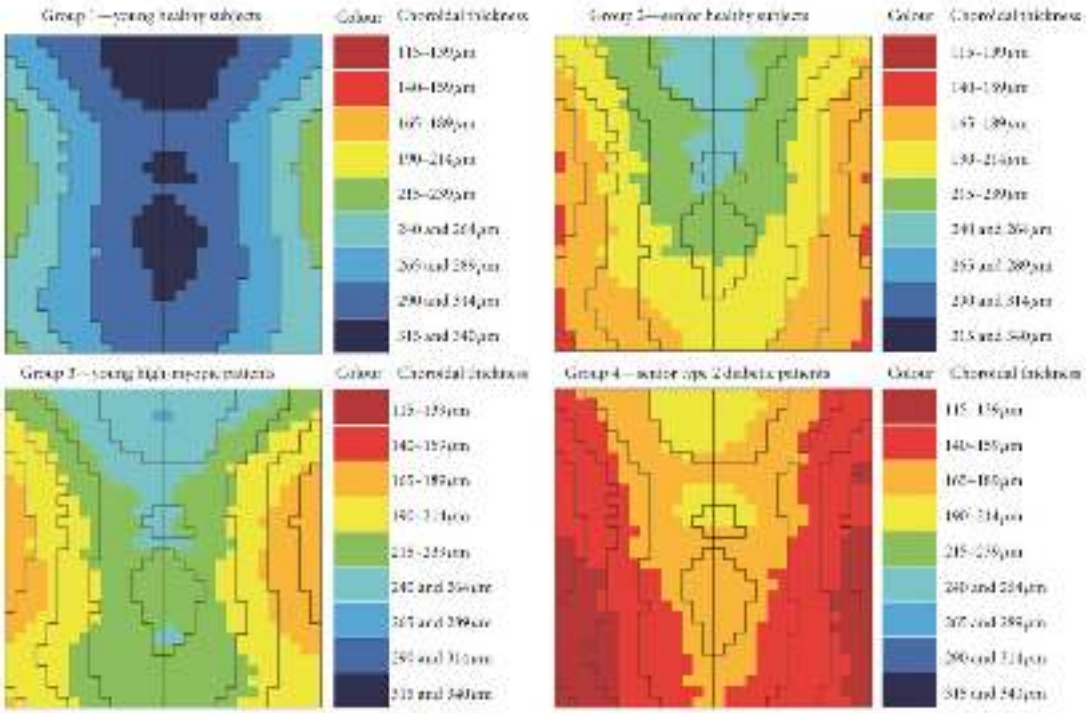



Figure 3: Two-dimensional representation of choroidal thickness.

[16]. One of the SS-OCT used so far for a deep comprehensive choroidal study has been Triton DRI. Its repeatability and reliability have been proved in healthy patients [18, 19] and in choroid-thickness thinning pathologies [20]. It gives similar measurements to the Zeiss Cirrus HD-OCT [21] (Carl Zeiss) although results should not be interchangeable [18]. It has been stated that automatic measurements reduce variability [22] although there is still little possibility of scan artifacts [23].

The most commonly used pattern is the ETDRS grid, as it is in retina, too. Nevertheless, the composition and functions of choroid has nothing to do with the ones of retina and its thickness does not follow the same pattern [5, 6, 12]. Although retinal thickness is not the same among ETDRS sectors, it does not differ too much [24], and that is why the ETDRS grid is an adequate useful pattern, whereas it might not be for choroid. However, no choroidal division has been proposed so far.

Choroid has usually been analysed with the ETDRS grid or with horizontal lines. At a first glance, the overall thickness map does not differ too much from the ones already published and mean CT values are similar, too. Some authors have described higher values of CT in superior parts [5, 6, 25] and the lowest in the outer macula area [5, 6, 26, 27], as well as we have. The fact of having analysed together right and left eyes should not have biased our study, as already stated by Chen et al. [28].

Shin et al. tried to make a choroidal map using radial OCT scans of the choroid and with the ETDRS grid, but they used a SD-OCT [26], and so the exact thickness values may differ. In our study, we found that the thickest choroid was always located in the superocentred area and the thinnest in temporal and nasal zones. With choroidal-thinning pathologies, the resulting CT map tends to be rather flat. However, the choroidal pattern differs depending on the pathology. Young healthy individuals show a mountain range pattern; aged healthy subjects, a mountain peak pattern; young high myopic, an inverted gorge pattern; and aged diabetic patients a gathered hills pattern, as displayed in Figures 3 and 4. This is why a 3D representation of CT has an importance, as it gives more information than ETDRS values alone.

The thickness range of 25 $\mu$m for every color range in our maps is acceptable, as it is higher than the possible internal variation of the OCT but not so high that it remained unaltered with affecting pathologies. Rahman et al. stated that a manually measured change greater than 23 $\mu$m in the subfoveal field may represent choroidal change when using SD-OCT with enhanced depth imaging (EDI) and manual measuring [22].

Although all the choroid and its sectors get significantly thinner with age, not all the sectors become equally affected. Baliq et al. studied CT variation with age using manual measurements, and they found that the central choroidal thickness increased with age, the most thinned sector was the nasal outer one, and the second most thinned was the inferior ones, what differs to some extent to our results [11]. The outer inferior ETDRS grid sector is the most thinned, and the outer nasal one is the less

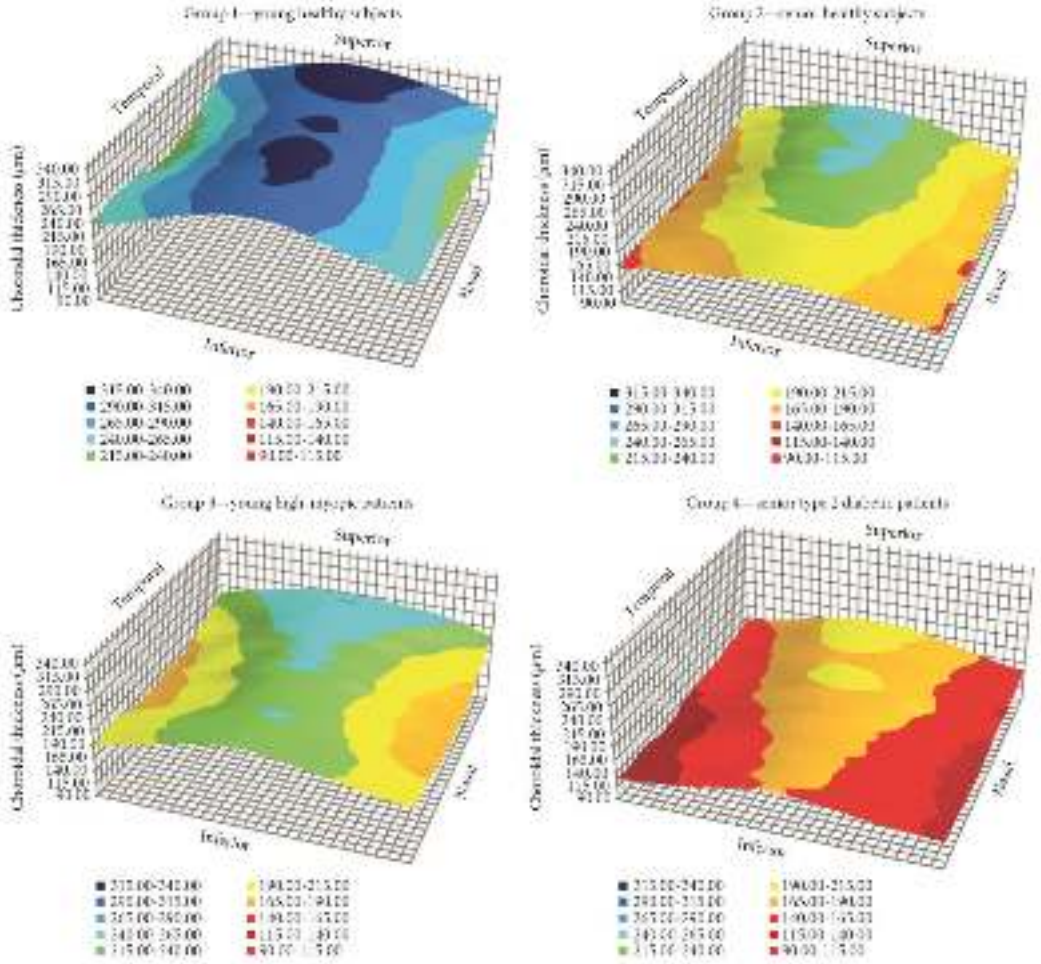



Figure 4: 3D maps of choroidal thickness.

thinned. As the latter has already been described as the thinnest choroidal zone even in healthy subjects, it is easy to understand that it is more difficult to achieve an even higher thinning.

On the contrary, high-myopic patients' choroid does not experience the same kind of thinning as with age. Their most thinned ETDRS sectors are the inferior and the nasal. Zhang et al. already found that the temporal choroid becomes less thinned than nasal, but they did not examine the superior or inferior choroid [12].

Finally, aged patients with mild and moderate DR suffer from a choroidal thinning which is softer in the outer nasal ETDRS sector. Their outer inferior ETDRS sector is affected from little thinning as well, but we should consider that this sector was already thinned because of age and then an even higher choroidal thinning would be rather difficult to achieve.

Thus, it is noticeable that, under these pathologies, there is a considerable flattening, and in those zones where CT was higher, choroidal thinning is also greater.

The strengths of this study include study-naïve patients and SS-OCT automatic measurements performed at the same day time. Furthermore, thickness maps seem easier to evaluate the choroid than manual measurements or ETDRS numerical values.

The main limitations of this study are a low number of young high-myopic patients and the small quantity of choroidal-thinning pathologies evaluated. It would be of interest how the whole macular choroid changes in other situations.

In conclusion, choroidal-thinning pathologies affect choroidal regions in a different way. This fact gains relevance especially in choroidal measurements because not all regions are interchangeable and CT should be measured in the proper place depending on the particular pathology. Therefore, lineal OCT examinations are inadequate for choroidal evaluation as superior and inferior macular regions remain unanalyzed. Second, choroidal thinning follows the following rule: the thicker the zone is in healthy subjects, the thinner it becomes when affected by any

pathology. Third, 3D representations of CT provide us with visual information which helps us to make an easier and faster general valuation. In general lines, the choroid in young healthy individuals follows a mountain range pattern; in aged healthy subjects, it follows a mountain peak pattern; in young high-myopic patients, it follows an inverted gorge pattern; and in aged diabetic patients, it follows a gathered hills pattern. All these pathologies tend to make a flat uniform choroid.

## Data Availability

All data of this study has been collected and stored at the Miguel Servet University Hospital in Zaragoza, Spain.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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# 10) Contributions of the Doctoral Student

This study, which comprises four related scientific articles, is aimed at understanding the choroidal changes that occur in T2D patients. First, an excellent repeatability of CT measurements using SS-OCT was demonstrated, what is essential before any rigorous deep study. Measuring choroid with an instrument giving different outcomes as a result of chance would be of no use at all. Second, it has been found that patients with DME (central RT ≥ 300 μm), and patients with DR have a thinner choroid than age-matched controls. As already discussed in the introduction, studies regarding CT in DME patients have reported different results. Further research would be of interest in order to find out the reason.

3D representations may be the most important contribution of this doctoral thesis. It has been the first time that analyses of the whole macular area have been used to generate visual representations of CT. These maps provide a quick simple assessment in a wide macular area at a glance. Not only has it shown us how the choroidal topography in young healthy individuals is, but it also has demonstrated us that it becomes affected in different ways depending on the pathology, and consequently different patterns may be distinguished. These topographic patterns do not seem to be related to retinal thickness, but further research is needed to confirm these results, as well as to clarify the reasons, pathophysiology and consequences.

The doctoral student has contributed to this work performing the study protocol, making statistical analyses and writing the published articles, as well as creating the 2D and 3D representations.

# 11) Conclusions

## a) Conclusions (EN)

1. The intrasession repeatability of CT measurements in healthy and T2D patients obtained with SS-OCT is excellent.
2. The choroid is thinner in T2D patients, moderate NPDR patients, and DME patients than in aged-matched healthy individuals.
3. CT follows an ellipsoid pattern in both nondiabetic and diabetic eyes, with diabetic eyes showing thinner measurements diffusely.
4. CT is not related to the duration of diabetes. HbA1c levels show only mild correlations with some central measurements of CT.
5. The choroidal pattern in young healthy individuals resembles a mountain range; with age, a mountain peak; and in aged T2D patients, gathered hills.

## b) Conclusiones (ES)

1. La repetitibilidad intrasesión de las mediciones de espesor coroideo en pacientes sanos y con DM 2 obtenidas con SS-OCT son excelentes.
2. La coroides está adelgazada en pacientes con DM 2, pacientes con retinopatía diabética no-proliferativa moderada, y pacientes con edema macular diabético, en comparación con sujetos sanos de la misma edad.
3. El grosor coroideo sigue un patrón elipsoide tanto en ojos no-diabéticos como diabéticos. Estos últimos muestran un adelgazamiento difuso.
4. El grosor coroideo no se correlaciona con la duración de la diabetes. Los niveles de HbA1c solo muestran correlaciones leves con algunas mediciones centrales de espesor coroideo.
5. El patrón coroideo en jóvenes sanos se parece a una cadena montañosa; con la edad, a un pico montañoso; y en pacientes añosos con DM 2, colinas agrupadas.

## c) Conclusions (FR)

1. La répétabilité intrasession des mesures de l'épaisseur choroïdienne chez des sujets sains et des patients avec DM type 2 obtenues avec SS-OCT est excellente.
2. La choroïde est plus maigrie chez des patients avec DM 2, chez des patients avec de la rétinopathie diabétique non proliférante modérée, et chez des patients avec de l'œdème maculaire diabétique que chez des témoins sains du même âge.
3. L'épaisseur choroïdienne suit un patron ellipsoïdal aux yeux non-diabétiques et diabétiques. Ces-ci montrent des mesures plus maigres diffusément.
4. L'épaisseur choroïdienne n'est pas corrélée avec la duration du diabète. Les niveaux de HbA1c montrent seulement des corrélations faibles avec quelques mesures centrales d'épaisseur choroïdienne.
5. Le patron choroïdien chez des sujets jeunes sains ressemble une chaine montagneuse ; avec l'âge, un sommet ; et chez des patients âgés avec DM 2, collines regroupées.

## d) Fazit (DE)

1. Die intrasitzunge Wiederholbarkeit der Vermessungen der Aderhautdicke in Gesdunden und in Patienten mit DM Type 2, die durch SS-OCT aufgenommen werden, sind ausgezeichnet.
2. Die Aderhaut wird dünner in Patienten mit DM 2, in Patienten mit mäßiger nichtproliferativer diabetischer Retinopathie, und in Patienten mit diabetischem Makulaödem als in gesunden altergleichen gesunden Personen.
3. Die Aderhautdicke befolgt ein ellipsoides Muster in beiden nicht diabetischen und in diabetischen Augen. Die Letztere zeigen dünnere Vermessungen überall.
4. Die Aderhautdicke correliert sich nicht mit der Diabetesdauer. Die HbA1c Spiegel zeigen nur eine schwache Korrelation mit ein paar zentralen Vermessungen der Aderhaut.
5. Die Aderhautdicke bei jungen Personen sieht wie eine Bergkette aus; mit Alter, wie einen Berggipfel aus; und beim alteren Patienten mit DM 2, wie einen umgekehrter Engpass aus.

# e) Conclusións (AN)

1. La repetitibilidat intrasesión de las medizións de gordaria coroidea a sanos i paziéns con DM 2 obtenidas con SS-OCT e eszelén.
2. La coroides está enfllacada a paziéns con DM, paziéns con retinopatía diabetica no proliferatiba amoderada i a paziéns con edema maculá diabetico que a controls sanos achustaus per edat.
3. La gordaria coroidea sigue un patrón elipsoide tanto a uellos no diabeticos i diabeticos. Istos zagueros muestran medizións enflacadas difusamén.
4. La gordaria coroidea no está correlazionada con la durazión de la diabetes. Los nibels de HbA1c solo muestran correlazións débils con bellas medizións zentrals de gordaria coroidea.
5. El patrón coroideo a indibiduos chobes sanos pareix una cadena montañosa; con la edat, una tuca montañosa; y a paziéns mayós con DM 2, pueyos agrupaus.

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# 13) Appendices

## a) Impact factor of the journals and themes

**Retina – The Journal of Retina and Vitreous Diseases**

Category – Ophthalmology

Impact factor in JCR – 3.815 (year 2018) – Q1

**PLoS One**

Category – Multidisciplinary sciences

Impact factor in JCR – 2.766 (year 2017) – Q1

**Canadian Journal of Ophthalmology**

Category – Ophthalmology

Impact factor in JCR – 1.305 (year 2018) – Q4

**Journal of Ophthalmology**

Category – Ophthalmology

Impact factor in JCR – 1.580 (year 2018) – Q3

## b) Co-authors agreement

Agreement of all co-authors in renouncing using these articles for their own doctoral thesis.

The following authors have already obtained the PhD degree:

- Pilar Calvo MD PhD FEBO
- Beatriz Abadía MD PhD FEBO
- Luis Pablo MD PhD
- Guayente Verdes MD PhD
- Antonio Ferreras MD PhD MBA

Escuela de Doctorado
Universidad Zaragoza

## RENUNCIA DE LOS COAUTORES DE LOS TRABAJOS PRESENTADOS COMO PARTE DE UNA TESIS DOCTORAL EN LA MODALIDAD DE COMPENDIO DE PUBLICACIONES

**1.- Datos personales del coautor**

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|---|---|---|
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**2.- Tesis Doctoral**

Título: Estudio de la coroides mediante tomografía de coherencia óptica swept source en sujetos sanos y pacientes diabéticos tipo 2

Autor: Francisco de Asís Bartol Puyal

Programa de doctorado: Medicina

**3.- Publicaciones que formarán parte de la tesis y de las que el firmante es coautor**

Abadía B, Bartol-Puyal F, Calvo P, Verdes G, Isanta C, Pablo L. Mapping choroidal thickness in patients with type 2 diabetes. Can J Ophthalmol.

Bartol-Puyal F, Isanta C, Ruiz-Moreno Ó, Abadía B, Calvo P, Pablo L. Distribution of Choroidal Thinning in High Myopia, Diabetes Mellitus, and Aging: A Swept-Source OCT Study. J Ophthalmol. 2019 Aug 15; 2019:3567813.

**RENUNCIA:**

Renuncio a que las publicaciones anteriores puedan ser presentadas como parte de otra tesis doctoral en la modalidad de compendio de publicaciones.

<lugar>,<fecha>

Zaragoza 13 de noviembre de 2019

Firma

Escuela de Doctorado
Universidad Zaragoza

## RENUNCIA DE LOS COAUTORES DE LOS TRABAJOS PRESENTADOS COMO PARTE DE UNA TESIS DOCTORAL EN LA MODALIDAD DE COMPENDIO DE PUBLICACIONES

| 1.- Datos personales del coautor | | |
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| 2.- Tesis Doctoral |
|---|
| Título: Estudio de la coroides mediante tomografía de coherencia óptica swept source en sujetos sanos y pacientes diabéticos tipo 2 |
| Autor: Francisco de Asís Bartol Puyal |
| Programa de doctorado: Medicina |

**3.- Publicaciones que formarán parte de la tesis y de las que el firmante es coautor**

Abadía B, Calvo P, Bartol-Puyal F, Verdes G, Suñén I, Ferreras, A. Repeatability of choroidal thickness measurements assessed with swept-source optical coherence tomography in healthy and diabetic individuals. Retina. 2019 Apr;39(4):786-79e.

Abadía B, Suñén I, Calvo P, Bartol F, Verdes G, Ferreras A. Choroidal thickness measured using swept-source optical coherence tomography is reduced in patients with type 2 diabetes. PLoS One. 2018 Feb 2;13(2):e0191877.

**RENUNCIA:**

Renuncio a que las publicaciones anteriores puedan ser presentadas como parte de otra tesis doctoral en la modalidad de compendio de publicaciones.

<lugar>,<fecha>

Maastricht 14 de noviembre de 2019

Firma:

# c) Approval from the Institutional Review Board

GOBIERNO DE ARAGON
Departamento de Sanidad, Bienestar Social y Familia

Informe Dictamen Favorable
Proyecto Investigación Biomédica
C.P.: CEI PI15/0159
10 de junio de 2015

Dña. María González Hinjos, Secretaria del CEIC Aragón (CEICA)

**CERTIFICA**

**1º.** Que el CEIC Aragón (CEICA) en su reunión del día 10/06/2015, Acta Nº 11/2015 ha evaluado la propuesta del investigador referida al estudio:

**Título: Relación de los parámetros antropométricos, citocinas plasmáticas y morfología retiniana con el grado de retinopatía diabética.**

**Investigador Principal: Antonio Ferreras Amez. HU Miguel Servet**

**Versión protocolo: 09/06/2015**
**Versión hoja de información a los participantes (pacientes y controles) y consentimiento informado: Versión 1; 10/06/2015**

**2º.** Considera que

- El proyecto se plantea siguiendo los requisitos de la Ley 14/2007, de 3 de julio, de Investigación Biomédica y su realización es pertinente.
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- Son adecuados tanto el procedimiento para obtener el consentimiento informado como la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el estudio.
- El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.
- La capacidad de los investigadores y los medios disponibles son apropiados para llevar a cabo el estudio.

**3º.** Por lo que este CEIC emite **DICTAMEN FAVORABLE** a la realización del proyecto.

Lo que firmo en Zaragoza, a 10 de junio de 2015

Fdo:

Dña. María González Hinjos
Secretaria del CEIC Aragón (CEICA)



Tel. 976 71 [illegible] Fax: 976 71 5[illegible] Correo electrónico: [illegible]

# d) Information sheet for the patient

**Hospital Universitario Miguel Servet**
Unidad oftalmológica de diabetes

Servicio de Oftalmología

## HOJA DE INFORMACIÓN AL PARTICIPANTE SIN DIABETES

Título del estudio: **Relación de los parámetros antropométricos, citocinas plasmáticas y morfología retiniana con el grado de retinopatía diabética.**

**Responsable del estudio:** Dr. Antonio Ferreras Tfno: 976 76 55 58

**Puede llevarse este documento**

La diabetes es una enfermedad en la que se produce un aumento de los niveles de azúcar en sangre. Si no se controla adecuadamente, puede afectar a la vista dañando la retina (retinopatía diabética), lo que puede ocasionar una disminución de la visión y en casos graves, ceguera.

Se han demostrado variaciones en la concentración plasmática de determinadas sustancias entre individuos sanos y diabéticos, con y sin retinopatía diabética, cuyo conocimiento podría contribuir a optimizar el manejo de la diabetes. Por este motivo, y con el objetivo de mejorar la calidad asistencial, los Servicios de Oftalmología y Endocrinología del hospital universitario Miguel Servet de Zaragoza están desarrollando este estudio de investigación en el que se compararán los niveles de determinados marcadores, mediciones oftalmológicas y antropométricas, entre sujetos sanos y pacientes diabéticos.

Usted no tiene diabetes y su participación aportará datos de normalidad para ser comparados con los de pacientes con diabetes. Básicamente, su participación en el estudio consistirá en realizar unas pruebas:

1. Un análisis de sangre y orina.
2. Una exploración física general: toma de presión arterial, medida de pliegues, y bioimpedancia.
3. Una evaluación oftalmológica completa, con evaluación de la agudeza visual, medida de la presión intraocular, fondo de ojo, retinografías, y tomografía óptica de coherencia. Todas estas pruebas son inocuas.

En caso de que alguna prueba saliera alterada, se le avisará para realizar una evaluación más exhaustiva. Si apareciera cualquier otro hallazgo casual, será citado en la unidad correspondiente del hospital para hacer el seguimiento oportuno.

La participación en este estudio no implica una disminución en su seguridad, sino la aceptación de la realización de las pruebas propuestas. La recogida de datos se hará de modo absolutamente confidencial y el anonimato de los datos estará garantizado.

Su participación en este estudio es totalmente voluntaria y puede abandonarlo en el momento en que así lo decida, sin que esto tenga repercusión alguna en su atención sanitaria futura.

Versión 1; 10/06/2015

**Hospital Universitario Miguel Servet**
Unidad oftalmológica de diabetes

Servicio de Oftalmología

# HOJA DE INFORMACIÓN AL PACIENTE

Título del estudio: **Relación de los parámetros antropométricos, citocinas plasmáticas y morfología retiniana con el grado de retinopatía diabética.**

**Responsable del estudio:** Dr. Antonio Ferreras Tfno: 976 76 55 58

**Puede llevarse este documento**

La diabetes es una enfermedad en la que se produce un aumento de los niveles de azúcar en sangre. Si no se controla adecuadamente, puede afectar a la vista dañando la retina (retinopatía diabética), lo que puede ocasionar una disminución de la visión y en casos graves, ceguera. Existen distintos tipos de tratamientos de la retinopatía diabética según su gravedad: láser, inyecciones intraoculares de fármacos o cirugía. A esto siempre se debe sumar un buen control de la diabetes, de la tensión arterial y de los lípidos sanguíneos.

Se han demostrado variaciones en la concentración plasmática de determinadas sustancias entre individuos sanos y diabéticos, con y sin retinopatía diabética, cuyo conocimiento podría contribuir a optimizar el manejo de la diabetes. Por este motivo, y con el objetivo de mejorar la calidad asistencial, los Servicios de Oftalmología y Endocrinología del hospital universitario Miguel Servet de Zaragoza están desarrollando este estudio de investigación en el que se compararán los niveles de determinados marcadores, mediciones oftalmológicas y antropométricas, entre sujetos sanos y pacientes diabéticos.

Se le realizará una analítica de sangre y orina y una exploración física general y oftalmológica, mediante el uso de aparatos específicos completamente inocuos. Si en el fondo de ojo aparecieran lesiones de retinopatía diabética relevantes o edema macular diabético también se le realizará una angiografía fluoresceínica. Antes de realizar la angiografía se le explicará con detalle en qué consiste y tendrá que firmar un consentimiento específico.

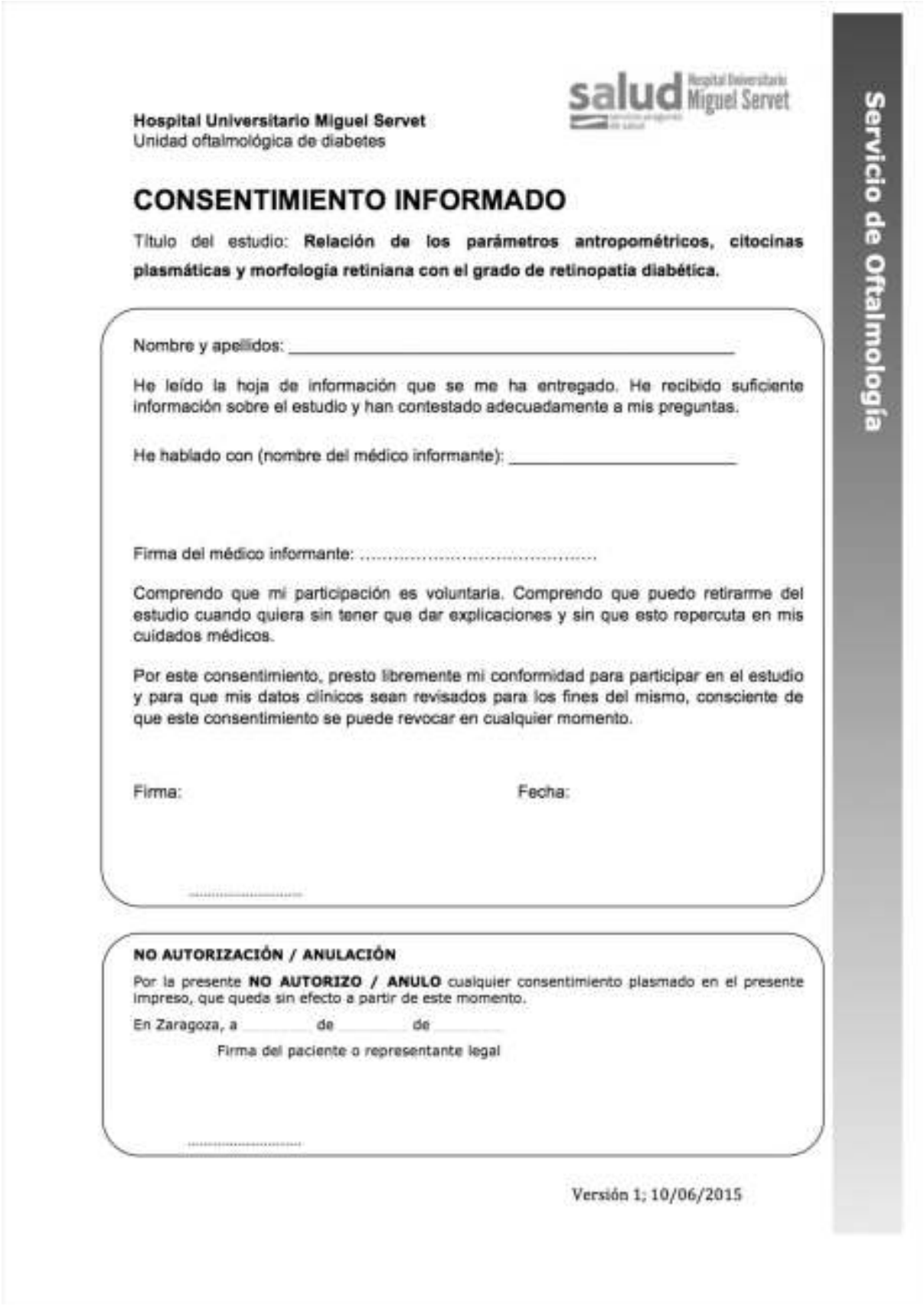
En caso de que alguna prueba saliera alterada, se le avisará para realizar una evaluación más exhaustiva. Si apareciera cualquier otro hallazgo casual, será citado en la unidad correspondiente del hospital para hacer el seguimiento oportuno.

La participación en este estudio no implica una disminución en su seguridad, sino la aceptación de la realización de las pruebas propuestas. La recogida de datos se hará de modo absolutamente confidencial y el anonimato de los datos estará garantizado.

Su participación en este estudio es totalmente voluntaria y puede abandonarlo en el momento en que así lo decida, sin que esto tenga repercusión alguna en su atención sanitaria futura.

Versión 1; 10/06/2015

# e) Informed consent



**Hospital Universitario Miguel Servet**
Unidad oftalmológica de diabetes

salud Hospital Universitario Miguel Servet

Servicio de Oftalmología

## CONSENTIMIENTO INFORMADO

Título del estudio: **Relación de los parámetros antropométricos, citocinas plasmáticas y morfología retiniana con el grado de retinopatía diabética.**

Nombre y apellidos: _____

He leído la hoja de información que se me ha entregado. He recibido suficiente información sobre el estudio y han contestado adecuadamente a mis preguntas.

He hablado con (nombre del médico informante): _____

Firma del médico informante: .....

Comprendo que mi participación es voluntaria. Comprendo que puedo retirarme del estudio cuando quiera sin tener que dar explicaciones y sin que esto repercuta en mis cuidados médicos.

Por este consentimiento, presto libremente mi conformidad para participar en el estudio y para que mis datos clínicos sean revisados para los fines del mismo, consciente de que este consentimiento se puede revocar en cualquier momento.

Firma: Fecha:

.....

**NO AUTORIZACIÓN / ANULACIÓN**

Por la presente **NO AUTORIZO / ANULO** cualquier consentimiento plasmado en el presente impreso, que queda sin efecto a partir de este momento.

En Zaragoza, a _____ de _____ de _____

Firma del paciente o representante legal

.....

Versión 1; 10/06/2015