Structural and metabolic retinal changes associated with mild cognitive impairment in type 2 diabetes

Pedersen, F. N., Stokholm, L., Lois, N., Yang, D., Cheung, C. Y., Biessels, G. J., Exalto, L., Simó, R., Peto, T., Pouwer, F., & Grauslund, J. (2023). Structural and metabolic retinal changes associated with mild cognitive impairment in type 2 diabetes. *Diabetes*. Advance online publication. https://doi.org/10.2337/db23-0025

Published in:
Diabetes

Document Version:
Peer reviewed version

Title:

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Running Title:

Retinal markers of cognitive impairment

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Word count: 3112

Tables and Figures: 5 tables and 2 figure.

Abstract

Type 2 diabetes is associated with cognitive impairment and a twofold increased risk of dementia compared to age-matched individuals without diabetes. Given that the eye and the brain share similar embryologic origin and anatomical features the retina offers a unique "window" to the brain. In this study we wanted to determine whether there was a difference in retinal imaging-based neuronal and vascular markers in individuals with type 2 diabetes with or without minimal cognitive impairment (MCI). We included 134 persons with type 2 diabetes. Based on neuropsychological tests the prevalence of MCI was 28%. We performed 7-field color fundus photos, optical coherence tomography (OCT), OCT-Angiography and retinal oximetry in order to analysis retinal markers. In a multivariable cluster analysis, persons with MCI had significant thinner macular retinal nerve fiber layer and macular ganglion cell layer, and less venular oxygen saturation in the nasal quadrant compared to those without MCI. There were no differences in retinal vessel density, fractal dimension, width, tortuosity or OCT-A markers. People with type 2 diabetes and MCI demonstrate alterations in retinal structure and metabolism, suggesting non-invasive retinal markers may be useful to detect those at risk of cognitive dysfunction in people with type 2 diabetes.

Highlights:

- **Why did we undertake this study?**
- **Type 2 diabetes is associated with minimal cognitive impairment (MCI). Therefore retinal and cerebral neurodegeneration may run in parallel.**
- **What is the specific question(s) we wanted to answer?**
- **To assess whether there was a difference in retinal structure, vessel and metabolic parameters in individuals with MCI.**
- **What did we find?**
- **We found those with MCI had thinner macular retinal nerve fiber layer, macular ganglion cell layer and less venular oxygen saturation.**
- **What are the implications of our findings?**

- **We suggest non-invasive retinal markers may be useful to detect those at risk of cognitive dysfunction.**

Introduction

Type 2 diabetes (T2DM) is associated with mild cognitive impairment (MCI), which is characterized by objective cognitive deficits on standard neuropsychological tests without affecting daily living [1]. The World Health Organization predicts a rapid increase in the number of individuals with T2DM and incident cognitive impairment, with an annual conversion rate from MCI to dementia of around 10% [2] and almost twofold higher risk of developing dementia in individuals with T2DM compared to age-matched individuals without diabetes [3]. Since diagnostics of MCI rely on extensive neuropsychological testing, there is a need to identify those at increased risk of cognitive impairment to ensure early diagnosis in order to manage modifiable risk factors (e.g. metabolic control) to slow progression of cognitive loss and to provide them with appropriate support.

Diabetes itself causes structural and vascular changes to the retina even in the absence of diabetic retinopathy (DR) [4]. This is considered related to retinal neurodegeneration and microangiopahy resulting in damage to the neurovascular unit ultimately leading to instability of the retina-blood-barrier [5]. As the retina and the brain share similar embryologic origin, retinal imaging might be useful to detect early pathology in the cerebral vasculature and parenchyma, as retinal and cerebral neurovascular degeneration often run in parallel [6]. This may provide researchers and clinicians the opportunity to utilize non-invasive retinal imaging-based markers for identifying individual with high risk for cognitive impairment and dementia.

Retinal sensitivity and eye fixation assessed by microperimetry have been proposed as non-invasive retinal tools for identifying and monitoring MCI in people with T2DM [7, 8]. Other retinal structural and metabolic markers have been less investigated within the T2DM population. A single cross-sectional study of 137 participants with T2DM reported venular tortuosity to be higher in persons with

cognitive impairment compared to healthy controls, but the study used a telephone interview only to assess cognitive status [9].

Therefore, the aim of the present study was to determine whether there was a difference in retinal imaging-based neuronal and vascular markers in individuals with T2DM with or without MCI.

Research Design and Methods

Study population

This was a prospective cross-sectional study including individuals with T2DM identified using the Funen Diabetes Database (FDDB), a regional diabetes database in the area of Southern Denmark established in 2003 [10]. The database provides information on relevant clinical information, including for example age, type of diabetes, body mass index (BMI), blood pressure, DR screening results and information on comorbidities, such as acute coronary syndrome and cerebrovascular incidents.

Potential eligible participants were invited to take part in this study using a secure digital mailbox [11], distributed for each citizens in Denmark between 25 November 2020 and 25 February 2022, and all examinations were performed at Odense University Hospital. A pre-screening based on eligibility criteria (inclusion and exclusion criteria) by telephone was performed in order to streamline recruitment. Criteria for eligibility were diagnosis of T2DM, age above 65 years, duration of diabetes of at least 5 years, and ability to provide informed consent. Individuals were excluded if they had a diagnosis of stroke or any neurodegenerative disease, if retinal neurodegeneration was already known to be present due to previous laser photocoagulation, glaucoma or diabetic macular edema or other eye disorders affection vision besides possible complications of DR, refractive error ≥6 diopters, media opacities precluding retinal imaging, severe systemic illness or personal circumstances that would

prevent the subject to fulfil the study protocol. If deemed eligible, individuals were allowed to participate with both eyes under the assumption that retinal changes may not be seen symmetrically.

Clinical examination

A medical and ophthalmological history as well as demographics (year of birth, sex, education) were obtained. Current use of antidiabetic agents and blood pressure medication was recorded. Duration of diabetes was obtained from the FDDB and cross checked with medical records. If a discrepancy was seen between medical records and FDDB, the earliest year of diagnosis was used to calculate diabetes duration. Marital status was categorized as having a partner or single. We measured weight and height and calculated BMI as well as abdominal circumference. Smoking status was registered as never, former or current smoker. Brachial arterial blood pressure was measured with participants sitting with Omron M6 (HEM-7001-E, Hoofddorp, The Netherlands), and mean arterial pressure was calculated as $BP_d+(BP_d+BP_s) / 3$ where BP_d and BP_s are the diastolic and systolic blood pressure, respectively. In addition, fasting (minimum 4 hours) venous blood samples were drawn to collect information on blood glucose levels, lipid profile, and renal function. Participants collected a morning urine sample to measure albuminuria; this was defined as normo-albuminuria if < 30mg/g; micro-albuminuria if between 30-300 mg/g, and macro-albuminuria when >300 mg/g. The geriatric depression score-15 was used to detect presence of depressive symptoms.

Cognitive assessment

All participants underwent a stepwise neuropsychological evaluation. Firstly, the Montreal Cognitive Assessment (MoCA) test was administered by a certified physician. Those with a MoCA score below 26 were considered to have potential cognitive impairment and were subsequently tested with a

neuropsychological test battery (NTB). The NTB comprised 13 tests covering five cognitive domains; processing speed (Digit Symbol Substitution Test and Trail-Making-Test A); attention and executive functioning (Trail-Making-Test B, letter fluency and backwards digit span); memory (Rey Auditory Verbal Learning Test direct, delayed and recognition, Rey-Österrieth Complex Figure Test delayed and forward digit span); visio-construction (Rey-Österrieth Complex Figure Test copy) and language (Boston Naming Test and Category fluency). Test scores were converted to percentile scores according to reference data [12-17]. Individuals were considered to have MCI if the average score of one or more domains were below the 15th percentile or if over half of the tests in a single domain were below the 5th percentile [18].

Outcome

We performed multiple imaging technologies. Our primary outcome is difference in retinal vessel saturation whereas secondary outcomes include differences in retinal vascular and structural parameters. Each retinal parameter will be described in the following sections.

Ophthalmologic examination

Best-corrected visual acuity (BCVA) was obtained prior to pupil dilation and prior to the undertaking of any imaging evaluations (see below), using Early Treatment Diabetic Retinopathy Study charts at 4 meters (Precision Vision, Illinois, USA). We performed a dilated eye examination using tropicamide 10 mg/ml and phenylephrine 10% including 45 degree 7-field color fundus photography (TRC-50DX fundus camera, Topcon, Tokyo, Japan). DR grading was undertaken by a certified grader according to the International Clinical Diabetic Retinopathy Disease Severity Scale [19], with each eye categorized

as level 0 (no DR), 1 through 3 (mild, moderate and severe none-proliferative DR), or 4 (proliferative DR).

Structural retinal microvascular markers

OCT markers

Central retinal thickness was measured using SD-OCT (Spectralis OCT Family Acquisition Module, V6.9a Heidelberg Engineering, Germany). OCT imaging acquisition settings were high speed, volume scan with ART 9. The automated segmentation protocol of the Spectralis OCT (Heidelberg Eye Explorer V1.10.2.0) was used to measure macular ganglion cell layer (mGCL) thickness and macular retinal nerve fiber layer (mRNFL) thickness. The automated segmentation was manually corrected for any misalignments. The scans were divided according to the ETDRS map into 1 mm, 3 mm and 6 mm rings. The inner ring was defined as the central thickness subfield, and the outer rings were divided into four zones designated as the superior, nasal inferior and temporal zones.

Retinal vessel analysis

Retinal structures including vessel width, density, tortuosity and fractal dimension were assessed using VAMPIRE-Web (Vessel Assessment and Measurement Platform for Images of the Retina, Universities of Dundee and Edinburgh, UK) [20]. In brief, 45-degree disc centered, color fundus photos were used, and three concentric zones were semi-automatically generated around the optic disc labeled zone A, B and C at 0.0-0.5, 0.5-1.0 and 0.5-2.0 disc diameters from the disc margin, respectively. The software color labelled venules blue and arterioles red. In cases where the software mislabeled retinal vessels, detected one vessel as two, or labelled a hemorrhage the annotation was manually corrected. The

retinal vessel width was calculated as the central retinal artery (CRAE) and vein equivalent (CRVE) in zone B [21]. Vessel density, tortuosity and fractal dimension were measured in zone C [22].

OCT-A markers

Macula centered 4.5x.4.5 mm OCT-A images were obtained with TRC-50DX fundus camera (Topcon, Tokyo, Japan). MATLAB (MathWorks, Natick, MA) was used for quantification of retinal microvasculature from OCT-A images, as previous described [23]. In short, markers of interest were (I) the area of the foveal avascular zone (FAZ) given by the total numbers of pixels within the region, (II) non-perfusion regions defined as dark areas from a binarized image larger than 0.02mm, (III) vessel density within the ETDRS grid (1, 3 mm) calculated as the areas not defined as non-perfusion regions over total area of the interested region, and (IV) fractal dimension calculated using a box-counting method in a skeletonized image. All the markers were measured in the superficial capillary plexus (SCP) and deep capillary plexus (DCP). We excluded scans with image quality below 40 according to Topcon software.

Measures of retinal oxygen saturation

Retinal vessel oxygen saturation measurements were performed in 50-degree disc centered images using the Oxymap Model T1 [24]. In short, two concentric circles were semi automatically placed around the optic disc with diameters 1.5 times and 3 times the optic disc diameter. The largest venule and arteriole in each quadrant were annotated in length between 50-200 um [25]. We performed both mean and quadrant arterial and venular saturation analyses. Images with quality below five were excluded according to the Oxymap software.

Ethical and Institutional Review Board (IRB) approvals

The study was performed according to the tenets of the Helsinki Declaration, and relevant permissions were obtained from the Region of Southern Denmark's record of data processing activities (Journal number 20/34731) and from the Danish National Committee on Health Research Ethics (S-20200050). The study was registered at http://www.clinicaltrials.gov before initiation (NCT04610749). Written informed consent was obtained from all participants.

Statistical analysis

Study sample characteristics are presented in Table 1 with categorical data presented with numbers and percentages, and numerical data with medians and interquartile range (IQR). Given that data from both eyes of participants were included, mixed model regression analysis with cluster robust standard error was used to test for difference in retinal markers between persons with and without MCI. We performed an unadjusted crude model and a multivariable model adjusting for age, sex, mean arterial pressure and presence (yes/no) of DR. Due to interaction between DR and MCI, we reported results for the entire group as well as stratified in groups with and without overt DR (Table 5). In a secondary analysis we calculated area under the curve for retinal parameters that were associated with MCI adjusted for age, sex, mean arterial pressure and presence of DR (Supplementary material). Missing data was considered as missing at random which included abdominal circumference (n=1), total cholesterol (n=1), LDL cholesterol (n=2), estimated glomeraular filtration rate (n=1), albumin excretion rate (n=1). In data available for regression analysis there were no missing values.. P-values below 0.05 were considered statistically significant.The study included multiple analysis, thus risk for spurios findings. We performed Bonferoni corrections based on 83 initial analysis. Results that were

still statistical significant after corrections are annotated in the tables. Abovementioned statistics were performed with STATA version 17.0 (StataCorp LLC, College Station, TX, USA).

Sample size was based on previous results regarding retinal vessel saturation and prevalence of MCI in T2DM. Power was performed by conducting a statistical power analysis using PROC POWER in SAS. With 200 included persons using a significance level of 5% the power would be 86%. With a reduction to 120 included participants the power would reduce to 80 % on a significance level of 5%.

Data and Resource Availability

Data is available upon reasonable request to the author.

Results

Overall, 134 participants (245 eyes) were eligible and included in this study (Figure 1). Upon reviewing MoCA scores, 65 participants scored below 26 points, of whom 38 participants (28% of the overall group) were categorized with MCI based on NTB results. The number of total impaired cognitive domains varied with 17, 11, 8 and 2 participants impaired in 1, 2, 3 and 4 domains, respectively. The most frequent domain impaired was memory (impaired in n= 18; 47%), and the least language (impaired in n= 8; 21%) (Figure 2).

Compared to individuals without MCI, participants with MCI had completed fewer years of education (9.0 years vs. 11.0 years p=<0.001) and were more often taking glucose lowering treatment, excluding insulin (97% vs 83% p=0.028) (Table 1). Persons with MCI had statistically significantly worse BCVA (84.0 vs 84.5 p=0.035) compared to individuals without MCI, but there was no difference between history of cataract surgery or presence of any overt DR. There were no difference between presence of

DR (yes/no) and MCI (32% vs. 21% p=0.23). In addition, sex, age, diabetes duration, marital status, BMI, smoking, blood pressure or history of ischemic heart disease was comparable between the two groups. There were no differences detected in HbA_{1c} , cholesterol levels, estimated glomerular filtration rate, or albumin excretion rate between those with or without MCI.

In a mixed regression model adjusted for age, sex, mean arterial pressure and presence of DR, mRNFL was thinner in the superior sector (inner region) (22.3µm vs. 24.1µm p=0.007), nasal sector (inner) (20.5 µm vs. 21.7 µm p=0.049) and nasal sector (outer region) (43.3µm vs. 46.5µm p=0.032) in individuals with MCI compared with those without MCI. This was also seen in the mGCL, with thinning in the inner region (p=0.029), inner superior (p=0.029), nasal (p=0.010), and inferior (0.027) sector in individuals with MCI compared to those without MCI. Likewise, participants with MCI had central macular thinning in the inner superior (p=0.018) and nasal (p=0.033) sectors when compared to those without MCI, after adjustment of age, sex and presence of DR (Table 2).

There was no statistically significant difference in vessel width for either arterioles or venules, vessel tortuosity, density or fractal dimension in the crude or adjusted model between groups (with or without MCI) (Table 3). Likewise, there was no statistical significant association between OCT-A markers including FAZ, macular vessel density or fractal dimension in the SCP or DCP and presence or absence of MCI (Table 4).

Compared to those without MCI, participants with MCI had lower venular saturation of oxygen in the upper nasal quadrant (61.0% vs. 56.4% p=0.028) in the adjusted model, but this was no longer statistically significant after stratification for presence of DR in the model (Table 5). There were also no statistically significant differences in mean retinal arterial or venular oxygen saturation levels between both groups. In an adjusted model for age, sex, mean arterial pressure and presence of DR the

AUC varied between 0.65-0.68 for retinal paramerters were we found a statistical significant association (Supplementary material).

Discussion

In the present study, 28% of T2DM participants fulfilling our criteria of MCI, had retinal neurovascular alterations based on the presence of a decreased thickness in the mRNFL as well as lower venular oxygen saturation in the upper nasal quadrant. We did not find any statistically significant differences in retinal vessel caliber, tortuosity, density, fractal dimension or OCT-A markers.

The prevalence of MCI in people with T2DM in the current study is lower than that found in a recent meta-analysis, which reported prevalence of 45% with rates ranging from 22% to 68% [26]. This systematic review included ten studies from Asia and two from Europe and reported a lower overall prevalence of MCI in European studies (37% vs 46%). However, this was not directly comparable to our study, as the European studies used Mini-Mental State Examination (MMSE) and MoCA to assess MCI, whereas MoCA was used as screening for possible cognitive dysfunction in the present study, supplemented by a robust NTB [27, 28]. In general, MMSE and MoCA are used as screening tests for cognitive impairment, which may have resulted in false positive MCI cases in the before mentioned studies, and caused the observed higher prevalence compared to our study.

Regarding retinal markers for MCI in T2DM, the thinning of mRNFL and mGCL found in the present study for those with T2DM and MCI is comparable with previous findings in samples without diabetes [29]. The thinning of the retinal layers may reflect a potential concurrent retinal and cerebral neurodegeneration. A recent large Magnetic Resonance Imaging study including 2131 participants reported no association between mRNFL thinning and a smaller brain volume. However, mRNFL thinning was found to be correlated with volume reduction in the occipital-parietal cortex in people

with multiple sclerosis [30, 31]. In this study, most of the differences in retinal parameters were found in the inner region. This could indicate that MCI is associated with lesions in specific retinal areas. This is strengthened by magnetic resonance imaging studies that have shown an association between regional changes in the mRNFL and regional cerebral atrophy in individuals with high genetic risk of AD [32], however it should be noted that results are inconsistent while others have not found a positive association [33]. Therefore, it remains uncertain whether retinal thinning could be a proxy measurement for cerebral degeneration.

We did not find any differences in retinal fractal dimension. Previous findings regarding fractal dimension and MCI have been inconsistent. For example a population-based-cross sectional study of 1202 participants found that cognitive impairment was more common in those with lower fractal dimensions, but in a subgroup analysis stratified for diabetes this association was no longer significant [34]. Furthermore, a recent cross-sectional study of 1431 participants, of which 22% had diabetes, found no significant association between fractal dimension and MCI [35]. Differences in results may be due to different variables considered relevant for the regression model used. Thus, while Cheung et al. [34] adjusted for age, sex, low income, low education, hypertension, smoking, hyperlipidemia and chronic kidney disease, O'Neill et al. [35] corrected for age, sex, alcohol consumption, smoking status, educational attainment, physical activity, history of cardiovascular disease, hypertension triglycerides, diabetes, medication, mean arterial blood pressure, body mass index and high-density lipoprotein.

A previous cross-sectional study of 137 individuals with newly diagnosed T2DM found a higher venular tortuosity in persons diagnosed with cognitive dysfunction by a telephone interview, but no alterations were observed in vessel width, fractal or arterial tortuosity [9]. Our study does not support an altered venular tortuosity in individuals with T2DM and MCI, but differences in results may be due to a dissimilarity in the analysis software used to assess vessel tortuosity. Differences in results may

279 also relate to differences in the accuracy of the diagnosis of cognitive impairment between studies
280 (phone interview versus detailed NTB). In general retinal vessel width, fractal dimension and retinal
281 vessel tortuosity has been associated with other disorders, including cardiovascular disease [36] and
282 cerebrovascular disease [37], which may indicate that this marker, on its own, may be to unspecific.
283 In the present study, the retinal venular oxygen saturation in the nasal quadrant appeared to be lower in
284 participants with MCI when compared to those without, although this was not statistically significantly
285 different after statistical adjustments. A small study including 42 people with MCI and healthy controls
286 found increased mean venular and arterial saturation in those with MCI, however diabetes was an
287 exclusion criteria and the study did not perform either a quadrant analysis which makes comparison
288 between studies difficult [38].
289 Strengths of the study include its prospective nature and the in-depth neuropsychological evalutation
290 which would be expected to have provided an accurate assessment of MCI, but we did not include
291 subjective cognitive complaints. Limitations include the relatively small number of participants and the
292 study´s cross-sectional design , which does not allow causal relationships to be examined. Furthermore,
293 grading's of retinal markers were not obtained by investigators masked to the cognitive status of
294 participants. Lastly, caution should be made when interpreting the data presented, with the potential of
295 spurious asscoiations due to multiple testing. It should be noted that only few associations were
296 statistical significant, but these might help guide future research.
297 In conclusion, we found MCI in almost one in three persons with T2DM, as well as changes in retinal
298 structural and metabolic markers. Longitudinal studies are warranted to further investigate the temporal
299 associations of structural, metabolic and functional retinal markers in people with T2DM and MCI. On
300 this regard, the "retinal and cognitive dysfunction in type 2 diabetes: unravelling the common pathways
301 and identification of patients at risk of dementia (RECOGNISED)" study (https://www.recognised.eu/),

funded by the European Union's Horizon 2020, which includes cross-sectional and longitudinal prospective clinical studies as well as experimental basic science studies, aims to elucidate biomarkers, including retinal biomarkers, of risk of cognitive impairment as well as pathogenic mechanisms of disease in people with T2DM.

Acknowledgments: Participants in the current study were also recruited for the "RECOGNISED" study (NTC04281186), if deemed eligible. The Authors would like to acknowledge the RECOGNISED (Retinal and cognitive dysfunction in type 2 diabetes: unravelling the common pathways and identification of patients at risk of dementia) consortium, funded by the European Union's Horizon 2020 research and innovation programme under grant agreement No. 847749.

Guarantors: FNP is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions: FNP recruited participants and performed the study. FNP analyzed the data except OCT-A images which was done by DY and CYC. FNP and LS performed the statistical analysis. FNP wrote the manuscript with input from all authors.

Funding/Support: This work was supported by Odense University Hospital PhD Foundation (grant number 4339) and Overlægerådets forskningsfond (A4651).

Conflict of Interest Disclosures: None reported

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Table 1: Descriptive data of individuals and eyes with and without mild cognitive impairment (MCI) in persons with type 2 diabetes.

	MCI		
	Yes	No	p-value
Individuals, n	38	96	
Sex, male %(n)	61% (23)	74% (71)	0.13
Age, years median (IQR)	74.0 (70.0, 75.0)	71.5 (68.5, 76.0)	0.20
Current partner status %(n)			0.39
Single	29% (11)	22% (21)	
Married or living together	71% (27)	78% (75)	
History of ischemic heart disease %(n)	24% (9)	20% (19)	0.62
Diabetes duration (years), median (IQR)	19.0 (14.0, 24.0)	19.0 (13.0, 23.0)	0.50
Years of education, median (IQR)	9.0 (7.0, 11.0)	11.0 (10.0, 13.0)	**<0.001**
BMI (kg/m^2), median (IQR)	28.8 (26.0, 31.2)	29.5 (26.1, 33.5)	0.45
Smoking %(n)			0.49
Current	5% (2)	9% (9)	
Never	34% (13)	41% (39)	
Former	61% (23)	50% (48)	
MAP (mmHg), median (IQR)	101.2 (93.3, 107.3)	102.0 (94.0, 109.5)	0.67
Abdominal circumference (Cm), median (IQR)	104.0 (100.0, 112.0)	108.0 (98.0, 118.0)	0.49
GDS-15, median (IQR)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	0.46
MoCA, median (IQR)	23.0 (21.0, 24.0)	26.0 (25.0, 27.0)	**<0.001**
Medication use %(n):			
Antihypertensive treatment			
No therapy	13% (5)	14% (13)	0.95
Mono therapy	26% (10)	16% (15)	0.15
Two-drug therapy	24% (9)	34% (33)	0.23
Three or more drug therapy	37% (14)	36% (35)	0.97
Antidiabetic treatment			
Glucose lowering treatment excluding insulin	97% (37)	83% (80)	**0.028**
Insulin treatment	45% (17)	53% (51)	0.38
Statin treatment	84% (32)	80% (76)	0.57
Laboratory tests:			
HbA_{1c} (%), median (IQR)	7.1 (6.7, 8.4)	7.3 (6.7, 7.9)	0.96
HbA_{1c} (mmol/mol), median (IQR)	54.5 (50.0, 68.0)	56.0 (50.0, 62.5)	
Total cholesterol (mmol/L), median (IQR)	3.7 (3.2, 4.2)	3.6 (3.2, 4.3)	0.85
LDL cholesterol (mmol/L), median (IQR)	1.5 (1.2, 2.0)	1.5 (1.3, 2.0)	0.73
HDL cholesterol (mmol/L), median (IQR)	1.3 (1.2, 1.6)	1.2 (1.0, 1.6)	0.32
Triglycerides (mmol/L), median (IQR)	1.6 (1.1, 2.1)	1.5 (1.1, 2.0)	0.80
eGFR (ml/min/1.73 m2), median (IQR)	75.0 (59.0, 87.0)	77.0 (57.5, 88.0)	0.99
Albumin excretion rate (mg/g), %(n)			0.28
<30	79% (30)	76% (73)	
30-300	21% (8)	18% (17)	
>300	0% (0)	6% (6)	
Eyes included, n	71	174	

Pseudophakia, %(n)	35.2% (25)	29.9% (52)	0.42
BCVA ETDRS letters, median (IQR)	84.0 (80.0, 85.0)	84.5 (82.0, 87.0)	**0.035**
Diabetic retinopathy, ICDR %(n)			0.29
Level 0	22.5% (16)	35.1% (61)	
Level 1	22.5% (16)	19.5% (34)	
Level 2	52.1% (37)	42.5% (74)	
Level 3	2.8% (2)	2.9% (5)	

Missing data: Abdominal circumference (n=1), Total cholesterol (n=1), LDL cholesterol (n=2), eGFR (n=1), albumin excretion rate (n=1). IQR: Interquartile range. ICDR: the International Clinical Diabetic Retinopathy. MAP: Mean arterial pressure. GDS-15: Geriatric depression scale. BMI: Body mass index. eGFR: estimated glomerular filtration. BCVA: Best corrected visual acuity. ETDRS: Early Treatment Diabetic Retinopathy Study.

Table 2 – Difference in retinal macular layers in individuals with type 2 diabetes with and without mild cognitive impairment (MCI).

	n	MCI yes	MCI no	P-value crude model	P-value multivariate adjusted model
Central retinal thickness					
Whole macular area	243	302.6 (297.7-307.5)	307.1 (303.7-310.5)	**0.048**	0.145
Central macular region, 1mm	243	279.4 (273.6-285.1)	285.0 (280.5-289.5)	**0.049**	0.130
Inner region, 3mm	243	326.3 (320.7-331.8)	332.1 (328.4-335.8)	**0.024**	0.092
Superior	243	327.4 (322.1-332.7)	335.4 (331.6-339.2)	**0.007**	**0.018**
Nasal	243	330.9 (325.2-336.6)	338.5 (334.7-342.3)	**0.011**	**0.033**
Inferior	242	325.7 (319.8-331.5)	328.9 (323.6-334.1)	0.139	0.466
Temporal	243	320.4 (314.7-326.1)	325.5 (321.8-329.3)	0.050	0.144
Outer region, 6mm	243	284.5 (279.5-289.5)	287.5 (284.1-291.0)	0.183	0.329
Superior	243	286.9 (281.5-292.2)	291.9 (288.2-295.7)	0.081	0.129
Nasal	243	297.5 (291.9-303.2)	302.3 (298.5-306.1)	0.128	0.174
Inferior	241	276.4 (271.0-281.9)	275.5 (271.2-279.8)	0.871	0.811
Temporal	242	276.1 (271.1-281.1)	280.3 (276.7-283.8)	0.078	0.183
Macula RNFL					
Whole macular area	243	25.8 (24.7-26.9)	27.1 (26.3-27.9)	0.141	0.055
Central macular region, 1mm	243	12.8 (12.2-13.4)	13.3 (12.9-13.8)	0.150	0.199
Inner region, 3mm	243	21.3 (20.4-22.2)	22.4 (21.7-23.2)	0.061	0.045
Superior	242	22.3 (21.2-23.3)	24.1 (23.2-25.0)	**0.018**	**0.007**
Nasal	243	20.5 (19.7-21.4)	21.7 (20.9-22.4)	0.054	0.049
Inferior	242	23.9 (22.6-25.2)	25.3 (24.4-26.2)	0.118	0.087
Temporal	243	18.4 (17.9-19.0)	18.6 (18.0-19.3)	0.599	0.590
Outer region, 6mm	243	33.6 (32.0-35.3)	35.2 (34.1-36.4)	0.345	0.121
Superior	242	34.9 (32.5-37.3)	36.4 (35.1-37.7)	0.564	0.282
Nasal	243	43.3 (40.9-45.6)	46.5 (44.7-48.3)	0.121	0.032
Inferior	241	36.0 (34.1-37.8)	37.4 (36.0-38.8)	0.533	0.216
Temporal	242	20.0 (19.5-20.6)	20.6 (19.9-21.2)	0.362	0.218
Macula GCL					

Whole macular area	243	35.4 (34.0-36.9)	37.1 (36.1-38.1)	**0.036**	0.055
Central macular region, 1mm	243	15.4 (14.3-16.4)	16.5 (15.5-17.6)	0.067	0.110
Inner region, 3mm	243	44.2 (42.2-46.2)	46.8 (45.5-48.1)	**0.021**	**0.029**
Superior	243	45.6 (43.6-47.6)	48.4 (47.0-49.8)	**0.019**	**0.021**
Nasal	243	44.6 (42.5-46.6)	47.7 (46.5-49.0)	**0.013**	**0.010**
Inferior	242	45.3 (43.5-47.1)	47.8 (46.5-49.2)	**0.033**	**0.027**
Temporal	243	41.0 (38.7-43.3)	43.5 (42.2-44.7)	0.056	0.066
Outer region, 6mm	243	31.6 (30.3-32.9)	32.5 (31.7-33.3)	0.181	0.258
Superior	243	31.6 (30.2-33.0)	32.1 (31.3-32.9)	0.408	0.555
Nasal	243	33.3 (31.8-34.7)	34.6 (33.6-35.5)	0.138	0.149
Inferior	240	29.8 (28.6-31.0)	30.1 (29.5-30.8)	0.683	0.670
Temporal	241	31.6 (30.1-33.2)	33.0 (32.1-33.9	0.119	0.143

Main analysis adjusted for sex, age, mean arterial pressure and present diabetic retinopathy. n: number of eyes included in the analysis. RNFL: Retinal nerve fiber layer. GCL: Ganglion cell layer. P-values still statistical significant after Bonferroni correction are annotated with a * (no statistical significant results after Bonferroni correction).

Table 3: Difference in retinal vascular markers in individuals with type 2 diabetes with and without mild cognitive impairment (MCI).

	n	MCI yes	MCI no	P-value crude model	P-value adjusted model
Vessel caliber (pixels)					
Arterioles	245	26.40 (25.77-27.02)	26.60 (26.28-26.92)	0.652	0.567
Venules	245	36.86 (35.7-38.00)	36.87 (36.31-37.43)	0.891	0.984
Vessel Tortuosity					
Arterial	245	-7.39 (-8.05-(-6.73))	-7.63 (-8.04-(-7.22))	0.821	0.547
Venular	245	-7.83 (-8.46-(-7.21))	-8.18 (-8.41-(-7.95))	0.383	0.313
Vessel Density (pixels)					
Arterioles	245	3413.61 (3194.18-3633.04)	3538.89 (3391.43-3686.35)	0.464	0.365
Venules	245	4608.35 (4288.18-4928.52)	4452.25 (4269.42-4635.08)	0.529	0.405
Fractal Dimension					
Arterioles	212	1.15 (1.13-1.17)	1.15 (1.14-1.16)	0.692	0.612
Venules	241	1.15 (1.13-1.17)	1.15 (1.14-1.16)	0.919	0.774
Total (Arterioles+venules)	245	1.31 (1.30-1.32)	1.32 (1.31-1.33)	0.402	0.327
DR yes	168	1.32 (1.30-1.33)	1.32 (1.31-1.33)	0.283	0.394
DR no	77	1.30 (1.26-1.33)	1.31 (1.29-1.32)	0.550	0.602

Main analysis adjusted for sex, age, mean arterial pressure and present diabetic retinopathy. In case of interaction, individuals were stratified in groups with and without diabetic retinopathy. n: number of eyes included in the analysis. DR: Diabetic retinopathy. P-values still statistical significant after Bonferroni correction are annotated with a * (no statistical significant results after Bonferroni correction).

Table 4: Difference in retinal structural markers in individuals with type 2 diabetes with and without mild cognitive impairment (MCI).

Superficial capillary plexus	n	MCI yes	MCI no	P-value crude model	P-value adjusted model
FAZ area (mm^2)	245	0.34 (0.28-0.41)	0.40 (0.32-0.49)	0.262	0.273
Vascular Density					
Circle	245	0.66 (0.63-0.69)	0.66 (0.64-0.68)	0.966	0.783
Core	245	0.34 (0.30-0.37)	0.31 (0.29-0.33)	0.295	0.261
Superior sector	245	0.71 (0.68-0.75)	0.71 (0.69-0.73)	0.982	0.849
Right sector	245	0.70 (0.66-0.75)	0.70 (0.67-0.72)	0.864	0.816
Inferior sector	245	0.65 (0.61-0.68)	0.65 (0.62-0.67)	0.867	0.987
Left sector	245	0.69 (0.65-0.72)	0.68 (0.66-0.71)	0.884	0.921
Non-perfusion area (mm^2)					
Circle	245	4.34 (3.95-4.73)	4.40 (4.19-4.61)	0.988	0.777
Core	245	0.52 (0.49-0.55)	0.54 (0.52-0.56)	0.301	0.265
Superior sector	245	0.86 (0.74-0.97)	0.87 (0.80-0.94)	0.951	0.867
Right sector	245	0.90 (0.76-1.04)	0.92 (0.84-0.99)	0.909	0.811
Inferior sector	245	1.00 (0.89-1.11)	1.03 (0.95-1.11)	0.980	0.732
Left sector	245	1.04 (0.93-1.15)	1.03 (0.95-1.11)	0.708	0.914
Fractal dimension	245	1.68 (1.67-1.68)	1.67 (1.67-1.68)	0.818	0.567
Deep capillary plexus					
FAZ area (mm^2)	245	0.60 (0.50-0.70)	0.61 (0.55-0.66)	0.886	0.895
Vascular Density					
Circle	245	0.49 (0.48-0.51)	0.49 (0.48-0.50)	0.780	0.703
Core	245	0.21 (0.17-0.25)	0.19 (0.17-0.21)	0.265	0.360
Superior sector	245	0.54 (0.52-0.57)	0.54 (0.53-0.56)	0.705	0.928
Right sector	245	0.50 (0.47-0.53)	0.50 (0.49-0.51)	0.969	0.982
Inferior sector	245	0.48 (0.46-0.51)	0.48 (0.46-0.49)	0.746	0.750
Left sector	245	0.51 (0.49-0.53)	0.50 (0.49-0.51)	0.581	0.568
Non-perfusion area (mm^2)					

Circle	245	7.62 (7.33-7.91)	7.80 (7.66-7.95)	0.334	0.291
Core	245	0.62 (0.59-0.65)	0.64 (0.62-0.65)	0.265	0.360
Superior sector	245	1.69 (1.60-1.77)	1.69 (1.64-1.73)	0.853	0.979
Right sector	245	1.67 (1.56-1.79)	1.77 (1.71-1.83)	0.156	0.139
Inferior sector	245	1.77 (1.67-1.87)	1.82 (1.76-1.89)	0.491	0.365
Left sector	245	1.84 (1.75-1.93)	1.85 (1.80-1.90)	0.857	0.844
Fractal dimension	245	1.71 (1.71-1.72)	1.71 (1.71-1.71)	0.846	0.571

Main analysis adjusted for sex, age, mean arterial pressure and present diabetic retinopathy. n: number of eyes included in the analysis. DR: Diabetic retinopathy. P-values still statistical significant after Bonferroni correction are annotated with a * (no statistical significant results after Bonferroni correction).

Table 5 – Difference in retinal vascular oximetry in individuals with type 2 diabetic with and without mild cognitive impairment (MCI).

	n	MCI yes	MCI no	P-value crude model	P-value adjusted model
Mean retinal arterial saturation (%):	243	89.92 (88.34-91.51)	91.43 (90.30-92.56)	0.470	0.144
DR yes	166	90.96 (89.57-92.34	92.46 (90.94-93.98)	0.397	0.165
DR no	77	88.10 (84.00-92.19)	89.30 (88.00-90.53)	0.676	0.594
Mean retinal venular saturation (%):	243	53.40 (50.31-56.48)	56.17 (54.47-57.86)	0.429	0.132
DR yes	166	55.60 (52.71-58.48)	57.43 (55.23-59.64)	0.567	0.326
DR no	77	50.66 (43.25-58.07)	52.87 (50.69-55.06)	0.837	0.579
Arterial saturation quadrant analysis (%):					
Upper nasal	242	93.20 (91.20-95.19)	94.71 (93.55-95.86)	0.547	0.207
DR yes	165	94.86 (92.92-96.80)	95.63 (94.16-97.09)	0.832	0.541
DR no	77	89.74 (85.50-93.98)	92.80 (91.14-94.45)	0.215	0.192
Lower nasal	237	91.68 (89.53-93.82)	94.40 (91.53-97.28)	0.252	0.179
DR yes		No interaction	No interaction		
DR no		No interaction	No interaction		
Upper temporal	243	89.75 (86.84-90.90)	89.75 (88.47-91.02)	0.963	0.488
DR yes	166	90.03 (88.10-91.96)	90.72 (89.07-92.37)	0.933	0.601
DR no	77	87.71 (82.67-92.75)	87.67 (85.81-89.52)	0.934	0.988
Lower temporal	239	85.93 (84.11-87.75)	87.08 (85.67-88.49)	0.709	0.327
DR yes	162	86.70 (84.44-88.96)	88.00 (86.33-89.67)	0.531	0.363
DR no	77	84.30 (80.03-88.58)	84.92 (82.65-87.19)	0.863	0.802
Venular saturation quadrant analysis (%):					
Upper nasal	241	56.40 (52.94-59.87)	60.93 (59.06-62.80)	0.131	**0.028**
DR yes	164	58.83 (55.37-62.30)	62.38 (59.99-64.78)	0.165	0.100
DR no	77	52.57 (45.18-60.00)	57.61 (55.34-59.96)	0.465	0.203
Lower nasal	241	56.53 (52.66-60.41)	56.63 (54.56-58.70)	0.776	0.967
DR yes		No interaction	No interaction		
DR no		No interaction	No interaction		
Upper temporal	242	52.76 (49.56-55.96)	56.19 (54.16-58.230)	0.409	0.083
DR yes	165	55.01 (52.05-57.96)	58.14 (55.60-60.67)	0.358	0.117
DR no	77	48.95 (41.37-56.54)	51.87 (48.89-54.85)	0.656	0.491
Lower temporal	238	47.49 (43.34-51.65)	51.05 (48.60-53.49)	0.430	0.153
DR yes	163	50.15 (45.75-54.54)	52.72 (49.78-55.67)	0.412	0.341
DR no	75	45.07 (36.05-54.10)	46.57 (42.72-50.42)	0.979	0.769

Main analysis adjusted for sex, age, mean arterial pressure and present diabetic retinopathy. In case of interaction, individuals were stratified in groups with and without diabetic retinopathy. N: number of eyes included in the analysis. DR: Diabetic retinopathy. P-values still statistical significant after Bonferroni correction are annotated with a * (no statistical significant results after Bonferroni correction).

Figure legends:

Figure 1: Flowchart of individuals included in the study.

Figure 2: Boxplot of domain scores in persons with type 2 diabetes with and without mild cognitive impairment.