Changes in inner retina thickness and macular sensitivity in diabetic 2 patients with moderate diabetic retinopathy

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Abstract

To analyze total retinal (RT) and inner retinal layers (IRL) thicknesses in type 2 diabetes mellitus (DM2) patients and retinal sensitivity, using swept source OCT (SS-OCT), and microperimetry.

A total of 54 DM2 subjects with moderate diabetic retinopathy (DR) with no signs of diabetic macular edema (DME) and 73 age-matched healthy individuals were assessed by SS-OCT to quantify retinal thickness in the nine macular areas of the ETDRS grid. Retinal sensitivity was measured by microperimetry with MAIA.

Mean ages were 64.06 ± 11.98 for the DM2 group and 60.79 ± 8.62 years for the control group. DM2 patients presented lower visual acuity (p < 0.001) and thicker RT (260.70 ± 19.22µm in the control group vs. 271.90 ± 37.61 µm in the DM2 group, p = 0.01). Retinal nerve fiber layer (RNFL) was significantly lower in the outer nasal area (50.38 ± 8.20µm vs 45.17 ± 11.25µm, p = 0.005) as ganglion cells and inner plexiform layers (GCL+) in DM2. A positive correlation between LDL-C and RNFL and a negative correlation between HDL-C levels and inner temporal and central RNFL thickness were detected. The central and inner nasal areas presented a negative correlation between RNFL (p = 0.015) and MAIA (p = 0.008), while the outer inferior area showed a positive correlation (p = 0.025).

Retinal sensitivity and macular RNFL thickness decrease in DM2 with moderate DR with no DME.

Introduction

Diabetic retinopathy (DR) prevalence is growing worldwide, and it is estimated to increase to 51% by 2045 (1). This makes it critical to investigate and determinate biomarkers to assess disease development and therefore improve its management and stop its progression.

DR is a microvasculopathy that induces changes in the inner retina, as well as ischemia, and increases the blood–retina barrier permeability. Not only vascular changes but also diabetic neurodegeneration (DN) take place early in the disease, firstly affecting the retinal ganglion cell bodies and their dendrites, which can be detected as diffuse thinning of the ganglion cell layer (GCL) and inner plexiform layer (IPL). Axons may undergo apoptosis, triggering thinning of the retinal nerve fiber layer (RNFL) (2). The ganglion cell complex (GCC), formed by the ganglion cell layer (GCL), the IPL and the RNFL, may also show a thickness reduction. These variations have been described as inner retinal layer (IRL) thickness changes in the absence of any DR modifications prior to the appearance of diabetic vascular signs detectable on fundus examination by an ophthalmologist (2).

The structural changes in DR can be quantitatively analyzed by new imaging techniques, mainly by high-speed noninvasive optical coherence tomography (OCT), allowing us to evaluate thickness and volume of the different retinal layers and the choroid. This method is more objective and accurate than ophthalmoscopy for identifying early structural alterations in diabetic retina. DN and RNFL loss in turn cause other modifications in several diagnostic tests, including electroretinogram (3), contrast sensitivity,
dark adaptation, and microperimetry alterations (4), which should be detected prior to the appearance of the first manifestations of DR.

The purpose of this study was to measure macular changes in the IRL thicknesses studied by SS-OCT in type 2 diabetes mellitus (DM2) patients with moderate DR and without diabetic macular edema (DME) compared to a healthy group and to correlate it with retinal function evaluated by microperimetry.

Methods

Study design

A total of 127 eyes, from 54 eyes of DM2 patients and 73 eyes of healthy subjects were included in our study. All of them were evaluated at the outpatient clinic of the Ophthalmology Department at the Lozano Blesa University Hospital in Zaragoza, Spain. The DM2 patients, which constituted group 1, had a level 43 on the Early Treatment Diabetic Retinopathy Study (ETDRS) classification (5), which corresponds to moderate DR, and without DME. Group 2 was formed by the healthy subjects with no previous history of ocular or systemic diseases. The study was approved by the local Ethics Committee (Clinical Research Ethics Committee of Aragon - CEICA PI19/252) and adhered to the tenets of the Helsinki Declaration. Each subject signed the informed consent.

Exclusion criteria for both groups were amblyopia or best corrected visual acuity (BCVA) lower than 20/40, spherical equivalent (SE) above +/- 5.50 diopters (D) or 3.00 D of astigmatism, intraocular pressure (IOP) over 20 mmHg or findings that suggested glaucoma, other macular diseases with macular impairment, impossibility to collect good quality OCT profile. Patients with uncontrolled arterial hypertension were also excluded.

Study protocol

All subjects underwent a complete ophthalmological exam, which includes BCVA. For statistical purposes, BCVA was recorded with the 100% contrast ETDRS test as the logarithm of the minimum resolution angle (logMAR) measured, axial length (AL) was calculated using Aladdin KR-1 W Series optical biometry system (Topcon Corporation, Tokyo, Japan) as the average of 5 measurements and expressed in mm and IOP measured by Goldmann tonometry. Eye fundus was examined by Clarus (Clarus 700®, Carl Zeiss Meditec AG, Jena, Germany) images.

Endocrinological data was collected from DM2 patients, including number of years since diagnosis, glycemic control measured by glycosylated hemoglobin, lipid profile, renal function parameters, and medication.

All the OCT were acquired by the same explorer (ABM) using the DRI-Triton SS OCT (Deep range imaging) (Topcon Corporation, Tokyo, Japan). The software version was the IMAGEnet 6 Version 1.22.1.14101®. Images whose quality scale (0 to 100) were lower than 60 were excluded. The different retinal layer and RT thicknesses values were expressed in micrometers (µm) in the different sectors of the ETDRD grid with
the 3D Macula protocol (Fig. 1): the central (C) area as a circle of 1 mm in diameter, surrounded by the parafoveal or inner ring which is 3 mm in diameter. This area was divided into 4 quadrants: inner superior (IS), inner temporal (IT), inner nasal (IN) and inner inferior (II)). The outer or perifoveal had a diameter of 6 mm and was divided into 4 quadrants: outer superior (OS), outer temporal (OT), outer nasal (ON), and outer inferior (OI).

To evaluate retinal sensitivity, the third-generation microperimetry (Macular Integrity Assessment Device [MAIA]; Topcon Corporation, Tokyo, Japan) was used for a complete evaluation with a 4 − 2 complete threshold strategy. To compare MAIA and OCT thickness results the sensitivity points generated by the microperimetry were divided in sectors. For an emmetropic eye, the MAIA 1° is equivalent to a circle with a diameter of 0.6 mm, 3° to a circle with a 1.8 mm diameter, and the MAIA 5° to a circle with a 3 mm diameter. In the central ETDRS ring we included the center point and the 1° sensitivity points (0.6 mm diameter). In the 3 mm ETDRS ring the 3° and 5° sensitivity points were located (diameters of 1.8 and 3 mm, respectively) the 3 mm circle of the ETDRS grid (6). Therefore, the average of the retinal sensitivity thresholds calculated for the 1° MAIA correspond to the central ETDRS circle, and the thresholds of the 3° and 5° circles correspond to the ETDRS inner or parafoveal ring (mean of 6 sensitivity points/quadrant; Fig. 2). Fixation was inspected manually.

The data was collected and exported to an Excel database (Microsoft Corporation, Redmond, WA, USA).

**Statistical analysis**

For the statistical analysis, we used the Statistical Package for the Social Sciences software (SPSS version 20, SPSS Inc., IBM Corporation, Armonk, NY, USA). First, we performed a descriptive cross-sectional analysis of the sample with demographic variables and clinical characteristics. Data normality was analyzed with the Kolmogorov–Smirnov test. Since most of the parameters had not a normal distribution, differences between groups were analyzed with the Mann–Whitney U test for independent samples. The Spearman's rank correlation coefficient test was conducted for bivariate analysis in the correlation of the anatomical outcomes. A value of p < 0.05 indicated statistical significance for all the analyses.

**Results**

**Demographics**

The mean age of the DM2 group was 64.06 ± 11.98 years (42–86 years) and for the control group it was 60.79 ± 8.62 years (42–83 years), with no differences between groups (p = 0.082) being found. Regarding sex distribution, 20.4% and 39.7% were females and 79.6% and 60.3% were males in the DM2 and control groups, respectively. The mean time since DM2 diagnosis was 2.50 ± 2.88 years (0–11 years). The patients had an adequate metabolic control of their disease, with the mean HbA1c being 7.58 ± 1.29%. Table 1 presents glycemic, lipid and renal function values.
BCVA reached significantly lower levels in the DM2 group ($p = 0.001$). No differences were found between groups in either AL ($p = 0.075$), SE ($p = 0.110$) or IOP ($p = 0.676$). Values are presented in Table 1.

### Table 1
Mean, standard deviation (SD) and statistical significance ($p$ value) of demographics, best corrected visual acuity (BCVA) in the LogMAR scale, spherical equivalent (SE) in diopters (D), axial length (AL) in mm and intraocular pressure (IOP) in mmHg between the control and type 2 diabetes mellitus (DM2) groups; and metabolic characteristics of type 2 diabetic (DM2) patients related to the duration and metabolic control of the disease. Abbreviations: HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride levels; GF, glomerular filtration; SD, standard deviation. HbA1c values are expressed in a percent, cholesterol, TG and creatine values in mg/dL and GF in mL/min. Differences that reached statistical significance ($p < 0.05$) are shown in red and bold.

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th></th>
<th>DM2 Group</th>
<th></th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.06</td>
<td>11.98</td>
<td>60.79</td>
<td>8.62</td>
<td>0.082</td>
<td></td>
</tr>
<tr>
<td>Sex (female-male %)</td>
<td>20.4–79.6</td>
<td></td>
<td>39.7–60.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from diagnosis (years)</td>
<td>2.50</td>
<td>2.88</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.58</td>
<td>1.29</td>
<td>12.89</td>
<td>1.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCVA (LogMAR)</td>
<td>0.04</td>
<td>0.05</td>
<td>0.12</td>
<td>0.17</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>SE (D)</td>
<td>0.03</td>
<td>1.58</td>
<td>0.37</td>
<td>1.70</td>
<td>0.110</td>
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<tr>
<td>AL (mm)</td>
<td>23.73</td>
<td>1.46</td>
<td>23.23</td>
<td>0.84</td>
<td>0.080</td>
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<tr>
<td>IOP (mmHg)</td>
<td>15.30</td>
<td>2.89</td>
<td>14.76</td>
<td>2.49</td>
<td>0.676</td>
<td></td>
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<tr>
<td>Disease progression time (years)</td>
<td>2.50</td>
<td>2.88</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.58</td>
<td>1.29</td>
<td>12.89</td>
<td>1.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>148.04</td>
<td>33.18</td>
<td>151.18</td>
<td>33.18</td>
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<td></td>
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<tr>
<td>HDL (mg/dL)</td>
<td>47.83</td>
<td>15.21</td>
<td>52.14</td>
<td>15.21</td>
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<td></td>
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<tr>
<td>LDL (mg/dL)</td>
<td>71.47</td>
<td>23.09</td>
<td>80.71</td>
<td>23.09</td>
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<td></td>
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<tr>
<td>TG (mg/dL)</td>
<td>122.24</td>
<td>51.71</td>
<td>135.71</td>
<td>51.71</td>
<td></td>
<td></td>
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<tr>
<td>GF (mL/min)</td>
<td>73.57</td>
<td>20.52</td>
<td>85.23</td>
<td>20.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatine (mg/dL)</td>
<td>1.05</td>
<td>0.49</td>
<td>1.05</td>
<td>0.49</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**OCT: total retina and IRL thickness assessment:**
We found statistically significant differences in the OT area, with a higher thickness value and higher standard deviation (SD) in the DM2 group (260.70 ± 19.22 µm in the healthy subjects vs. 271.90 ± 37.61 µm in the DM2 group, with p = 0.010). Additionally, significant differences were found in the ON area between the DM2 group and the control group for the RNFL in IS, IT and in the IN quadrant when analyzing the GCL + protocol (GCL + IPL), as shown in Fig. 2. The GCL + protocol (ILM - IPL/INL [GCC], which corresponds to the GCL + plus the RNFL thickness) revealed a statistically significant diminished GCC thickness for the DM2 group when compared to the healthy group (Fig. 2). The diminution affected the horizontal quadrants except the IN and IS areas.

**MAIA Retinal sensitivity assessment:**

MAIA microperimetry obtained significantly higher retinal sensitivities in the control group with differences in macular integrity (77.82 ± 28.04 vs 64.84 ± 30.02; p = 0.005) and total mean threshold (24.45 ± 3.63 vs 26.69 ± 2.26; p < 0.001) as represented in Table 2.

**Table 2**

<table>
<thead>
<tr>
<th>Retinal sensitivity (dB)</th>
<th>Control</th>
<th>DM</th>
<th>Control vs DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular integrity</td>
<td>64.84 ± 30.02</td>
<td>77.82 ± 28.04</td>
<td>0.005</td>
</tr>
<tr>
<td>Average threshold</td>
<td>26.69 ± 2.26</td>
<td>24.45 ± 3.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fixation stability P1</td>
<td>88.25 ± 13.03</td>
<td>77.96 ± 26.02</td>
<td>0.162</td>
</tr>
<tr>
<td>Fixation stability P2</td>
<td>96.78 ± 4.71</td>
<td>89.26 ± 17.31</td>
<td>0.016</td>
</tr>
<tr>
<td>BCEA 63 area</td>
<td>1.82 ± 1.93</td>
<td>4.33 ± 6.65</td>
<td>0.121</td>
</tr>
<tr>
<td>BCEA 63 angle</td>
<td>2.39 ± 62.12</td>
<td>9.20 ± 50.55</td>
<td>0.637</td>
</tr>
<tr>
<td>BCEA 95 area</td>
<td>45.35 ± 5.79</td>
<td>12.84 ± 20.03</td>
<td>0.142</td>
</tr>
<tr>
<td>BCEA 95 angle</td>
<td>2.39 ± 6.11</td>
<td>4.64 ± 50.25</td>
<td>0.956</td>
</tr>
<tr>
<td>Fixation loses (%)</td>
<td>4.20 ± 10.71</td>
<td>7.34 ± 17.99</td>
<td>0.432</td>
</tr>
</tbody>
</table>

**Structural and functional correlations:**
Correlations between OCT findings (RT and RNFL thickness) and other parameters including age, years of DM evolution and glycaemic control were studied using the Spearman's rank correlation coefficient test. Significant negative correlations were found between RT and age in the outer ETDRS ring areas (p < 0.05). The same trend was obtained between the GCL + protocol and age (p < 0.05) and between almost all the outer rings from the GCL + + protocol and age (p < 0.05), as shown in Fig. 3. Additionally, central ring for total RT and age expressed a positive significant correlation (R = 0.327; p = 0.018). No significant correlations were observed between RNFL thickness and MAIA sensitivity with age, disease evolution or HbA1c levels, as indicated in Fig. 3.

MAIA sensitivities and RNFL thickness in the C and IN areas were negatively correlated (r=-0.324, p = 0.021; and r=-0.443, p = 0.001, respectively) but no significant correlation was found between MAIA sensitivities and GCL + thickness in any of the analyzed sectors in the DM2 group, as represented in Fig. 4. In addition, positive significant correlations between MAIA sensitivities and GCL + + thickness in the OI and ON areas were detected (r = 0.339, p = 0.015; and r = 0.316, p = 0.025, respectively).

**RNFL and GCL thicknesses correlations:**

Correlations between RNFL and GCL thicknesses and metabolic characteristics of DM2 patients were evaluated. There were different significant correlations, as shown in [Suppl. Tables 1, 2 and 3].

**Conclusions**

Our results suggested structural and functional changes in patients with moderate DR without DME. Even though early changes in preclinical DR are still to be determined, numerous studies have demonstrated early neurodegeneration prior to DR manifestations, with an impairment of the neurovascular unit, including neurons, glia and vasculature (7), and structural and functional changes (8). The neurodegeneration will progress as soon as the vascular lesions appear with a higher impairment of the retinal neurons.

The inner retina is more susceptible to metabolic stress because of its higher metabolic demand and relatively lower blood perfusion. Chronic hyperglycemia is thought to affect retinal ganglion cells, triggering their function and leading to their impairment and death, with consequent GC-IPL and RNFL thickness loss (9). The retinal neural cell apoptosis could be related to neurofilament accumulation in RNFL, secondary to changes in retrograde axonal transport, a rise in the extracellular glutamate levels due to the impairment of the Müller cells, with toxicity over the neurons, an increase in neurotoxic factors (10), and reactive changes in microglia (8). Moreover, the production of erythropoietin and inflammatory mediators associated with increased vascular endothelial growth factor may cause vascular damage and impair the ability to regulate local blood flow (10, 11).

We found total RT thinning at the parafoveal ring with a reduction in both GCL and IPL thickness, as has been demonstrated by previous studies (9, 10), suggesting that ganglion cells are one of the most susceptibles to the neurodegenerative and vascular effects in the DM patients. In the same way as has
already been demonstrated in several neurodegenerative diseases, such as glaucoma, multiple sclerosis, Parkinson’s disease or Alzheimer’s disease, neurodegeneration was expressed by macular RNFL thinning. Specifically, we found significant differences located in the ON quadrant compared to healthy controls, similar to other researchers, such as Carpineto et al. (13) or Jia et al. (14). There are few previous studies evaluating macular RNFL thinning, focusing on the peripapillary RNFL (pRNFL) thickness, with variability in the results and the affected quadrants (13–17). These discrepancies may be explained by differences in age, glycemic status, DR severity, DM duration and comorbidities of the studied populations, in addition to using different imaging modalities and programs to measure pRNFL.

GCL and the RNFL were positively correlated in the central area with age in the DM2 group, with a significant negative correlation with all the perifoveal ETDRS areas. Although the GCL + and GCL ++ presented a significant negative correlation in the outer ring (OS, OT, OI and ON), there was no significant correlation between the RNFL and age, which may support ganglion cell loss before the RNFL is affected. Rasheed et al. described an association between DR and diabetic neuropathy. Patients with neuropathy showed significant thinning in the GC-IPL earlier than in the pRNFL. Srinivasan et al. suggested that ganglion cell loss is a predictor of diabetic peripheral neuropathy (16).

RNFL thickness deterioration was not detected with DR progression, diabetes progression time or glycemic variability in this study. Contrary to our results, other researchers, such as Shi et al. (18) and Dashmana et al. (17), demonstrated that thinning of the RNFL in the superior quadrant had a significant correlation with diabetes duration, suggesting that the thinning of this sector could be the primary structural change in DR. Carpineto et al. (13) described that both the average (r = −0.236, p = 0.033) and inferior quadrants (r = −0.216, p = 0.049) of RNFL thickness had a negative correlation with HbA1c.

We also analyzed systemic risk factors (including serum lipid levels, blood pressure, and glucose levels) to determine their involvement in diabetic retinal changes. We excluded patients with bad control of their arterial blood pressure trying to avoid confusing factors. Our results revealed a significant positive correlation between LDL-C and RNFL (r = 0.285, p = 0.037) and a significant negative correlation between HDL-C levels and IT (r=-0.362, p = 0.007) and C global RNFL thickness (r=-0.292, p = 0.032). Similar results were detected when evaluating C global GCL + and GCL++ (r=-0.379, p = 0.007; and r=-0.383, p = 0.005, respectively). Other researchers had already found negative correlations between RNFL thinning and HDL, such as Shi et al., who determined a correlation with temporal pRNFL thickness (r = −0.223, p = 0.042) (18). Cholesterol is an important component of myelin and regulates membrane fluidity and signaling proteins. An increase in total cholesterol (TC) and LDL has been related to adverse effects on the RNFL (19). Additionally, HDL cholesterol has been associated with a thinning of the RNFL in multiple sclerosis (r=-0.15, p = 0.008). This discordance has been postulated to be related to blood–brain barrier breakdown and the extravasation of immune cells through the vascular endothelium in other neurodegenerative diseases (20). The involvement of the HDL pathway in visual dysfunction has been determined in age-related macular degeneration and supports the plausibility of the associations we have identified (21).
We also found that triglycerides (TGs) presented positive correlations with GCL + thickness in the OS, II and IS areas ($r = 0.296, p = 0.037$; $r = 0.307, p = 0.030$; and $r = 0.296, p = 0.037$, respectively), which to our knowledge has not been determined previously in the literature. In the same way, previous studies have described a positive correlation between TG levels and INL thickness in DM1 subjects ($r = 0.48, p = 0.011$) (22). This may differ from Shi et al. results, which revealed a negative correlation between RNFL thickness in the inferior quadrant and TG ($r = -0.232, p = 0.035$) (18). These findings may promote future lines of work to determine the role of serum lipids in retinal neurodegeneration prevention.

Contrary to our expectations, creatinine levels were positively correlated with the central area of the RNFL and the GCL + and GCL ++ thicknesses ($r = 0.452, p = 0.001$; $r = 0.475, p < 0.001$; and $r = 0.448, r = 0.001$, respectively) and negatively associated with filtrate rate (FR) deterioration ($r = -0.465, p < 0.001$; $p = -0.371, p = 0.08$; and $r = 0.383, p = 0.008$, respectively). Previous works have described retinal thinning as a biomarker of renal impairment in diabetic patients ($p = 0.009$) (23). Srivastav et al. found positive correlations between RNFL thinning and increases in serum urea and creatinine levels in patients with different DR stages (24).

Regarding the relationship between structural and functional findings, we correlated macular ETDRS grid areas with the corresponding microperimetry points. We did not contemplate GC displacement from their receptive, as evidence is not strong enough due to great variability between subjects (25, 26). Despite decreased retinal sensitivity could be reflected by the significantly worse BCVS, correlations support our results. We determined negative correlations between the RNFL in the IN and in the C areas with retinal sensitivity measured by MAIA, not presented when evaluating the GCL+, similar to Orduna et al. (27). Clinical diabetes may critically affect patients’ vision, even producing permanent visual acuity loss. The diagnosis and follow up of these patients requires adequate functional tests and microperimetry obtains an exact fundus-related quantification of retinal sensitivity (28). There is substantial evidence of reduced microperimetric sensitivity in diabetic patients either with or without DR compared to healthy nondiabetic subjects, evaluated by different microperimetry equipment, including Optos OCT/SLO/microperimeter (29), MP1/Nidek Technologies (17), MP-3/Nidek (30) or, as in our study, Macular Integrity Assessment Device [MAIA]. Contrary to our results, no significant correlation between retinal sensitivity and retinal thickness was found by previous researchers such as Chai et al. (8) or Rohrschneider et al. (4).

In conclusion, our results suggest that the structure (total retinal, GC-IPL and RNFL thicknesses) and function (retinal sensitivity) of the retina display some changes in moderate diabetic patients. The diagnosis of RNFL thinning in DM patients without DR prior to the appearance of other DR signs would enable an accurate approach to this disease with personalized assessment based on the DR course or stage. Future studies require a larger sample size which would include patients in different stages of the disease and both DM1 and DM2. Although systemic risk factors are expected to be involved in retinal neurodegeneration in DM2 patients, the role of these factors remains largely unknown.

Declarations
ACKNOWLEDGMENTS

Authors’ contributions

F-E.G., S-C.AI. and D-B.MD. analyzed and interpreted the patient data regarding ophthalmic disease. B-M.A., B-A.S., S-P.M. and D-B.MD. performed the ocular examination of the eye. B-M.A., P.I. and O-H.E. were a major contributor in writing the manuscript. A.J. and P.I. have a substantial contribution in the draft and revision of the work. All authors read and approved the final manuscript.

Guarantor Statement

B-M.A. 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.

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Conflicts of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

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References


**Figures**

![Figure 1](image-url)
A/ Grid of macular sectors for the DRI-Triton Swept-Source OCT (SS-OCT) for the 9 areas of the ETDRS grid in a right eye (OS, Outer Superior; OT, Outer Temporal; OI, Outer Inferior; ON, Outer Nasal; IS, Inner Superior; IT, Inner Temporal; II, Inner Inferior, IN: Inner Nasal; C, Central). B/ Mean retinal sensitivity in dB measured by the MAIA microperimeter and correlated with 9 areas of the ETDRS grid. C/ DRI-Triton (SS)-OCT profile showing the protocols used in the study: Total retina (from the internal limiting membrane (ILM) to the boundary between the retinal pigment epithelium [RPE] and the photoreceptor layer [OS/RPE limit]), GCL+ protocol (from the internal boundary of the ganglion cell layer [GCL; line RNFL/GCL] up to the external limit of the IPL [the IPL/INL line]), and GCL++ protocol (from ILM to the IPL/INL line [GCC]).
Figure 2

Mean±standard deviation (SD) of total retina, retinal nerve fiber layer (RNFL), GCL+ protocol (GC-IPL) and GCL++ protocol (ILM - IPL/INL [GCC]) thicknesses measured using DRI-Triton SS-OCT and mean retinal sensitivity in dB measured by the MAIA microperimeter in patients with type 2 diabetes mellitus (DM2) and in healthy controls and their comparison (p-value) in the 9 areas of the early treatment diabetic retinopathy study (ETDRS) grid (OS, Outer Superior; OT, Outer Temporal; OI, Outer Inferior; ON, Outer Nasal;
IS, Inner Superior; IT, Inner Temporal; II, Inner Inferior; IN: Inner Nasal; C, Central), where temporal quadrants are represented left and nasal quadrants are represented right. Statistically significant differences (p<0.05) are marked in bold with a grey background.
Correlation coefficients and statistical significance (p-value) of retinal, retinal nerve fiber layer (RNFL), GCL+ (GC-IPL), GCL++ protocol (ILM - IPL/INL [GCC]) thickness and mean retinal sensitivity in dB measured by the MAIA microperimeter represented in the nine areas of the early treatment diabetic retinopathy study (ETDRS) grid (OS, Outer Superior; OT, Outer Temporal; OI, Outer Inferior; ON, Outer Nasal; IS, Inner Superior; IT, Inner Temporal; II, Inner Inferior, IN: Inner Nasal; C, Central; and where temporal quadrants are represented left and nasal quadrants are represented right) with age, time of DM evolution and glycosylated hemoglobin (HbA1c) levels (%) in DM2 patients. The values that reached statistical significance (p<0.05) are shown in bold with a grey background.

Figure 4

Correlation coefficients and statistical significance (p-value) between MAIA retinal sensitivity and retinal nerve fiber layer (RNFL), GCL+ (GC-IPL) and GCL++ protocol (ILM - IPL/INL [GCC]) in DM2 patients in the nine areas of the early treatment diabetic retinopathy study (ETDRS) grid (OS, Outer Superior; OT, Outer Temporal; OI, Outer Inferior; ON, Outer Nasal; IS, Inner Superior; IT, Inner Temporal; II, Inner Inferior, IN: Inner Nasal; C, Central; and where temporal quadrants are represented left and nasal quadrants are represented right). The values that reached statistical significance (p<0.05) are shown in bold with a grey background.

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