FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

SÉRGIO PESTANA DOMINGOS

Functional Characterization of Eyes with Diabetic Macular Edema, submitted to intravitreal anti-VEGF treatment

ARTIGO CIENTÍFICO

ÁREA CIENTÍFICA DE OFTALMOLOGIA

Trabalho realizado sob a orientação de:

PROFESSOR DOUTOR JOÃO FIGUEIRA

DR. MIGUEL RAIMUNDO

ABRIL/2018

Faculdade de Medicina da Universidade de Coimbra
Mestrado Integrado em Medicina – Trabalho Final

Functional Characterization of Eyes with Diabetic Macular Edema, submitted to intravitreal anti-VEGF treatment

Artigo Científico

Área Científica de Oftalmologia

Sérgio Pestana Domingos
sergiopestana_1@hotmail.com

Trabalho realizado sob a orientação de:
Professor Doutor João Figueira
Dr. Miguel Raimundo

Abril/2018

Table of Contents

1. List of abbreviations 2

2. Abstract / keywords 3

3. Introduction 5

4. Methods 8

4.1. Study design

4.2. Study procedures

4.3. Optical Coherence Tomography Acquisition and Grading

4.4. Microperimetry retinal sensitivity Acquisition and Grading

4.5. Data analysis

5. Results 11

5.1. Demographic characterization

5.2. Treatment response groups according to BCVA after anti-VEGF injections

5.3. Retina sensitivity differences between control subjects and DME patients at Baseline

5.4. Retina sensitivity (microperimetry) before and after anti-VEGF

5.5. Correlations with BCVA

5.6. Correlations with OCT

6. Discussion 17

7. Conclusion 19

8. Acknowlegments 20

9. References 21

1. List of abbreviations

BCVA – Best corrected visual acuity

BRB – Blood-retinal barrier

CFP – Colour fundus photography

CRT – Central retinal thickness

DM – Diabetes mellitus

DME – Diabetic macular edema

DR – Diabetic retinopathy

ETDRS – Early treatment diabetic retinopathy study

OCT – Optical coherence tomography

IVT – Intravitreal

MD – Mean deviation

MP – Microperimetry

MS – Mean sensitivity

NPDR – Non-proliferative diabetic retinopathy

PDR – Proliferative diabetic retinopathy

PRN – *Pro re nata*

VEGF – Vascular endothelial growth factor

2.Abstract / Keywords

Purpose –Most clinical trials in diabetic macular edema (DME) use visual acuity as a primary functional endpoint. However, visual acuity is a fovea-biased retinal function test and fails to evaluate functional improvement in the remaining macular retina, which might impact vision-related quality of life. In this study, we propose to evaluate microperimetry as a functional marker in eyes with DME undergoing ranibizumab treatment.

Design – A prospective, exploratory, and observational study.

Methods – Treatment-naïve DME patients underwent a loading dose of 3 monthly injections of ranibizumab, followed by a pro re nata treatment protocol. At baseline and at specific timepoints (3 months, 6 months and 12 months), every subject was evaluated with best corrected visual acuity (BCVA), optical coherence tomography (OCT) and microperimetry (MP). MP sensitivity was measured and averaged in 3 rings. Follow-up was maintained for 12 months after the first injection.

A control group composed of 20 age-matched diabetic patients without DME was recruited. Group comparisons (DME vs control) and paired comparisons (at baseline and after treatment) were conducted, by BCVA response (poor responders – decrease/increase < 5 ETDRS letters; moderate responders - increase ≥5 and <10 letters; good responders – increase >10 ETDRS letters).

Results – 27 eyes with DME from 27 patients were enrolled. MP sensitivity in all 3 rings was lower in DME vs diabetic controls (p<0,001). After a 3-injection course of ranibizumab, an improvement of mean sensitivity in all rings was noticed in DME group, being overall statistically significant (9,69±5,52 to 11,18±3,74) (p=0,022). MP mean sensitivity was significantly correlated with BCVA improvements (r=0,54; p=0,026) after loading dose, and inversely correlated with central retina thickness (r=-0,501) (p=0,015).

Conclusions – MP is a functional exam with the ability to characterize baseline central retina dysfunction in DME, demonstrate early functional improvement following treatment with anti-VEGF agents, while also correlating to commonly used functional and structural outcomes. We believe MP might be a clinically useful biomarker of functional improvement in eyes with DME treated with intravitreal antiangiogenics.

Keywords: microperimetry, MP1, diabetic macular edema, DME, diabetes, diabetic retinopathy

3.Introduction

Diabetic retinopathy (DR) and diabetic macular edema (DME) affects blood vessels in the light-sensitive tissue called retina that lines the back of the eye.[1] It is the most common cause of vision loss among people with diabetes and a leading cause of vision impairment and blindness among working-age adults.[2,3]

DR can be classified according to different severity levels in the Early Treatment Diabetic Retinopathy Study (ETDRS) scale. Five stages are recognized, the first being "no apparent retinopathy". As the name implies, there are no diabetic fundus changes. The second stage is "mild non-proliferative retinopathy" (NPDR) and it is characterized by the presence of a few microaneurysms. The third stage is "moderate NPDR" which is characterized by the presence of microaneurysms, intraretinal haemorrhages or venous beading. "Severe NPDR", the fourth stage, is characterized by either severe retinal haemorrhages in the 4 quadrants, or venous beading in at least 2 quadrants, or even moderately severe intraretinal microvascular abnormalities in at least 1 quadrant. The final stage is "proliferative diabetic retinopathy" (PDR). PDR is characterized by neovascularization of the disc, neovascularization of the retina, neovascularization of the iris, neovascularization of the angle, vitreous haemorrhage or tractional retinal detachment.[4]

Advanced stages of DR are characterized by the growth of abnormal retinal blood vessels secondary to ischemia. These blood vessels grow in an attempt to supply oxygenated blood to the hypoxic retina and are promoted by high levels of vascular endothelial grown factors (VEGF) present in diabetic patients. Production of VEGF is also responsible for changes on blood-retinal barrier (BRB), increasing vessels permeability and causing accumulation of fluid within retinal layers. These changes lead to an increase of retinal thickening in the macular area, diabetic macular edema (DME).[1,3]

DME occurs after breakdown of the blood-retinal barrier (BRB) due to leakage from dilated hyperpermeable capillaries and microaneurysms. [1] It is a common complication of the diabetic retinopathy and the main responsible for visual impairment in these patients. [5]
Currently, in the presence of DME, the gold standard treatment is intravitreal injections of anti-VEGF agents, like ranibizumab (Lucentis®), which proved to be superior versus modified Early Treatment Diabetic Retinopathy Study (ETDRS) macular laser therapy on both structural and functional recovery.[2,3]

Anti-VEGF drugs are injected into the vitreous gel to block VEGF, which, as mentioned, stimulates abnormal blood vessels growth and fluid leakage. As such, blocking VEGF can reverse abnormal blood vessel growth and decrease fluid in the retina.[1,3,6] Moreover, anti-VEGF have a favourable overall risk profile, with no proven increase in arterial thromboembolic events and a very small risk of endophthalmitis per injection.[2]

The Diabetic Retinopathy Clinical Research Network protocol I [2] trial showed that approximately 50% of patients in the ranibizumab with deferred laser arm gained 10 letters or more from baseline. The mean change in visual acuity was 3 ETDRS letters in the laser arm compared with 9 letters in the pooled ranibizumab arms. However, with expanded follow-up, the results showed a subgroup that had minimal improvement despite repeated therapy. 29% of patients treated with ranibizumab plus deferred laser gained no more than 4 letters at 2 years.[2,6] Randomized clinical trials to date have used best corrected visual acuity (BCVA) as the primary endpoint, whereas secondary endpoints focused on structural changes as central retinal thickness.[2] Because of their size and purpose, the pivotal trials have not addressed the differences between ranibizumab and macular laser in terms of detailed functional and structural outcomes that include detailed visual function tests; they have done so only in terms

of a foveal dominated visual acuity test and central retinal thickness change on optical coherence tomography (OCT).[2] Tests of generalized retinal function are lacking, failing to evaluate functional improvement in the remaining macular retina, which might impact vision-related quality of life.

Microperimetry is a technique used to obtain quantitative and reliable measurements of retinal sensitivity. It is based on the projection of several stimuli of different intensities in a macular grid of points with direct correlation of fundus changes. With this technology, we are able to evaluate luminous sensitivity in foveal and macular regions. Precise retinal point locations can be evaluated, aided by an eye-tracking system. Microperimetry is thus interesting to follow-up patients submitted to macular treatment.

With all of this in mind, the main objective of this study is to better characterize the functional vision of patients with DME under anti-VEGF treatment and evaluate the effects of this therapy on microperimetry derived parameters. We also aim to test if microperimetry could be a suitable predictor for visual response to treatment. That would entail a better functional characterization of patients with DME before and after treatment, beyond simple central visual acuity.

4.Methods

4.1.Study Design

A sub-analysis of a prospective, exploratory, and observational study conducted at AIBILI and CHUC (NCT01947881-CHARTRES) was performed in diabetic Type 2 patients receiving the same interventional treatment for DME, during a period of 12 months. Adult patients with type 2 diabetes and treatment-naïve centre-involving DME were enrolled, as defined by a central subfield thickness of 300 μm or more in the study eye, evaluated using spectral-domain OCT, and with a BCVA below 79 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. Exclusion criteria were (1) previous anti-VEGF or macular laser treatment (in both eyes), (2) other causes of macular edema (in the study eye), (3) cataract precluding fundus observation, (4) proliferative diabetic retinopathy, either active or treated in the previous 3 months, (5) aphakia, (6) uncontrolled glaucoma, (7) arteriothrombotic event in the previous 6 months, (8) pregnancy and breastfeeding and (9) glycosylated haemoglobin of more than 11.0%. An age-matched control group was also recruited and underwent the same baseline evaluation. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional review board and ethics committee of AIBILI, Coimbra, Portugal. Written informed consent was obtained from all study patients. Patients were treated and followed according to the standard practice for DME treatment with ranibizumab intravitreal (IVT) injections as described in the Summary of Product Characteristics (SmPC): loading dose of three monthly injections followed by a *pro re nata* (PRN, “as needed”) injection regimen.

4.2.Study Procedures

All included patients performed an initial visit (V1-Baseline) with the following procedures: clinical history (medical history, demographics, and concomitant medications); vital signs,

metabolic analysis; biomicroscopy; intraocular pressure with Goldmann tonometry; ophthalmoscopy; BCVA (using the ETDRS scale); SD-OCT (HD-OCT Cirrus, Zeiss Meditec); and microperimetry (MP1 Microperimeter Nidek, Gamagori, Japan).

After baseline visit (V1), all patients were treated with three monthly IVT injections of anti-VEGF ranibizumab for 3 months (loading dose – V2, V3 and V4) and monitored at each visit before injection with BVCA, OCT and MP measurements. One month after the last injection of the loading dose period i.e., 3 months after the first injection (V5 – month 3), BCVA, OCT, CFP and MP1 procedures were repeated, and patients continue to receive injections under a PRN regimen if the central retinal thickness remained ≥ 300um. Patients were monitored monthly with BCVA, and OCT examinations. Best-corrected visual acuity, OCT, CFP and MP were repeated 6 months after the first injection (V6 – month 6) and 12 months after the first injection (V7 – month 12).

4.3. Optical Coherence Tomography Acquisition and Grading

A Macular Cube 512 x 128 scan and 2 macular 5 HD lines (at 180° and 90°) were acquired in all patients using HD-OCT Cirrus 5000 (Zeiss Meditec, Dublin). Central retinal thickness, perifoveal, and parafoveal retinal thicknesses were quantified using Macular Cube maps, automatically given by the equipment.

4.4. Microperimetry retinal sensitivity acquisition and Grading

Microperimetry was performed on all subjects using MP1 Microperimeter (Nidek, Gamagori, Japan). The following standard parameters were used in DME patients: a fixation target consisting of a red cross, white, monochromatic background at 4 asb; stimulus size of Goldman III, with 200 msec projection time; customized radial grid of 45 stimuli covering the central 12º (onto the fovea), 1º apart (inner stimuli) and 2º apart (outer stimuli).

The starting stimulus light attenuation was set at 10 dB. A 4-2 double staircase strategy was used with an automatic eye tracker that compensates for eye movements. Pre-test training was performed and five minute mesopic visual adaptation was allowed before starting the test. All subjects underwent microperimetry with dilated pupils. Mean retinal sensitivity was evaluated at 2º, 4º and 6º of raddi, approximately covering 1 mm, 3 mm and 6 mm of the central retina area on OCT mapping (S1, S2 and S3 ring areas). Overall Mean Sensitivity (MS) and overall mean deviation (MD) were also measured and considered for analysis.

4.5. Data analysis

One month after the loading dose, at visit 5 (V5-month 3), patients were categorized according to their BCVA evolution from baseline and were stratified in three treatment response group: 1) good responders (≥ 10 ETDRS letters gained); 2) moderate responders (> 5 and <10 ETDRS letters gained); 3) poor responders (< 5 ETDRS letters gained or loss of visual acuity).

Morphologic SD-OCT characteristics and microperimetry retinal sensitivity were compared between treatment response groups using an ANOVA test or the Student T test.

The paired student T test was used to compare the average evolution of morphologic SD-OCT characteristics and microperimetry retinal sensitivity before and after treatment.

The Pearson correlation coefficient was determined to evaluate the relationship between morphologic SD-OCT characteristics and microperimetry retinal sensitivity.

Statistical analysis was performed with Stata version 13 (StataCorp LP, College Station, TX).

5.Results

5.1.Demographic characterization

A total of 47 subjects were included, 27 diabetic patients with DME submitted to anti-VEGF treatment from the cohort of the CHARTRES study, and 20 diabetic patients without DR in a control group.

DME patients and controls were not significantly different in terms of age (66,9±5,14 vs 63,15±21,54) (p=0,387) or proportion of females (13, 56,5% vs 10, 43.5%, p=0.058). A statistically significant difference was found in mean BCVA letters, between both groups, with controls having a higher mean BCVA (65,63±7,68 vs 82,60±2,56) (p<0,001).

5.2.Treatment response groups according to BCVA after anti-VEGF injections

According to BCVA changes from baseline to Visit 5 (1 month after 3 monthly injections of ranibizumab), 14 patients (51,85%) were considered good responders (≥ 10 ETDRS letters gained after treatment), 7 patients (25,93%) were considered moderate responders (> 5 and <10 ETDRS letters gained), and 6 patients (22,22%) were considered poor responders (< 5 ETDRS letters gained or loss of visual acuity).

Baseline characteristics (demographics, metabolic factors, diabetes duration, BCVA) for all study population, and by treatment response, are summarized in Table 1.

Treatment response groups are not significantly different in terms of BCVA at baseline, (66,83±8,61 vs 65,00±9,75 and 65,43±6,68) (p=0,356) despite poor responders showed higher mean BCVA letters. All other baseline characteristics were also not significantly different among groups, except Diabetes duration that was higher in the poor responders group (21.92±9.42 months, p=0.032).

Table 1. Baseline characteristics of the study population and according to BCVA response.

	Study Population (n = 27)	Good Responders (n = 14)	Moderate Responders (n = 7)	Poor Responders (n = 6)	p-value
Demographics					
Age, years, mean ± SD	66,90 ± 5,14	66,39 ± 6,26	66,81 ± 4,03	68,18 ± 3,68	0,707
Females, n (%)	10 (43,48)	4 (40)	2 (20)	4 (40)	
Disease characteristics					
Diabetes duration	16,78 ± 7,91	17,65 ± 6,94	10,64 ± 4,53	21,92 ± 9,42	0,032
DME duration, mean ± SD, years	4,22 ± 7,61	2,07±4,68	6,71±12,34	6,33±5,85	0,156
BCVA (ETDRS scale)	65,63 ± 7,68	65,43 ± 6,68	65,00 ± 9,75	66,83 ± 8,61	0,356
Metaolic factors					
HbA1C, mean ± SD, %	7,74 ± 1,62	8,11 ± 1,76	7,79 ± 1,48	6,82 ± 1,22	0,493

5.3. Retinal sensitivity differences between control subjects and DME patients at baseline

There was a significant difference in mean sensitivity and mean deviation between subjects and controls. Control subjects have higher mean sensitivity than DME patients (19,45±0.5 vs 9,69±5,52) ($p < 0.001$) and a significantly lower mean deviation (-0,52±0,48 vs -9,57±5,13).

Also, considering microperimetry by ring topography, a statistically significant difference was observed between mean sensitivity of controls and DME patients in all rings. From mean sensitivity in C1 (central ring) to C3 (outer ring), respectively 19,36±0,76 vs 8,07±5,58 ($p<0,001$), and 19,51±0,55 vs 9,42±5,52 ($p<0,001$), 19,45±0,5 vs 9,69±5,52 ($p<0,001$).

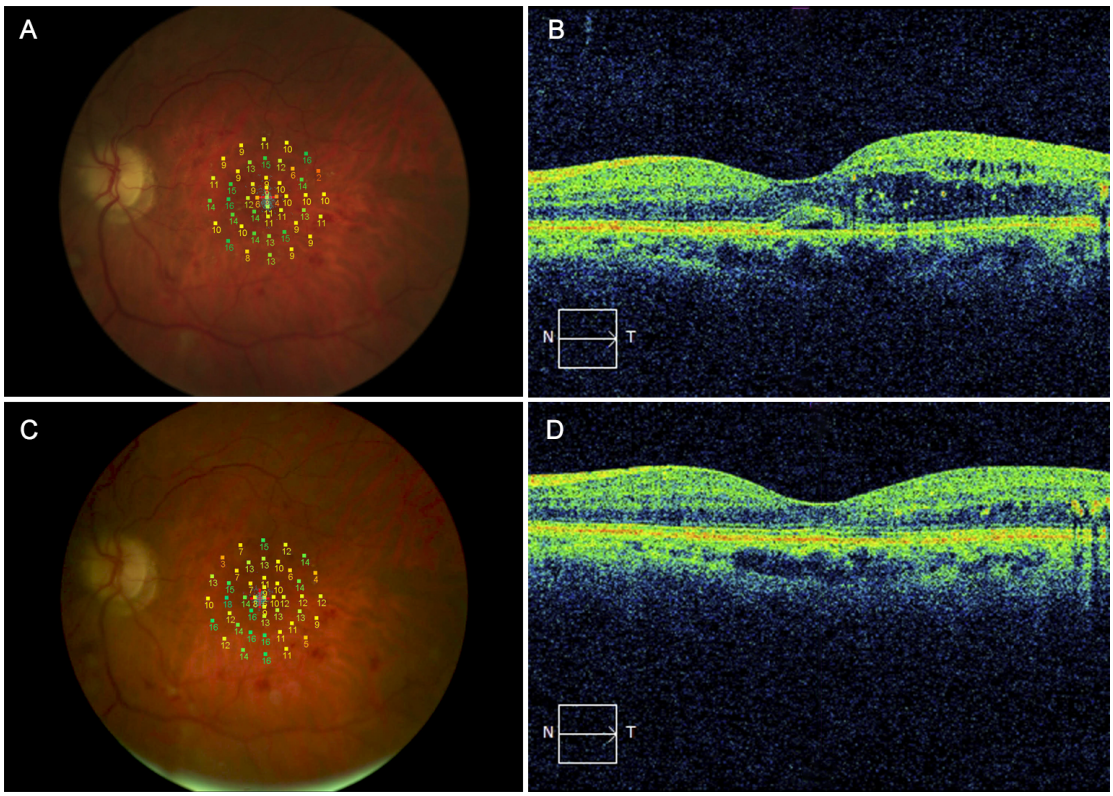

Fig. 1. Both MP sensitiviy and OCT macula thickness improved during treatment.
A – MP sensitivity map at baseline; B - Macula thickness at baseline; C – MP sensitivity map at V5 (1 month after loading dose); D - Macula thickness at V5 (1 month after loading dose).

5.4. Retinal sensitivity (microperimetry) before and after anti-VEGF treatment

Regarding retinal sensitivity changes (MP) in DME patients submitted to anti-VEGF treatment, there was a statistically significant increase in mean sensitivity in the overall tested area between baseline and V5 (9,69 ± 5,52 to 11,18 ± 3,74) (p=0,022). Following this significant increase after loading dose, mean sensitivity gradually decreased until V7, as Figure 2 illustrates, reaching 10,52 ± 4,6 in V6 and to 9,24 ± 3,98 in V7. This decrease from V5 to V7 is statistically significant (p<0,001). (see Fig. 1 and Fig. 2).

When evaluating retinal sensitivity by ring topography, results are similar. There is a statistically significant increase in all three rings (C1, C2 and C3) from V1 to V5, (p=0,012; p=0,023; p=0,022, respectively). Likewise, there is a statistically significant decrease in all three rings from V5 to V7, (p=0,001; p<0,001; p=0,001, respectively).

When analyzing sensitivity by treatment response groups, poor responders have significantly lower mean sensibilities when compared to moderate and good responders at baseline, 7,50±4,38 vs 8,83±4,99 and 11,06±6,12 respectively, (p=0,011).

One month after the loading dose treatment, at V5, mean sensitivity increased in all groups, being specifically significant in the good responders group with a mean gain of + 2,72 dB (p=0,011), increasing from 11,06±6,12 to 13,20±3,66 (see Fig. 2).

Six months after treatment (V6), mean sensitivity increased in poor and moderate responders, while decreasing in the good responders group, 8,57±1,71 to 10,42±6,56 and 10,08±3,64 to 10,85±4,62 vs 13,2±3,66 to 10,41±4,15 respetively, (p=0,996). The opposite was seen 12 months after treatment (V7), where both poor and moderate responders had lower mean sensitivities compared to good responders, 6,34±3,74 and 7,99±5,33 vs 10,90±2,44 (p=0,024) respectively. (see Fig.2)

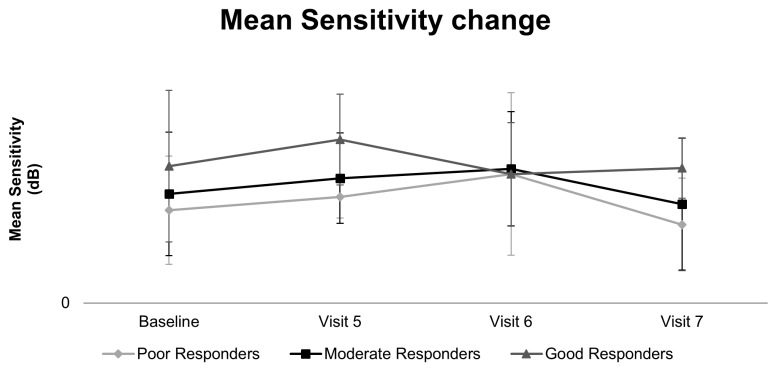

Fig. 2. Increase of retinal sensitivity from Baseline to Visit 5 (1 month after loading dose), Visit 6 (6 months after 1st injection), Visit 7 (12 months after 1st injection), by treatment response groups.

5.5. Correlation with BCVA

At baseline, mean retinal sensitivity was not significantly correlated with BCVA (r=0,20; p=0,412). However, after loading dose (v5 – 1 month after loading dose) these two functional measurements showed a moderate significant correlation (r=0,54; p=0,026).

5.6. Correlation with OCT

At baseline, our results demonstrated a moderate to good negative correlation between structure (OCT) and function (retinal sensitivity) (r=-0,501) (p=0,015) (see Fig. 4 and 5) showing that when retinal thickness is increased, there is an impairment of retinal sensitivity. This is true not only for central ring (r=-0,564, p=0,006) but also for the other 2 concentric rings (2C: r=-0,569 p=0,006 3C: r=-0,459 p=0,031). After treatment and during the follow-up period, these correlations weakened, but are still present 12 months after the 1st anti-VEGF injection (r=-0,276 p=0,226).

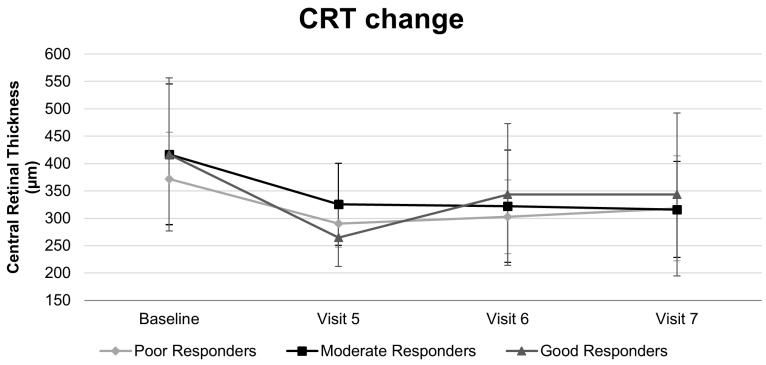

Fig. 3. Decrease of retinal thickness by tratment response from Baseline to Visit 5 (1 month after loading dose), Visit 6 (6 months after 1st injection), Visit 7 (12 months after 1st injection)

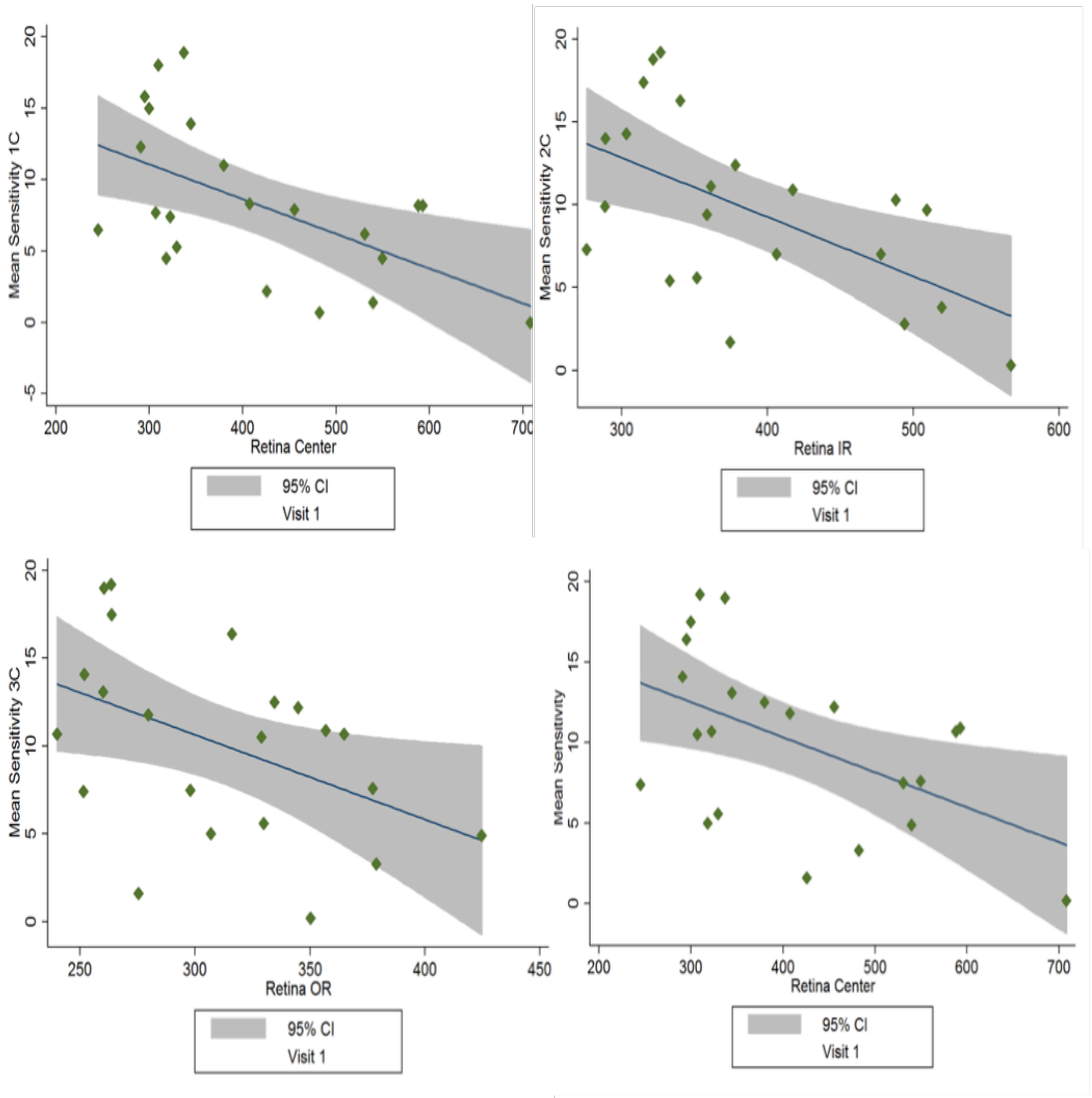

Fig. 4. Correlations between MP sensitivity and Retinal Thickness (OCT), analysed by rings and in the overall tested area at baseline
Mean Sensitivity 1C: MP sensitivity in the central ring (2º); Mean Sensitivity 2C: MP sensitivity in the inner ring (4º); Mean Sensitivity 3C: MP sensitivity in the outer ring (12º); Retina Centre: central 1 mm x; Retina IR: inner ring (3mmx); Retina OR: outer ring (6mm x)

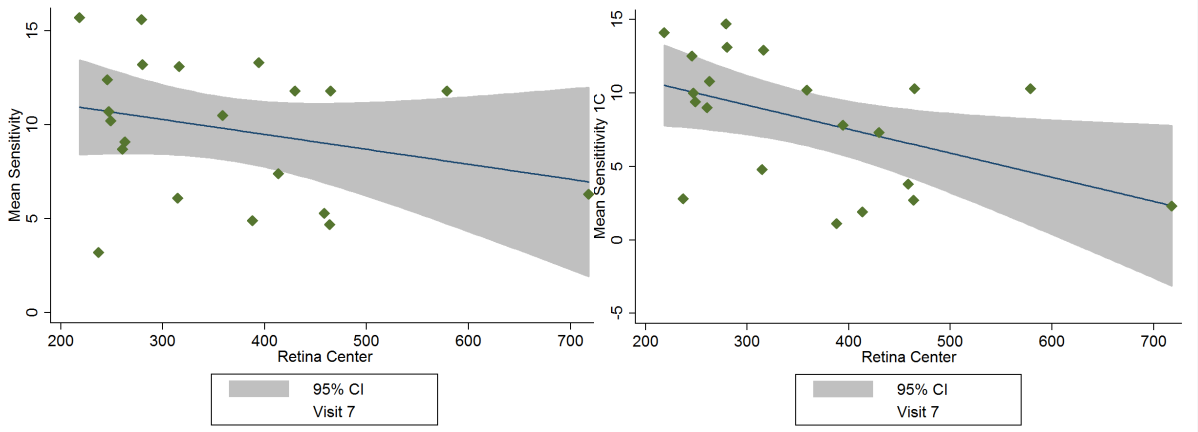

Fig. 5. Correlations between MP mean sensitivity in the central ring and overall tested area with CRT (OCT) in the central 1mm, at Visit 7

6.Discussion

In this study we started by comparing our cohort of DME patients with a control cohort of 20 eyes of age-matched diabetic patients without DR. Mean sensitivity was significantly lower in DME patients in all studied MP rings, demonstrating the ability of MP to characterize macular dysfunction attributable to DME. These results agree with the published literature.[7,8] Increased sensitivities from the center to the periphery were also apparent in our results, with MP sensitivity being the lowest in the innermost foveal ring.

We prospectively evaluated changes in microperimetry after ranibizumab treatment on DME patients. Since MP is a functional exam, we looked at MP changes in three clinical (BCVA) response categories: poor responders, moderate responders and good responders. We have shown that after a ranibizumab loading dose treatment (3 monthly injections), there was a clear increase of retinal sensitivity in all responders groups, mainly in good responders and particularly in the central ring. This strongly supports the efficiency of ranibizumab in the treatment of DME in improve macula-wide visual function, beyond conventional central visual acuity

Since visual acuity as measured by letter charts, evaluates predominantly foveal function, this might be why improvements in the good responders are more pronounced in the central ring. In the future, it would be interesting to evaluate other functional measures and correlate them to eccentric MP changes, such as multifocal ERG.

It was also demonstrated that BCVA improvement was moderately and significantly correlated with mean sensitivity improvement, particularly after treatment, showing the potential that MP has as a functional measure with potential clinical utility. In addition, a significant, moderate and negative correlation was found between MP sensitivity (both

overall and by ring topography) and central retina thickness in OCT. Thus, MP shows some degree of correlation with commonly used functional and anatomical outcomes in DME.

To the best of our knowledge only a small number of studies were done prospectively and in treatment naïve patients that quantitatively evaluated the effects of anti-VEGF in DME using MP and correlations to both functional (BCVA) and structural (CRT) markers. Like Reznicek L et al [9], we also establish a positive correlation between anti-VEGF therapy effects on CRT and functional outcomes (BCVA and MP), both at baseline and after treatment, showing that these results are maintained even after a longer follow-up period (12 months). However, this study mixed diabetes types I and II which may influence the DME resolution as well as MP sensitivities due to different disease onset ages.

Other study (Malagola R et al)[10] also showed similar results, however, not in treatment naïve patients but in a population of persistent DME with previous laser therapy, which may have a potential impact in MP sensitivity values.

Strengths of our study include the prospective, self-controlled design and the comparative baseline evaluation vs age-matched controls. When comparing to similar studies, it has a longer follow-up period. Our approach allows for a thorough evaluation of MP changes in DME, both at baseline and after Anti-VEGF treatment, as well as possible functional/structural correlates.

7.Conclusions

DME contributes to loss of vision in DR. When comparing our DME cohort to diabetic, age-matched control group we were able to show that DME patients had lower retinal sensitivity at baseline (overall and by ring topography).

When evaluating by treatment response groups, after a loading dose (3 monthly injections) of intravitreal ranibizumab, overall and ring sensitivity improved significantly, particularly in good BCVA responders (and mainly in the central ring).

We also found evidence of structural function correlations, namely between MP sensitivity and central retinal thickness in OCT as well as BCVA.

In conclusion, MP is a functional exam with the ability to characterize baseline central retina dysfunction in DME, demonstrate early functional improvement following treatment with anti-VEGF agents, while also correlating to commonly used functional and structural outcomes. We believe MP might be a clinically useful biomarker of functional improvement in eyes with DME treated with intravitreal antiangiogenics.

8.Acknowlegments

Ao meu orientador, Prof. Doutor João Figueira agradeço por ter acreditado em mim, por me ter dado esta oportunidade e por todo o conhecimento que me transmitiu durante a orientação deste trabalho.

Agradeço ao meu co-orientador, Dr Miguel Raimundo, pela a ajuda prestada a nível da supervisão do trabalho realizado.

À Ana Rita Santos, por todas as suas horas perdidas nas múltiplas partes deste trabalho e pela forma como me recebeu e integrou na equipa do AIBILI.

À Dalila Alves por todo o trabalho estatístico.

Obrigada pelo vosso tempo, paciência e pela oportunidade de desenvolver este trabalho sob a vossa orientação.

Gostava ainda de agradecer à Carolina Dias por toda a ajuda com o inglês, formatações e apoio.

Por último, à minha mãe, por me incrementar um espírito critico e me despertar interesse para a oftalmologia.

Sérgio Pestana Domingos

Coimbra, 26 de março de 2018

9.References

1. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: Pathophysiology, screening, and novel therapies. Diabetes Care. 2003;26(9):2653–64.
2. Comyn O, Sivaprasad S, Peto T, Neveu MM, Holder GE, Xing W, et al. A Randomized Trial to Assess Functional and Structural Effects of Ranibizumab versus Laser in Diabetic Macular Edema (the LUCIDATE Study). Am J Ophthalmol [Internet]. 2018 Mar 25;157(5):960–970.e2. Available from: http://dx.doi.org/10.1016/j.ajo.2014.02.019
3. Reznicek L, Cserhati S, Seidensticker F, Liegl R, Kampik A, Ulbig M, et al. Functional and morphological changes in diabetic macular edema over the course of anti-vascular endothelial growth factor treatment. Acta Ophthalmol. 2013;91(7):529–37.
4. Wu L, Fernandez-Loaiza P, Sauma J, Hernandez-Bogantes E, Masis M. Classification of diabetic retinopathy and diabetic macular edema. World J Diabetes [Internet]. 2013;4(6):290–4. Available from: http://www.wjgnet.com/1948-9358/full/v4/i6/290.htm
5. Velaga SB, Nittala MG, Parinitha B, Sadda SR, Chhablani JK. Correlation between retinal sensitivity and cystoid space characteristics in diabetic macular edema. Indian J Ophthalmol [Internet]. 2016;64(6):452–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27488154%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4991177
6. Santos AR, Costa MÂ, Schwartz C, Alves D, Figueira J, Silva R, et al. OPTICAL COHERENCE TOMOGRAPHY BASELINE PREDICTORS FOR INITIAL BEST-CORRECTED VISUAL ACUITY RESPONSE TO INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT IN EYES WITH DIABETIC MACULAR EDEMA: The CHARTRES Study. Retina [Internet]. 2017;

Available from: http://insights.ovid.com/crossref?an=00006982-900000000-96941%0Ahttp://www.ncbi.nlm.nih.gov/pubmed/28613220

7. Okada K, Yamamoto S, Mizunoya S, Hoshino A, Arai M, Takatsuna Y. Correlation of retinal sensitivity measured with fundus-related microperimetry to visual acuity and retinal thickness in eyes with diabetic macular edema. Eye. 2006;20(7):805–9.
8. Montesano G, Gervasoni A, Ferri P, Allegrini D, Migliavacca L, De Cillà S, et al. Structure-function relationship in early diabetic retinopathy: A spatial correlation analysis with OCT and microperimetry. Eye. 2017;31(6):931–9.
9. Reznicek L, Cserhati S, Seidensticker F, Liegl R, Kampik A, Ulbig M, et al. Functional and morphological changes in diabetic macular edema over the course of anti-vascular endothelial growth factor treatment. Acta Ophthalmol. 2013;91(7):529–36.
10. Malagola R, Spinucci G, Cofone C, Pattavina L. Prospective microperimetry and OCT evaluation of efficacy of repeated intravitreal bevacizumab injections for persistent clinically significant diabetic macular edema. Int Ophthalmol. 2013;33(3):261–267.