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Facultat d'Òptica i Optometria de Terrassa

MÀSTER UNIVERSITARI EN OPTOMETRIA I CIÈNCIES DE LA VISIÓ

TREBALL FINAL DE MÀSTER

ESTUDI TOMOGRÀFIC DELS FOTORECEPTORS DE LA RETINA EN PACIENTS DIABÈTICS SENSE RETINOPATIA O AMB RETINOPATIA NO PROLIFERATIVA LLEU

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13 de juny de 2016

Facultat d'òptica i optometria de Terrassa

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La Sra. Gemma Julio Morán com a directora del treball,

CERTIFICA

Que la Sra. Mireia Sánchez Soler ha realitzat sota la seva supervisió el treball *Estudi tomogràfic dels fotoreceptors de la retina en pacients diabètics sense retinopatia o amb retinopatia no proliferativa lleu* que es recull en aquesta memòria per optar al títol de màster en Optometria i Ciències de la Visió.

I per a què consti, signo/em aquest certificat.

Sra Gemma Julio Morán

Director/a del TFM

Terrassa, 30 de maig de 2016

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ESTUDI TOMOGRÀFIC DELS FOTORECEPTORS DE LA RETINA EN PACIENTS DIABÈTICS SENSE RETINOPATIA O AMB RETINOPATIA NO PROLIFERATIVA LLEU

RESUM

La retinopatia diabètica (DR) provoca alteracions microvasculars que condueixen a isquemia, alteració de la barrera hematorretiniana, neovascularització i edema macular.

L'objectiu d'aquest estudi és analitzar les possibles alteracions dels fotoreceptors en els estadis inicials de la DR, i estudiar la seva influència en l'agudesa visual i la visió del color.

Quaranta-quatre ulls de 44 diabètics tipus 2 sense DR o amb DR no proliferativa lleu es van comparar amb 44 ulls sans de 44 pacients.

Es va avaluar l'agudesa visual, la visió del color, i mitjançant la OCT es va analitzar l'estat de les capes membrana limitant externa (ELM), unió del segment intern/segment extern (IS/OS) i el segment extern dels cons (COST), les cúpules ELM i IS/OS, el gruix macular central, i el gruix del complex intern de la retina nasal i temporal a 1000 i 2000µm del centre de la fòvea.

Els resultats van mostrar una pèrdua significativa de les cúpules de ELM i IS/OS. El grup diabetis mellitus (DM) sense DR va mostrar una gruix significativament menor a 1000µm del centre de la fòvea. Aquests ulls també van mostrar una menor agudesa visual quan la COST no era visible.

En conclusió, hi ha evidències d'alteració dels fotoreceptors en els estadis inicials de la DR i poden estar relacionades amb la patogènesis de la DM.

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ESTUDIO TOMOGRAFICO DE LOS FOTORRECEPTORES DE LA RETINA EN PACIENTES DIABETICOS SIN RETINOPATIA O CON RETINOPATIA NO PROLIFERATIVA LEVE

RESUMEN

La retinopatía diabética (DR) provoca alteraciones microvasculares que conducen a isquemia, alteración de la barrera hematorretiniana, neovasculairzación y edema macular.

El objetivo de este estudio es analizar las posibles alteraciones de los fotorreceptores en los estadios iniciales de la DR, y estudiar su influencia en la agudeza visual y la visión del color.

Cuarenta y cuatro ojos de 44 diabéticos tipo 2 sin DR o con DR no proliferativa leve se compararon con 44 ojos sanos de 44 pacientes.

Se evaluó la agudeza visual, la visión del color, y mediante la OCT se analizó el estado de las capas membrana limitante externa (ELM), unión del segmento interno/segmento externo (IS/OS) y el segmento externo de los conos (COST), las cúpulas ELM e IS/OS, el grosor macular central, y el grosor del complejo interno de la fóvea nasal y temporal a 1000 y 2000µm del centro de la fóvea.

Los resultados mostraron una pérdida significativa de las cúpulas ELM e IS/OS. El grupo diabetes mellitus (DM) sin DR mostró un grosor significativamente menor a 1000µm del centro de la fóvea. Estos ojos también mostraron una menor agudeza visual cuando la COST no era visible.

En conclusión, hay evidencias de alteraciones en los fotorreceptores en los estadios iniciales de la DR y pueden estar relacionadas con la patogénesis de la DM.

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TOMOGRAPHIC STUDY OF RETINAL PHOTORECEPTORS IN DIABETIC PATIENTS WITHOUT RETINOPATHY OR WITH MILD NON PROLIFERATIVE RETINOPHATY

ABSTRACT

Diabetic retinopathy (DR) causes alterations leading to ischemia, increased of blood-retinal barrier, neovascularization and macular oedema.

The aim of this study is to analyze the possible morphological changes of photoreceptors in the early stages of DR, and study their influence on visual acuity and colour vision.

Forty-four eyes of 44 type 2 diabetics without DR or mild non proliferative DR were compared with 44 healthy eyes of 44 patients.

Visual acuity and colour vision was evaluated, also by OCT the state of the external limiting membrane (ELM), inner segment / outer segment junction (IS/OS) and cone outer segment tips (COST) layers of the retina, the ELM and IS/OS dome-shaped, the central macular thickness, and the inner retinal complex thickness nasal and temporal was evaluated at 1000 and 2000µm from the centre of the fovea.

The results showed a significant loss of ELM and IS/OS dome-shaped. The diabetes mellitus (DM) group without DR showed significantly lower thickness at 1000µm from the centre of the fovea. This eyes also displayed significantly lower visual acuity when COST were not visible.

In conclusion, there are evidences of photoreceptor alterations in the early stages of DR and it may be related to the pathogenesis of DM.

COVER LETTER

Dear Editor,

Attached you will find the paper entitled "Tomographic study of retinal photoreceptors in diabetic patients without retinopathy or with mild non proliferative retinopathy", which we are submitting for publication in *British Journal of Ophthalmology* as an original article.

To determinate the possible morphological changes of photoreceptors in the early stages of diabetic retinopathy, and study their influence on visual acuity and colour vision. The state of retinal layers by optical coherence tomography (OCT) were analysed, and compared with visual acuity and colour vision.

We would be very grateful for any comments or suggestions you may wish to make.

Thank you for your attention.

Yours sincerely,

Mireia Sánchez

TITLE PAGE

Title of the article: Tomographic study of retinal photoreceptors in diabetic patients without retinopathy or with mild non proliferative retinopathy

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Keywords: Diabetic Retinopathy, Optical Coherence Tomography, Foveal Bulge, Visual Acuity.

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ABSTRACT

Background/aims: Diabetic retinopathy (DR) is a progressive condition resulting from diabetes mellitus, and is the leading cause of blindness in people of working age in developed countries. Our aim is to analyse foveal morphological changes, in diabetic patients without clinically manifested diabetic retinopathy, or at initial stages of this ocular disorder and to study the influence of these changes in visual acuity and colour vision.

Methods: Forty-four eyes of 44 patients with type 2 diabetes mellitus without or with mild no proliferative DR were compared with 44 healthy eyes of 44 patients with similar age and sex. Visual acuity and colour vision was evaluated, also by optical coherence tomography (OCT) the state of the external limiting membrane (ELM), inner segment / outer segment junction (IS/OS) and cone outer segment tips (COST) layers of the retina, the dome-shaped appearance of ELM and IS/OS, the central macular thickness, and the nasal and temporal inner retinal complex thickness was evaluated at 1000 and 2000 µm from the centre of the fovea.

Results: The results showed a significant loss of ELM IS/OS domes. COST distribution was similar in both groups. DM group without DR showed significantly lower IRCT thickness at 1000 µm of the centre. This eyes also displayed significantly lower visual acuity when COST were not visible, compared to cases with unaltered COST.

Conclusion: Photoreceptor alterations in the early stages of diabetic retinopathy may be related to the pathogenesis of diabetes mellitus.

MAIN TEXT

INTRODUCTION

American Diabetes Association[1] defines, diabetes mellitus (DM) as a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. Chronic hyperglycaemia is associated with long-term damage, dysfunctions and failure of various organs, especially eye, kidney, nervous and cardiovascular systems. According to the aetiology, DM is divided mainly into two groups. The DM type 1 is caused by a deficiency of the absolute secretion of insulin while type 2 is caused by a combination of resistance to insulin action along with an inadequate compensatory insulin secretion. The latter is the most common type. It is estimated that by 2030 the number of people with diabetes will reach 366 million, 4.4% of the world population.[2]

The chronic vascular complications affect especially the vision of patients. Ocular manifestations are: cataracts, diabetic macular oedema (DME) and diabetic retinopathy (DR). DR is a progressive condition with microvascular alterations that lead to retinal ischemia, an increased permeability of the blood-retinal barrier, retinal neovascularisation and macular oedema.[3,4] DR[5] can be proliferative and non-proliferative and its presence is determined by the appearance of changes in the fundus. Non-proliferative DR shows three degrees of intensity: mild, moderate and severe, depending on the severity and frequency of funduscopic alterations.

Often, untreated patients with DR suffer severe visual loss.[4] In developed countries DR is the leading cause of blindness in people of working age[6] and has a considerable economic and social impact, especially in health systems. An appropriate management of patients with DR, it would save more than 90% of visual loss cases,[7,8] it is extremely important to classify the severity of DR and to establish the appropriate therapy as soon as possible.

Optical coherence tomography (OCT) is a technique commonly used in ophthalmology to evaluate retina state and to predict visual results. Its high resolution images allows analysing the different photoreceptor structures at foveal level, displayed as subcellular layers. In DME

cases OCT images show a disruption of the internal retina layers: external limiting membrane (ELM), photoreceptor inner segment / outer segment junction (IS/OS) and a reduction in the length of the outer segment of the central foveal cones, as well as in some patients a serous neurosensory detachment.[9,10] However, the photoreceptors role in the pathogenesis of DR has been largely overlooked, although these cells represent the majority of the mass and the metabolic activity of the retina.[11]

There is some evidence, in animal studies, that point to involvement of photoreceptors in the origin of the RD.[11] In addition, it was reported that the DR is less severe in retinitis pigmentosa patients,[12] a disease that destroys photoreceptors.

Currently, only two clinical studies have analyzed the involvement of photoreceptors in patients with different RD severity.[9,13] Our group aims to analyse foveal morphological changes, in diabetic patients without clinically manifested DR, or at initial stages of this ocular disorder and to study the influence of these changes in visual acuity and colour vision. This new approach may improve DR early detection and minimize the effects that this condition leads to patient vision.

MATERIALS AND METHODS

Forty-four eyes of 44 patients with type 2 DM without or with mild no proliferative DR were compared with 44 healthy eyes of 44 patients with similar age and sex. Patients suffering from a disease that affects the blood vessels in the retina, who have retinal surgery or laser, retinal detachment or vitreous haemorrhage where excluded. Eyes with opacity obstacles to obtaining quality images with the OCT and patients with systemic inflammatory diseases (rheumatoid arthritis, asthma ...), neoplasm, dialysis, coronary artery disease, etc., were also excluded because high levels of vascular endothelial growth factor (VEGF) have been associated with alterations in outer retinal layers. Eyes that have been diagnosed and/or treated for different diseases that may cause macular thickening or poor delineation of foveal layers (macular oedema eyes with subretinal or intraretinal fluid, hard exudates, staphyloma with high myopia, venous occlusion, epiretinal membrane, vitreomacular traction, etc.) were also excluded. The study was approved by the Ethics Committee for Clinical Research of

Hospital de Terrassa-*Consorci Sanitari de Terrassa*, and all patients were informed and gave their written consent.

First, the fundus under mydriasis was analyzed at the ophthalmological exploration to classify the type of RD. The ocular media were also explored and the intraocular pressure was measured with the Goldman tonometer.

Optometric exploration included: a brief anamnesis, the best-corrected visual acuity (BCVA) with the Snellen optotype in decimal scale. Colour vision was evaluated with two specific tests: Ishihara and Farnsworth-Munsell D-15 (FM D-15) tests. Ishihara test is used to diagnose and classify the changes in colour vision, at the level of red-green axis. FM D-15 test identify the defect in colour vision; protanomaly (reduced sensitivity to red) deuteranomaly (reduced sensitivity to green) or tritanomaly (reduced sensitivity to blue). In both test, the number of errors were recorded.

The study of the foveal morphology was carried out using a Cirrus HD-OCT 4000. (Carl Zeiss Meditec Inc., Dublin, CA; version 5.0.0). This is a non-invasive analysis that allows obtaining cross sections images of ocular tissues in vivo. This technique is widely used to study the fovea and optic nerve. OCT performs a picture with the macular cube scan mode to obtain data of central macular thickness and 5 lines raster scan allows classifying the state of the retina external layers. The ELM, IS/OS and cone outer segment tips (COST) layers were classified in three categories. If they were absent in the OCT image, were classified as category 0. If they were present as a dashed line, were classified as category 1. If they were as a continuous line, were classified as category 2. Also, presence/absence of ELM and IS/OS dome-shaped appearance due to the higher length of the central photoreceptors, also named foveal bulge (FB), was categorized and the central macular thickness was automatically measured in µm. In addition, the inner retinal complex thickness (IRCT) was measured, by a masked observer, from nerve fiber layer to inner nuclear layer, in nasal and temporal side, at 1000 (IRCT1) and 2000 µm (IRCT2) from the centre of the fovea.

Exploratory analysis of the studied variables was carried out. In order to analyze changes, student t test and Fisher's exact test were used for interindividual comparisons between controls and DM group. Paired t-test was applied for intraindividual comparisons describing

IRCT differences in different locations of the same eye. SPSS V19 was used for statistical analysis and a significant level of $p<0.05$ was considered. Normal variable distribution was assessed with the Kolmogorov-Smirnov test.

RESULTS

Foveal description

From the 44 eyes of 44 DM patients, 32 (73%) showed no DR and 12 (27%) were classified as mild no proliferative DR. The ELM and IS/OS layers in the three groups (control, no DR, and mild non-proliferative DR group) always showed cat 2. **Table 1** illustrates distribution of COST category in the three groups. See **figure 1** for typical examples of OCT foveal pattern.

	COST distribution		
	Cat 0	Cat 1	Cat 2
Control	6 (13%)	14 (32%)	24 (55%)
DM without DR	6 (19%)	9 (28%)	17 (53%)
DM with mild non-proliferative DR	5 (42%)	5 (42%)	2 (16%)

Table 1. *Distribution COST category in the three groups.*

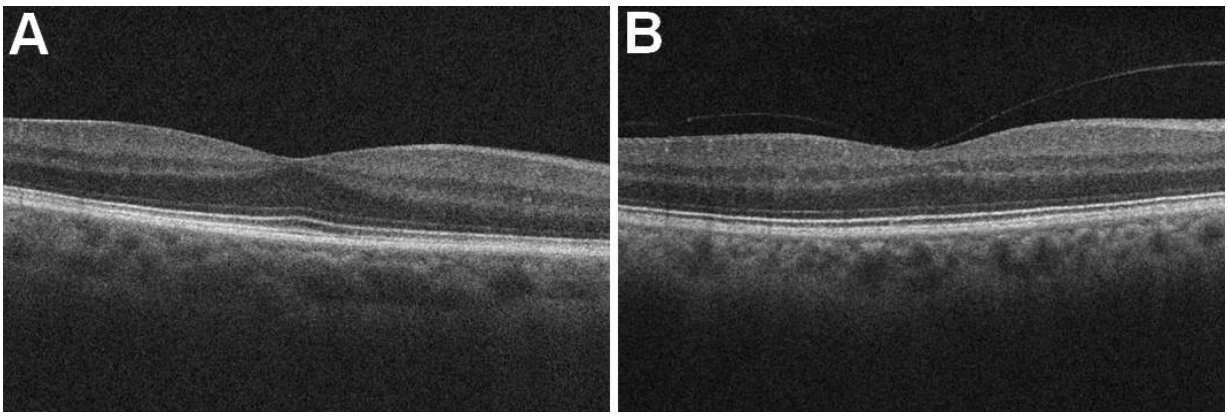

Figure 1. *Spectral domain optical coherence tomography (OCT) showing the foveal bulge (FB) categories. A and B showed category 2 at external limiting membrane (ELM), inner segment /*

outer segment junction (IS/OS) and cone outer segment tips (COST). A shows presence of dome-shape appearance in both, ELM and IS/OS, and B shows absence of this foveal characteristics.

ELM and IS/OS bulges were present in 32 (73%), and 42 (95%) healthy eyes, respectively, in 13 (42%) and 21 (68%) eyes in DM group without DR, and in 4 (33%) and 7 (58%) in DM group with mild non-proliferative DR.

Summary statistics of IRCT thickness in the three groups is presented in **table 2**.

		Nasal IRCT1	Nasal IRCT2	Temporal IRCT1	Temporal IRCT2
Control	Mean	202	193	179	159
	Median	200	193	178	157
	SD	23	23	17	17
	Min	164	143	136	120
	Max	252	244	224	200
DM without DR	Mean	198	187	171	151
	Median	192	187	171	152
	SD	24	15	14	14
	Min	167	157	144	124
	Max	248	215	193	186
Mild non-proliferative DR	Mean	191	198	170	155
	Median	195	198	166	158
	SD	24	16	14	12
	Min	149	160	152	132
	Max	226	216	197	171

Table 2. *IRCT1: Inner retinal complex thickness at 1000µm of the foveal centre; IRCT2: Inner retinal complex at 2000µm of the foveal centre. All the values expressed in µm.*

Mean central macular thickness was 260±23 (205 to 294) in healthy eyes, 261±23 (224 to 315) in DM group without DR and 262±22 (224 to 292) in DM with mild non-proliferative DR.

Comparisons between control and DM group without DR

The studied characteristics of the 32 eyes with type 2 DM without DR were compared with the 44 healthy eyes of 44 healthy volunteers with similar age and sex. No comparisons were made with the group with mild non-proliferative DR due to the reduced number of cases included in the study.

When compared with control group, DM without DR underwent significant loss of ELM and IS/OS bulges ($p<0.05$; Chi2 test and $p<0.01$; Fisher's exact test, respectively) but COST distribution was similar in both groups.

Both, healthy and DM without DR, displayed significantly higher IRCT thickness in nasal than in temporal locations ($p<0.001$; paired t test) and measures at 1000 µm from the centre of the fovea were significantly higher than measures at 2000 µm ($p<0.01$; paired t test).

The comparisons in equivalent locations between healthy and DM without DR showed no significant differences, except for temporal IRCT1. In this specific location DM without DR group displayed a slight but significant IRCT decrease ($p<0.05$; student's t test) with a mean difference of 8 µm (95% confidence interval = 0.5-15 µm).

No significant differences were found in central macular thickness between both groups.

Visual acuity and Colour vision in DM patients

The mean of BCVA was 0.82±0.16 in DM group without DR and 0.89±0.21 in DM group with mild non-proliferative DR.

By Ishihara test, no errors were displayed in the 90% of the cases in DM group without DR, 2 patients had an error and 1 patient made 2 errors. No errors were displayed in DM group with mild non-proliferative DR.

Summary statistics of Farnsworth-Munsell D-15 test for the two groups of DM is displayed at **table 3**.

		Number of errors	SI	CI	Angle
DM without DR	Mean	2.5	1.7	1.60	32.6
	Median	2	1.6	1.61	62
	SD	2.82	0.42	0.57	57.2
	Min	0	1.11	1	-83.9
	Max	11	2.78	2.97	81.4
Mild non-proliferative DR	Mean	2.4	1.8	1.6	40
	Median	2	1.6	1.63	62
	SD	2.5	0.51	0.52	57.2
	Min	0	1.4	1	-83.9
	Max	9	3.2	2.3	89.6

Table 3. *SI: Selectivity index (quantifies the amount of polarity or lack of randomness in a cap arrangement); CI: Confusion Index (quantifies the degree of colour loss relative to a perfect arrangement of caps); Angle (identifies the type of colour defect)*

Comparisons of the visual acuity among DM eyes without DR with different COST classification and presence/absence of ELM and IS/OS dome-shaped appearance were carried out. Significant differences were only found between eyes with COST=2 and eyes with COST=0 ($p=0.035$; ANOVA). The mean difference in BCVA in this comparison (COST=2 vs COST=0) was 0.78 with a 95% confidence interval from 0.98 to 0.62.

No comparisons of colour vision tests results were made because of the reduced number of errors found in the DM group without DR.

DISCUSSION

The results of this study showed that type 2 DM patients without signs of DR have anatomical changes at foveal level. IRCT seems to keep the normal relationship between nasal and temporal thickness but temporal location near the centre of the fovea could tend to be thinner than in normal eyes. The COST distribution was similar in both groups, but significant differences in BCVA were found between DM eyes with COST=2 and COST=0.

Our results showed no differences between control and DM group at the COST layer. This may be because this layer is difficult to discriminate, and its categorization is less reliable (it would be expected that all control group had COST = 2). However, at DM group without DR we seen significant differences between BCVA according to COST classification. Tendency to the lack of COST seems to induce visual acuity lost.

No others morphological changes seems to be determinants to BCVA neither colour vision. Nevertheless, it is worth mentioning that sample size was calculated to detect changes at FB level, but not to detect if other changes may be determinants of BCVA or colour vision. A big sample may be necessary to get more conclusive results in this part of our aim.

There is evidence suggesting that photoreceptors contribute to vascular disease in diabetic retinopathy.[11] Two hypotheses have been raised: hypoxia and oxidative stress.[12] Our results agree with some studies with animals reporting that, at least, some photoreceptors degenerate early in the course of diabetes. A study in diabetic-induced rodents show an increased basement membrane thickness in diabetic retina.[14] Park et al[15] found a slight reduction in the thickness of the inner retina and a remarkable reduction in the outer nuclear layer 24 weeks after the inset of diabetes.

There are few studies with patients. Occasional case reports suggest photoreceptor loss in diabetes or DME,[16] but there has been no systematic demonstration that photoreceptors are lost in diabetic patients, with the exception of autopsy evidence showing that the S-cones selectively are lost in DR.[17] Some studies related less severe morphological changes with visual loss in diabetic patients,[18,10] but it is most studied in DME. IS/OS and ELM have been identified as useful parameters for optical coherence tomography evaluation of foveal

photoreceptor layer integrity in DME.[18,19] In DME, photoreceptor outer segment length of the central subfield was less[10] than the mean cone OS length in the fovea of healthy subjects,[20] suggesting shortening of the photoreceptor outer segment length in diabetes or macular oedema.

Two studies have analyzed the involvement of photoreceptors in patients with different DR severity in type 2 DM. Murakami[9] evaluate the association between visual acuity with pathologic changes in morphology, macular thickness, and the status of ELM in DR, visualized by Spectralis OCT. They classified 3 types: cystoid macular oedema (CME), serous retinal detachment (SRD) absence of either (diffuse type). They found that the intact ELM might represent better visual acuity in eyes with the CME type and diffuse type but not in eyes with the SRD type in DR. CME type and diffuse type, a disrupted ELM or parafoveal thickening was significantly correlated with poor visual acuity. Jain[13] correlate the serum levels of VEGF and intercellular adhesion molecule-1 (ICAM-1) with the severity of retinopathy and disruption of the ELM and IS/OS junction in type 2 DM. They classified 3 types: diabetes patients without retinopathy, with non-proliferative diabetic retinopathy, and with proliferative diabetic retinopathy. Their study showed that disruption of the ELM occurred even before disruption of the photoreceptor IS/OS junction. They hypothesized that increases in the level of diabetic retinopathy resulted in decreased biological activity of the ELM and IS/OS junction, which in turn resulted in the disruption of these layers and a decrease in visual acuity. An increase in serum VEGF and ICAM-1 levels is associated with an increase in the severity of diabetic retinopathy and the grade of ELM and IS-OS junction disruption.

A histological study by Nork[21] whit different techniques showed and widespread loss of the S-cones in retinal detachment and diabetic retinopathy, which means that acquired tritan-like colour vision loss could be caused by selective loss of the S-cones. Greenstein et al[22] study also studied about the sensitivity of the S-cone (blue) in retinal disease: retinitis pigmentosa, insulin-dependent DM and open-angle glaucoma. All of them showed a greater loss in sensitivity of an S than an M cone, however, the diabetic patients showed a more selective loss. These results suggest that multiple factor may be involved and that the combined effects of metabolic abnormalities and hypoxia contribute to the selective loss.

In conclusion, for the first time, we found that type 2 DM patients without DR or any other clinical retinal complication could tend to loss FB. This early alteration in central cone membranous discs might be related to the pathogenesis of DM. IRCT in type 2 DM patients without DR seems to keep the normal relationship between nasal and temporal thickness but temporal location near the centre of the fovea could tend to be thinner than in normal eyes. It may be an early sign of DR or diabetic polyneuropathy. Further studies are needed to better understand pathogenesis of anatomical changes in the photoreceptors and their relationship with diabetic retinopathy.

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LEGENDS FOR DISPLAY ITEMS

Tables

Table 1. Distribution COST category in the three groups.

Table 2. IRCT1: Inner retinal complex thickness at 1000µm of the foveal centre; IRCT2: Inner retinal complex at 2000µm of the foveal centre. All the values expressed in µm.

Table 3. SI: Selectivity index (quantifies the amount of polarity or lack of randomness in a cap arrangement); CI: Confusion Index (quantifies the degree of colour loss relative to a perfect arrangement of caps); Angle (identifies the type of colour defect)

Figures

Figure 1. Spectral domain optical coherence tomography (OCT) showing the foveal bulge (FB) categories. A and B showed category 2 at external limiting membrane (ELM), inner segment / outer segment junction (IS/OS) and cone outer segment tips (COST). A shows presence of dome-shape appearance in both, ELM and IS/OS, and B shows absence of this foveal characteristics.

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