INCURSION IN A CONTRAST SENSITIVITY CHANGES RELATED TO NON-PROLIFERATIVE DIABETIC RETINOPATHY

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Abstract

The paper followed the possible relationship between variability of contrast sensitivity tests and glycemic level in non-proliferative diabetic retinopathy using Spectral Domain OCT (SD-OCT), during daytime, related to changes of normal retinal layers. For this task, we investigated eyes with non-proliferative diabetic retinopathy (mild, medium and severe forms) by assessing the contrast sensitivity through Pelli Robson Test and micro-perimeter and retinal thickness using SD OCT. The images were analyzed using two software: ImageJ and Maviiss 1.5 (Mtf-bAsed Visible and Infrared Imaging System Simulation). The diabetic group was matched by similar control group (for age and sex) of healthy eyes. Our results showed a correlation between the retinal thickness during daytime, contrast sensitivity loss and glycemic variations that can be used as further investigation tool.

Keywords: *contrast sensitivity, glycaemia, OCT, diabetic retinopathy, retinal thickness*

1. INTRODUCTION

Diabetes mellitus (DM), a disease affecting approximately 29 million people or 9% of United States' population and 8.5% of Europe's population [**1**], is a metabolic disorder secondary to chronic hyperglycemia, a condition which leads to different pathologies including micro and macrovascular complications like retinopathy, neuropathy, nephropathy, ischemic heart disease, cerebrovascular disease and peripheral vascular disease [**2**]. Classically, DM has two etiologies, classified as type 1 and type 2. In type 1 DM, hyperglycemia is the direct result of destruction of beta pancreatic cells, while type 2 DM is the result of insulin resistance and, subsequently, of beta pancreatic cells dysfunction [3].

Although the American Diabetes Association guidelines for type 2 DM indicate a random glycemic level > 200 mg/dl or a jeun glycemic level > 125 mg/dl, recent proofs suggest that the body goes through important metabolic changes previous to the presence of manifest DM [**3**].

Diabetic retinopathy (DR) represents an important cause of deterioration of vision and blindness for the patients affected by the disease. Moreover, decreased visual acuity secondary to DR has a negative impact on patients' quality of life and their ability to successfully cope with the disease [**4**]. Clinically, blindness is caused by progressive damage of the retinal microvasculature which leads to ischaemia, retinal edema and neovascularization. Retinopathy is associated with both types of DM, being the main cause of acquired blindness in adult Americans [**5**]. Optical coherence tomography (OCT) is a non-invasive imagistic method which allows microscopic visualization of the retinal morphology. Theoretical basis of OCT was established by mathematicians D. Huang and M. R. Hee (D. Huang, E.A.

Swanson, J.S. Schuman, M.R. Hee, C.A. Puliafito, J.G. Fujimoto et all: *Optical coherence tomography*. Science. 1991; 254 (5035), 1178-1181). Optical coherence tomography derives from low coherence optical interferometry, using radiations from the near IR domain (NIR).

In our study Cirrus™ HD-OCT model has been used, produced by Carl Zeiss Meditec, Inc., class II (acc. 21 CFR 886.1570). Cirrus™ HD-OCT is a computerized instrument that acquires and analyzes cross-sectional tomograms of anterior and posterior ocular structures (including cornea, retina, retinal nerve fiber layer, macula and optic disc). It employs non-invasive, non-contact, low-coherence interferometry to obtain high-resolution images. Functioning principle of Cirrus™ HD-OCT is shown in fig. 1.

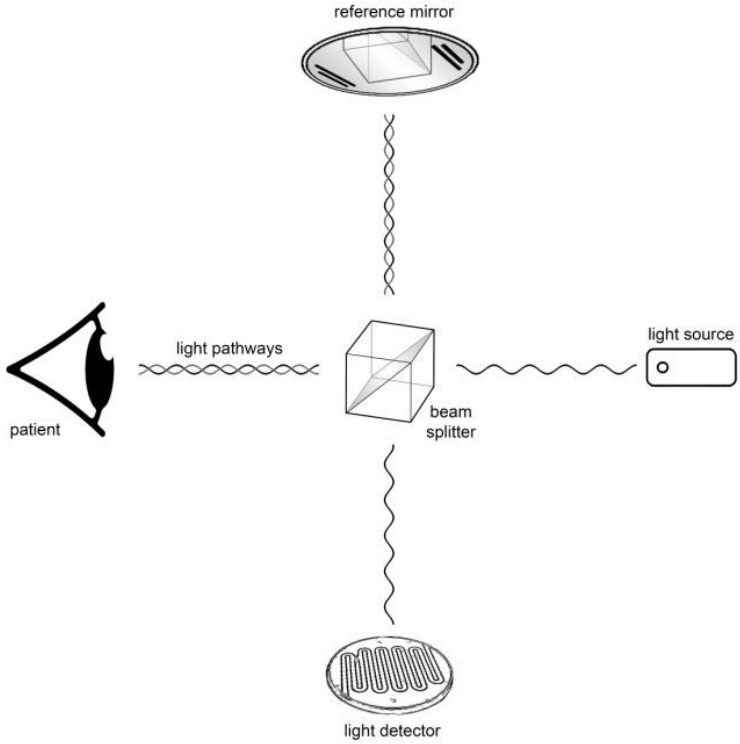


Figure 1. Functioning principle of OCT.

Retinal thickness is calculated by the software of the OCT machine which measures automatically the retinal layers, creating retinal maps that can be compared with the normative database, allowing monitoring of the evolution and treatment in time. Optical coherence tomography can show other characteristics of diabetic retinopathy, like hard exudates from the outer plexiform layer, visualized as hyperreflective areas, can detect intraretinal and subretinal fluid, visualized as hyporeflective spaces, can even detect subclinical macular edema. [**6**]. Through OCT loss or destruction of other retinal layers can be demonstrated, for example, photoreceptor layer or retinal nerve fiber layer, which helps with the differential diagnosis of decreased vision in a diabetic patient. It is useful in the diagnosis of vitreoretinal interface, epiretinal membrane and vitreomacular traction [**7-10**].

2. MATERIALS AND METHODS

2.1. Materials

2.1.1. Study group

The present study is based on OCT images from 24 patients with diabetic retinopathy, and 19 patients without diabetic retinopathy in the control group, with variable levels of glycaemia, between 9:00 and 18:00 o'clock. We excluded the rest of the patients included in the study, up to 80 screened patients, either because of medical reasons they couldn't undergo ophthalmological investigation with OCT according to medical protocol or because of poor acquisition score of the OCT images. A score below 3/10 is associated with a poor quality image for Cirrus [**33**] and the scans with such low score weren't introduced in the analysis with ImageJ. For each patient and each eye considered we have done 4 measurements. As a result, we analyzed 33 eyes from patients with diabetic retinopathy and 26 eyes from patients without diabetic retinopathy and diabetes.

Optical coherence tomography image acquisition was limited by the transparency of the optical ocular media, by the ocular movements during scanning and also by the OCT device performance. Mean age for the diabetic retinopathy patients was 66.4 years (minimum age was 48 and maximum age was 92 years), and mean age for the control group was 67.6 years (minimum age was 43 years and maximum age was 80 years). The diabetic patients were taking oral antidiabetic treatment and only 5 were on insulin.

As an example, we present a macular cube 512x128 for an eye without diabetic retinopathy in figure 2.

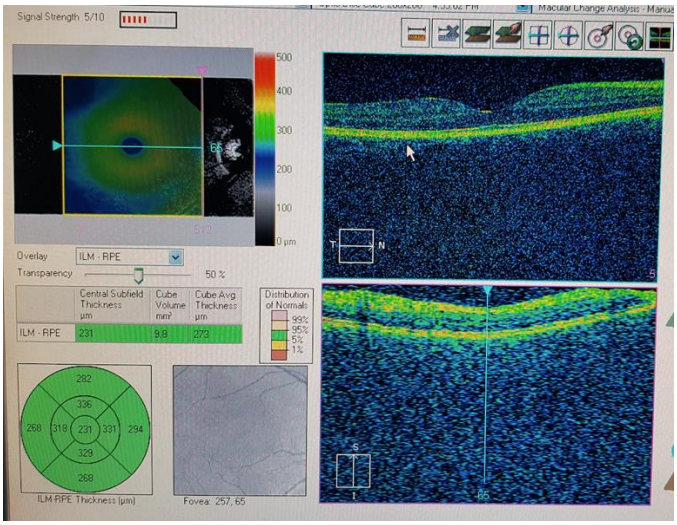


Figure 2. Macular Cube, female, 50 years of age, RE

Working hypothesis are the following:

The human eye can be compared with a camera, made of a lens (corresponding to the natural human lens), detection matrix (represented by the retinal photoreceptors) and medium between the lens and the detection matrix (equivalent to the aqueous humor). In this hypothesis, Maviiss software allows simulation of the modulation transfer function (MTF) related to visual acuity and lens parameters, detection matrix and medium between the lens and the detection matrix (aqueous humor) and the retina. We considered the following data:

- Focal length of the lens (the nodal point of the eye) =18 mm from the retina;
- Contrast sensitivity (1%), which represents the minimum visible, meaning the minimum contrast of an object enough to make it distinct from the background; contrast sensitivity decreases with reduction in illumination;
- Maximum resolution [mrad] = 0.3 mrad (or minute of arc) and which represents the discrimination capacity;

- Pupillary diameter = 5 mm;
- Retinal diameter = 22 mm (we analyzed a small retinal area, 1 mm in diameter) corresponding to the possibilities of Maviiss program;
- 512 photoreceptor cells analyzed in the fovea; it is known that the number of detection elements (photoreceptor cells) = 125 million (5 million cones and 120 millions rodes), which means that the human eye has approximately 600 Mpixeli, and in the fovea (the center of the visual field) there are 10 Mpixeli; the size of a pixel is 380 mm^2/600,000,000 = 0.6 microns, but for the simulation we considered a reduced area of 512x512=262144 photoreceptor cells. If the area of a photoreceptor cells is 0.6 µm, then the area analyzed in the fovea is 1.2 mm^2;
- Lens refraction variations appear because of increased glycemic level.

2.1.2. Protocol

This study was conducted according to an ethical Committee regulation and all patients signed an informed consent.

In our study, we based our analysis on the images scanned by Cirrus OCT Zeiss device from 43 patients with variable glycaemia, each recorded during daytime (from 9:00 - 18:00), from one or both eyes (in total 59 eyes). Glycaemia level was measured with Beurer GL 42/dl glucometer, at the following times of the day: 9-12-15-18. At the same time, we measured systemic blood pressure with Beurer apparatus. Along OCT measurements, we also utilized Pelli-Robson contrast sensitivity test for determining MTF.

We took into consideration the fact that the retina is not even, the fovea being responsible for the central visual acuity (having a high density of photoreceptors), and the periphery having a lower photoreceptor density, responsive only when there are low frequency signals (between 20-50 cy/degree). For the analysis we considered MTF and contrast transfer function (CTF), knowing that contrast neuronal sensitivity function (CSF) has a peak value of approximately 1 to 8 cycles/ degree (1 degree = 157 mrad).

We used two software for the data analysis: one for image analysis (ImageJ), and respectively one for image simulation (Maviiss 1.5).

The method employed in this study is based on the fact that GI (glycemic index) variations lead to variations of VA, and CS (contrast sensitivity) respectively, CS being the opposite of threshold contrast (CT; the lowest contrast necessary to be able to see the Pelli Robson test). Taking into consideration that it is difficult to appreciate how CS will evolve depending each patient's GI (see below figure 3), we decided to see OCT as an additional method to appreciate the correlation between CS and GI.

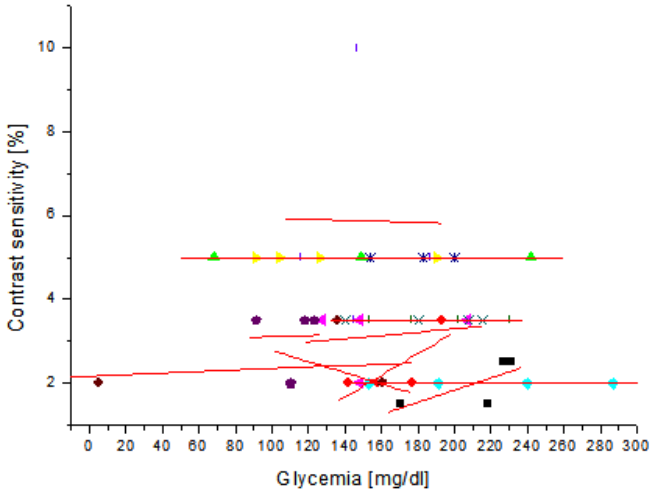


Figure 3. Contrast sensitivity variation depending on the level of glycaemia for right eye in 20 patients

Moreover, the similarity between the results obtained with Pelli-Robson contrast sensitivity test and OCT could allow a higher reliability in these tests.

2.2. Methods

In our study, we used two software for the data analysis: one for image analysis (ImageJ [**25**]), and respectively one for image analysis and simulation (Maviiss 1.5 [**26**]). The data was obtained from a group of 43 patients, each tested during a day (between the hours 9:00 - 18:00 o'clock), with optical coherence tomography (OCT) and Pelli-Robson contrast sensitivity test at one or both eyes. For data analysis, we considered the modulation transfer function (MTF) and the contrast transfer function (CTF).

3. RESULTS

3.1. Image simulation with Maviiss 1.5

An example of image simulation of MTF for a patient with OCT introduced in the window of Maviiss 1.5 software is shown below in Figure 4.

The advantages of using image simulation with Maviiss 1.5 are as follows:

- Allows the evaluation of the influence of introducing some systems of optical filters in front of the lens, as a method of improving CS;
- Allows the evaluation of reduction of CS through defocusing given by GI (figure 5), and also visual prognosis of the deterioration of CS based on defocusing compared to mean CS.

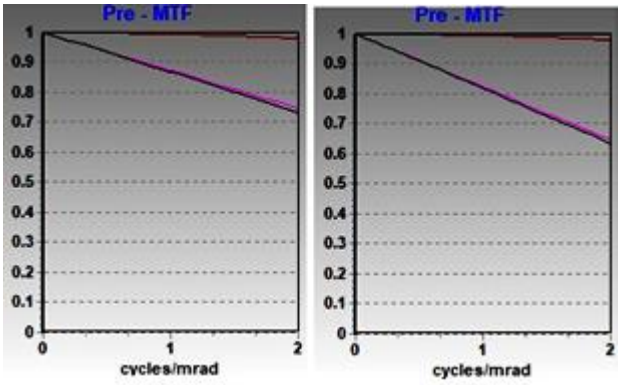


Figure 4. Modulation transfer function variation precalculated with Maviiss 1.5 using a 0.5 μm filter (left), respectively 0.7 μm filter (right)

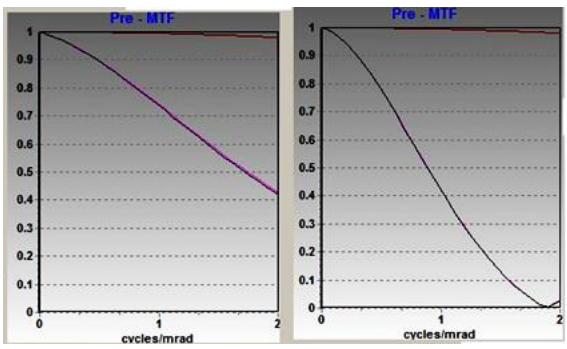


Figure 5. MTF variation precalculated with Maviiss 1.5 in the case of simulating the variation of contrast sensitivity by 50% defocusing (left) and 100% (right)

Because testing a patient with a pupillary size of 3 mm offers a 20% better MTF than the situations in which the pupillary diameter is 5 mm (Maviiss 1.5 limitation, which doesn't allow a value less than 5 mm), the results will be amended by 10-20% for pupils with 4 and 3 mm diameter. To appreciate quantitatively the influence of GI on the image blurriness we considered two distinct lens defocusing values: 0.50 and 1.0;

- We compared the values of mean GI versus OCT (figure 6);
- We chose two extreme values of central retinal thickness from the OCT scans and we associated them with the MTF variations (taking into consideration that there is a proportionality with the photoreceptor density)

For the study of the correlation between the GI and CS, the data is synthetically presented in tables 1 and 2 and represented in figures 6, 7 and 8.

Table 1. Patients with diabetic retinopathy

Age (years)	Glycaemia (mg/dl) 9:00	Glycaemia (mg/dl) 12:00	Glycaemia (mg/dl) 15:00	Glycaemia (mg/dl) 18:00	Contrast sensitivity (%) 9:00	Contrast sensitivity (%) 12:00	Contrast sensitivity (%) 15:00	Contrast sensitivity (%) 18:00
68	147	134	211	181	25	15	15	25
59	170	227	218	231	15	25	15	25
63	177	193	142	158	2	3.5	2	2
77	138	100	204	111	3.5	5	2	5
66	207	148	127	148	3.5	3.5	3.5	2
63	91	126	104	190	5	5	5	5
92	100	108	208	196	3.5	3.5	3.5	5
65	254	219	243	185	3.5	5	5	5
67	123	91	110	118	3.5	3.5	2	3.5
68	161	105	136	160	2	2	3.5	2
53	176	153	230	202	3.5	3.5	3.5	3.5
76	208	180	140	215	3.5	3.5	3.5	3.5

Table 2. Patients without diabetes mellitus

Age (years)	Glycaemia (mg/dl) 9:00	Glycaemia (mg/dl) 12:00	Glycaemia (mg/dl) 15:00	Glycaemia (mg/dl) 18:00	Contrast sensitivity (%) 9:00	Contrast sensitivity (%) 12:00	Contrast sensitivity (%) 15:00	Contrast sensitivity (%) 18:00
79	170	109	108	134	2	2	3.5	2
79	186	115	144	146	3.5	5	3.5	5
62	167	133	174	197	2	2	2	2
74	128	183	132	151	1.25	2	1.25	2
72	120	198	156	171	3.5	3.5	3.5	3.5
67	156	193	123	132	2	3.5	2	2
66	137	99	94	145	2	3.5	3.5	5
78	133	178	196	161	5	10	5	10
74	121	133	120	151	3.5	10	5	2
74	121	133	120	151	2	2	3.5	2

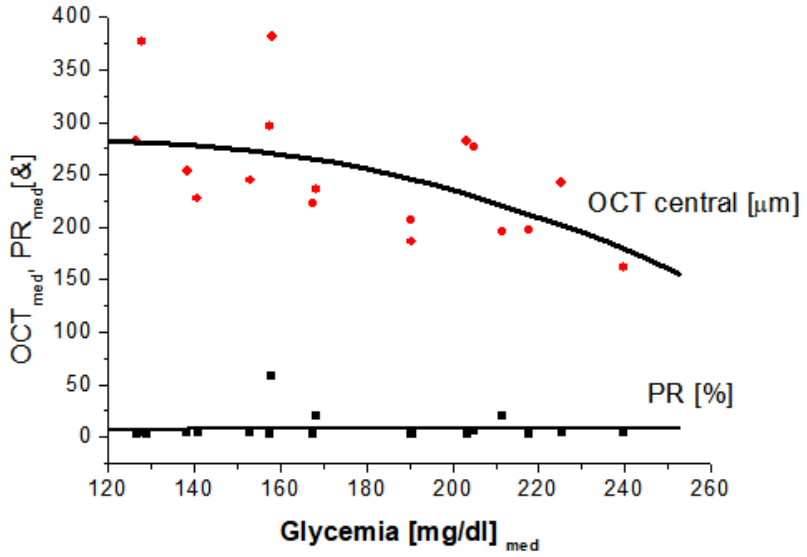


Figure 6. Optical coherence tomography variations depending on mean GI in patients with diabetes. Contrast sensitivity increases slowly with glycemic level, but the central retinal thickness in the foveal area decreases markedly in patients with glycemic levels above 180.

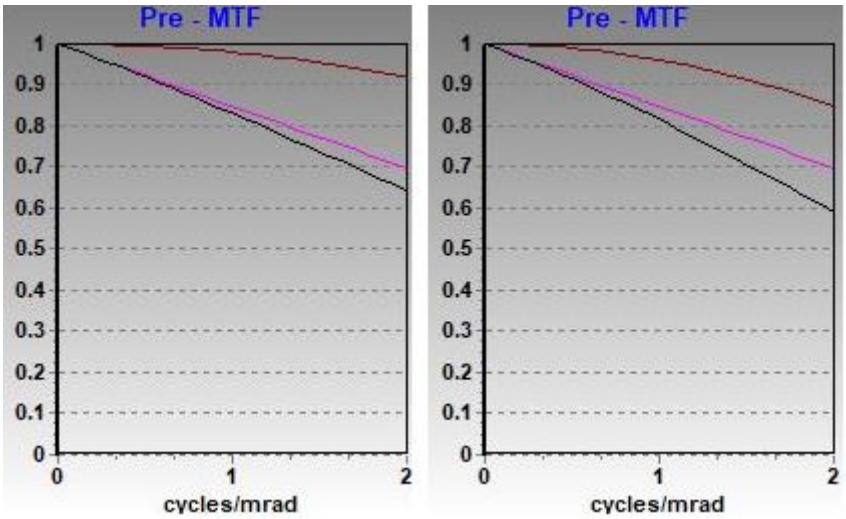


Figure 7. Modulation transfer function variation with mean glycemic level, realized with Maviiss 1.5, for a 40% variation of OCT (between 275 corresponding to GI of 140 and 175 corresponding to GI of 240)

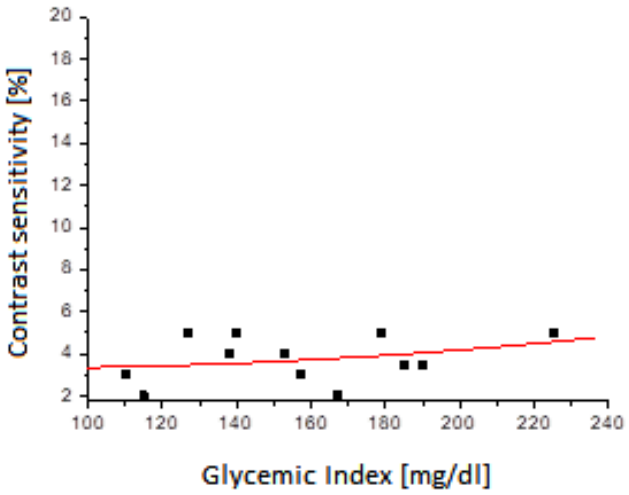


Figure 8. Mean variation of contrast sensitivity compared to glycemic level for right eye. We can notice that a GI increasing leads to a reduction in CS.

Although individual variations are significant, the mean variation of CS depending on the GI is relatively small in the interval 100-240.

For further information, the data was recorded with ImageJ for the mean retinal thickness of the photoreceptor layers (tables 3 and 4), then the following graphs show the relationship between the foveolar thickness and the glycemic index for the patients with and without diabetes (figure 10 and figure 11).

3.2. Image analysis with IMAGEJ

Macular Cube 512x128 images were individually processed with ImageJ. The variation of two parametres was observed: the photoreceptor layer thickness and the area occupied by this, transversally, compared to the total area of the section in the foveolar zone. Photoreceptor layer thickness was measured in three different points: one central and two peripheral, symmetrical to the first one, respecting the size of the foveola. (Figure 9).

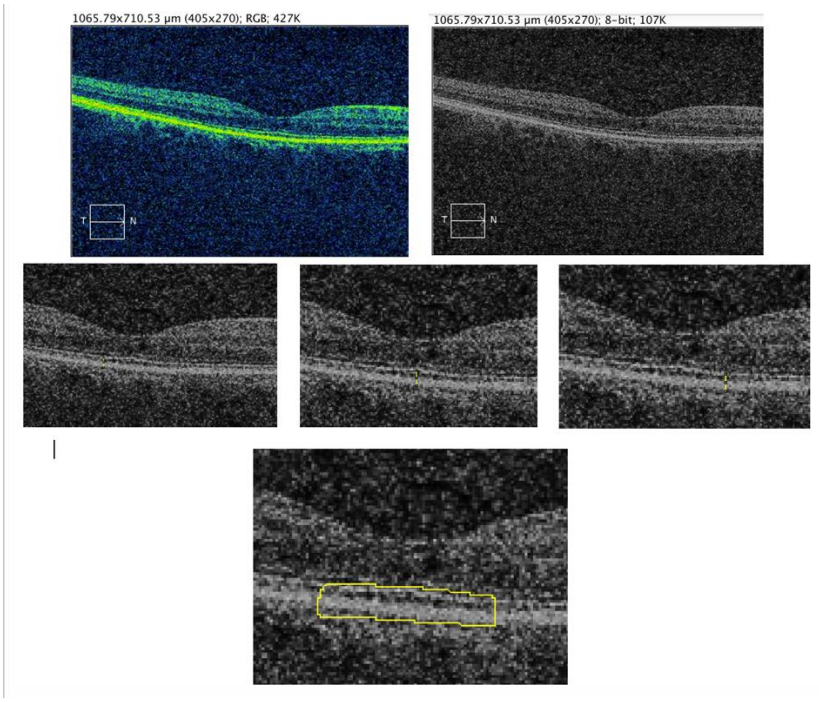


Figure 9. Steps taken during image processing for measuring photoreceptor layer thickness and area using ImageJ.

The advantage of using ImageJ was the possibility of measuring distances directly, with 1 µm precision. Also, we could delimitate the foveolar zone of the photoreceptor layer for calculating the total area and the one corresponding with the rodes and the cones, so that we could determine the report of the two areas.

Table 3. Patients with diabetic retinopathy

Age	Sex	Time	Glycemic Index (mg/dl)	Ratio photoreceptor cells area/ total foveolar area	Mean foveolar thickness (μm)
59	F	9.00	170	97.59%	28.95
		12.00	227	92.62%	26.32
		15.00	218	95.01%	28.95
		18.00	231	98.31%	30.70
65	M	9.00	245	97.54%	29.82
		12.00	179	93.38%	29.23
		15.00	118	97.10%	28.07
		18.00	271	92.69%	26.32
53	F	9.00	176	97.79%	24.56
		12.00	153	96.41%	24.12
		15.00	230	90.72%	22.81
		18.00	202	94.49%	22.81
53	M	9.00	186	98.07%	25.88
		12.00	250	95.27%	24.12
		15.00	185	98.21%	24.12

		18.00	199	98.00%	24.12
76	F	9.00	208	94.73%	24.56
		12.00	180	93.27%	23.25
		15.00	140	98.31%	24.12
		18.00	215	94.07%	24.56
69	F	9.00	114	97.84%	24.12
		12.00	141	98.16%	23.69
		15.00	225	97.51%	25.00
		18.00	282	94.13%	22.80
58	F	9.00	287	93.66%	25.44
		12.00	240	94.22%	23.25
		15.00	191	95.37%	25.00
		18.00	153	95.44%	24.56

Table 4. Patients without diabetes mellitus

Age	Sex	Time	Glycemic index (mg/dl)	Ratio photoreceptor cells area/ total foveolar	Mean foveolar thickness (μm)
79	F	9.00	170	93.24%	23.25
		12.00	109	96.70%	22.81
		15.00	108	97.22%	21.64
		18.00	134	97.50%	23.83
79	F	9.00	186	95.83%	24.09
		12.00	115	98.97%	24.56
		15.00	144	98.55%	22.81
		18.00	146	97.21%	25.00
72	F	9.00	120	97.79%	24.56
		12.00	198	95.56%	24.12
		15.00	156	97.52%	24.12
		18.00	171	97.09%	23.68
67	F	9.00	156	95.57%	21.05
		12.00	193	95.57%	22.00
		15.00	123	98.15%	21.49
		18.00	132	97.45%	21.74
66	M	9.00	137	97.66%	20.18
		12.00	99	98.99%	19.74
		15.00	94	99.40%	18.86
		18.00	145	93.18%	21.49
78	M	9.00	133	94.62%	24.17
		12.00	178	95.58%	23.68
		15.00	196	93.83%	24.12
		18.00	161	97.37%	21.16

The data from the two tables was worked and the results are shown in figure 10.

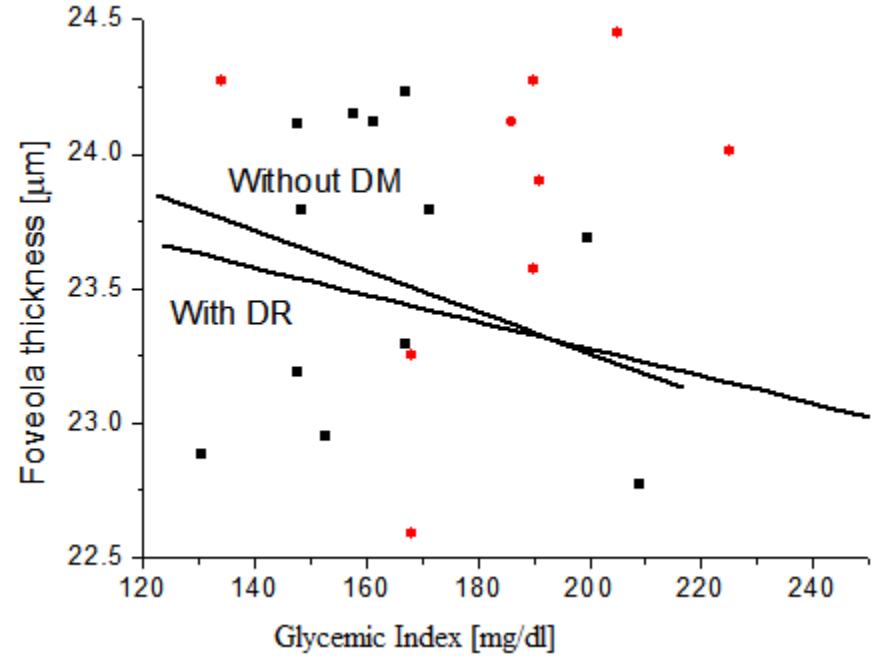


Figure 10. The variation of foveolar thickness compared with the glycemic index in patients with diabetic retinopathy and those without diabetes mellitus

We have noticed that, in diabetic patients, the foveolar thickness decreased less compared to the one in patients without diabetes mellitus.

4. DISCUSSIONS

In patients without DM, macular thickness is not related to age, although is generally higher in men compared to women [**15**]; so, in Goeebel's opinion [**16**]: the mean foveal thickness is approximately 153 µm, respectively 249 µm in the temporal parafoveal region, and 268 µm in the nasal parafoveal region. Some authors report a normal macular thickness of 212[µm] ± 20 [µm] for the fovea [**17**].

In patients with DM, according to another paper [**16**], retinal thickness was increased to 307 µm in the fovea, 337 µm in the temporal retina, and 353 µm in the nasal retina, respectively; the macular thickness is approximately 270 µm [**18**]; visual acuity decreased along with the macular thickness [**19**]. Moreover, the density of photoreceptors decreased the more the glucose level increased. [**20**]. The variations of retinal thickness produce daily variations of ocular refraction, and also variations of visual acuity (referred to as spatial frequency SF, different depending the blood glucose level) **[21**]. Also, some authors [**21**] use contrast neuronal sensibility function (CSF); in their opinion, contrast sensibility (CS) and visual acuity are affected in DM. Other authors [**22**] use the modulation transfer function (MTF), as an indicator of the ability of the patient's eye to reproduce (transfer) some details (or SF) of the testing retinal area; the authors [**22, 23**] define CS as the ability to recognize details; between CS and threshold contrast (CT) there is a reverse proportionality, meaning CS = 1/CT (Contrast Sensitivity = $1/C_{threshold}$). For example, if CS is 4, CT = 1/4 = 0.25. Many a time, contrast is measured as percentage [**24**], the proportion multiplying by 100; so, for example, if the lowest perceived contrast is 5%, contrast sensibility will be 100/5 = 20 or, if the lowest contrast perceived by a person is 0.6%, contrast sensibility will be CS = 100/0.6 = 170.

In the present paper we are evaluating the influence of the glucose level/glycemic index (GI) on the quality of the vision, based on contrast sensitivity function (CSF), using modulation transfer function (MTF) and OCT. Modulation transfer function allows similar information to CSF, as we can notice in the following papers [**22**, **25-27**]; also, MTF has the advantage of highlighting the influence of the main optical components: lens, aqueous humor and retina, based on similarities between a camera and the eye [**26, 27**].

We have to mention that VA is the point where the CS line intersects the spectral frequency (SF) line [**23**]. There is the possibility of making a prediction of the influence of defocusing over CSF, taking into consideration that the optical changes lead to changes in MTF, and MTF behaves like CSF in this respect; a correlation between defocusing and MTF, respectively CSF is mentioned in this paper [**27**]. Maximum CSF is, according to this paper **[23**] between 2-5 cy/degree (or 0.028-0.011 cy/mrad), which corresponds to a value of MTF of 0.5-0.9 [**26**].

David Atchieson [**28**] used diffraction modulation transfer functions and model eyes to predict the effect of defocus on the contrast sensitivity function (CSF)

The importance of MTF is given by the ability of this function to be correlated to optical components (lens, aqueous humor and retina), according to this:

$$MTF_{eye}=MTF_{abberation}\cdot MTF_{defocus}\cdot MTF_{retina}$$

We have to mention that the variations of GI during a day, between 7:00 - 21:00 o'clock, have been analyzed in the paper [**29**], using MTF and VA, for pupillary diameters of 3 and 5 mm.

In our paper we show that by using optical filters with corrective lenses we can obtain a better contrast sensitivity because, as the glycemic index increases, VA decreases (similar to defocusing) [**05-32**]. Other efficient investigation and evaluation methods in diagnosis and treatment are presented in following papers [**33, 34**].

In the paper [**35-39**], Fumiki Okamoto, 2000, showed that the GI variation leads to hyperoptical variations, which can be improved by placing lenses in front of the eye, as treatment for improving CS. An alternative solution is represented by usage of optical filters with a wave length specific to yellow, even though we do not obtain a significant CT increase.

Starting from the paper [**40**], where it is mentioned the delimitation of the photoreceptor layer (ISel – photoreceptor inner segment ellipsoid band), we have selected the foveolar area to calculate the exact area occupied by cone and rod cells from the entire surface. As Saxena et al. [**35-38, 40**], there are situations in which the inferior limit can't be well demarcated on the OCT image from the Retinal pigmentation epithelium (RPE). Our study showed that, mostly in patients with diabetic retinopathy, the overlap between RPE and ISel is so pronounced that the area delimitated in ImageJ contained, inevitably, parts of RPE. This has not been as frequent in the patients without DM. For both groups we have to take into consideration a small percentage of error from this overlap.

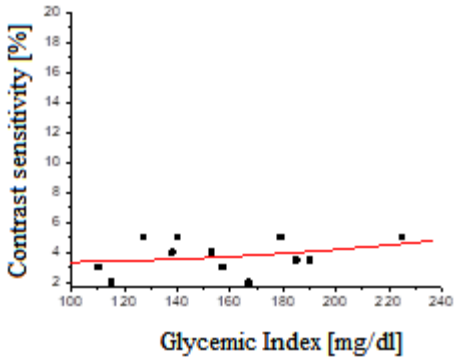


Figure 11. Patients with diabetes

Graph according table 1 regarding mean CS versus mean glycemia (σ_d=±0.45). Mean CS is **3.9**, and mean GI is **161.** Even if personal variations are significant, variation of CS with glycaemia is relatively small in the interval 100-240. This is why we have to consider the graph with foveolar thickness versus glycemic index.

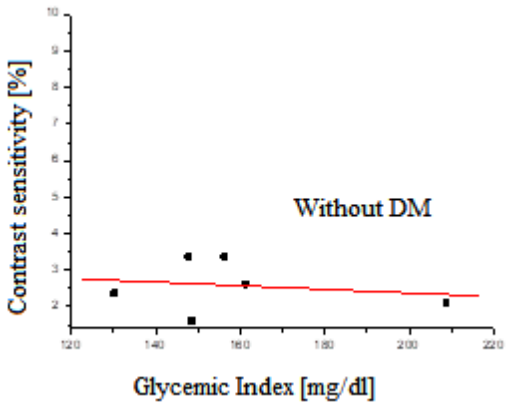


Figure 12. Patients without diabetes.

We represented in the graph mean CS versus mean GI in patients without diabetes mellitus. Mean CS is **2.58**, (σ_d=±0.7), so better CS than in diabetic patients.

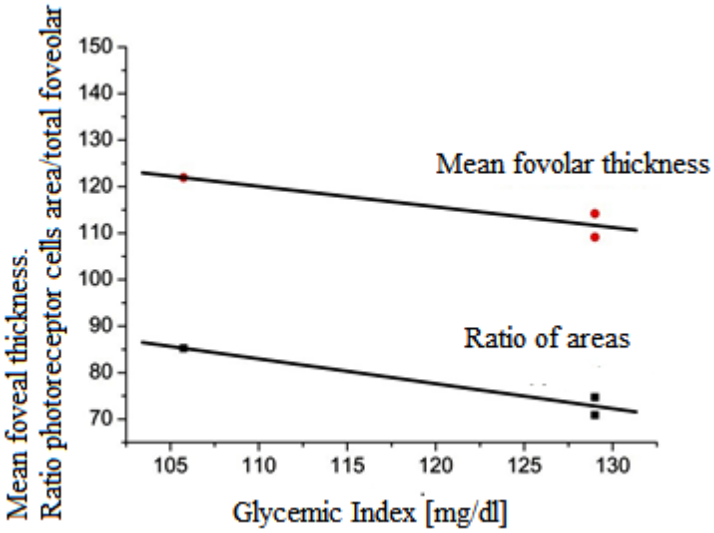


Figure 13. Graphic interpretation of the results from Table 3

5. CONCLUSIONS

Our results showed a correlation between the retinal thickness during daytime, contrast sensitivity loss and glycemic variations that can be used as further investigation tool.

New perspectives suggested by the results of our study allow proposing ImageJ software as a follow-up method for GI variations correlated with retinal thickness and using MTF function as an improvement method to contrast sensitivity correlated to glycemic variations.

Maviiss 1.5 software ensures a synthetically and objective appreciation of the image quality based on determination of MTF.

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