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A BRIEF STUDY ABOUT THE INFLUENCES OF GLYCEMIA VARIATIONS IN A NON-PROLIFERATIVE DIABETIC RETINOPATHY

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Abstract. *The present study is dedicated to some relationships between the variability of the contrast sensitivity and glycemic index in non-proliferative diabetic retinopathy. In this task, the authors have used Spectral Domain Optical Coherence Tomography (SD-OCT) image investigation and Pelli Robson Test during daytime, related to changes of parafoveal retinal layers with more 20 diabetic patients, with over 30 eyes available for analyses. For matched control group, the authors investigated 19 non-diabetic patients. Our results showed a correlation between the para-temporal and para-nasal retinal thickness during daytime, contrast sensitivity loss and glycemic variations that can be used as further investigation tool.*

Keywords: parafoveal diabetic retinopathy, retinal thickness, contrast sensitivity, glycemic index

1. Introduction

More 29 million people or 9% of the United States' population and 8.5% of Europe's population [1] are affecting by diabetes metabolic secondary disorders, like retinopathy, neuropathy, nephropathy, ischemic heart disease, cerebrovascular disease and peripheral vascular disease. [2].

The most frequently met is the diabetes as a result of insulin resistance, with a random glycemic level > 200 mg/dl or *a jeun* glycemic level > 125 mg/dl [3].

Diabetic retinopathy is an important cause of deterioration of vision for the patients affected by the disease and has a negative impact on patients' quality of life and their ability to successfully cope with the disease [4]. Retinopathy associated with diabetes is the main cause of acquired blindness in adult Americans [5].

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Optical coherence tomography (OCT) is a non-invasive imagistic method which allows microscopic visualization of the retinal morphology. The present study is based on OCT images (taken with Cirrus^{TM} HD-OCT model, produced by Carl Zeiss Meditec, Inc., aclass II) 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. A score below 3/10 is associated with a poor-quality image for Cirrus [26]. The authors analyzed 33 eyes from patients with diabetic non-proliferative retinopathy and 26 eyes–from patients without diabetic retinopathy and diabetes; 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) [5]. The diabetic patients were taking oral antidiabetic treatment. 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, 10-14]. 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 [5, 7-10].

2. Materials and methods.

2.1. Protocol used.

This study was conducted according to an ethical Committee regulation and all patients signed an informed consent [5]. For each patient has been recorded during daytime, at 9.00 am, 12.00 pm, 3.00 pm and 6 pm, OCT scanned images, glycaemia, systemic blood pressure and Pelli-Robson test. The authors 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).

2.2. Methods [5].

The data was obtained from a group of 23 patients, having diabetic retinopathy and 19 non-diabetic patients, each tested during a day (between the hours 9-18:00 o'clock), with spectral domain optical coherence tomography (SD-OCT) (Fig. 1) and Pelli-Robson contrast sensitivity test at one or both eyes. From OCT were collected values for retinal thickness in four different areas: nasal-parafoveal (N-para), inferior-parafoveal (I-para), superior-parafoveal (S-para), and temporal-parafoveal (T-para) (Fig. 2).

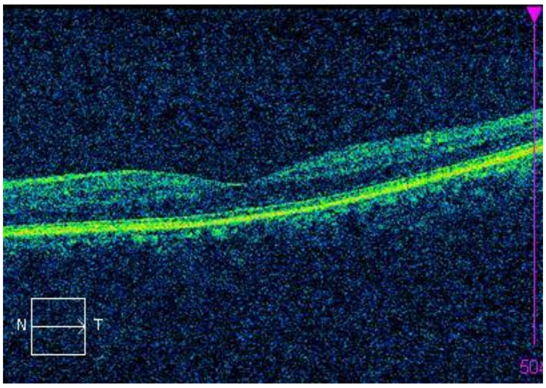

Fig. 1. Macular image from SD-OCT (macular cube)

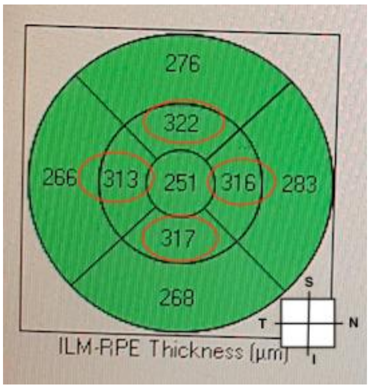

Fig. 2. Values for retinal thickness in four different para areas: nasal, inferior, superior and temporal.

3. Results

We compared the values of mean GI versus OCT (figure 3), the data being synthetically presented in tables 1 and 2.

Table 1. Variation of CS with GI for patients with diabetic retinopathy

Age (years)	Glycemia (mg/dl) 9:00	Glycemia (mg/dl) 12:00	Glycemia (mg/dl) 15:00	Glycemia (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. Variation of CS with GI for patients without diabetes mellitus

A1„	Glycemia (mg/dl) 9:00	Glycemia (mg/dl) 12:00	Glycemia (mg/dl) 15:00	Glycemia (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

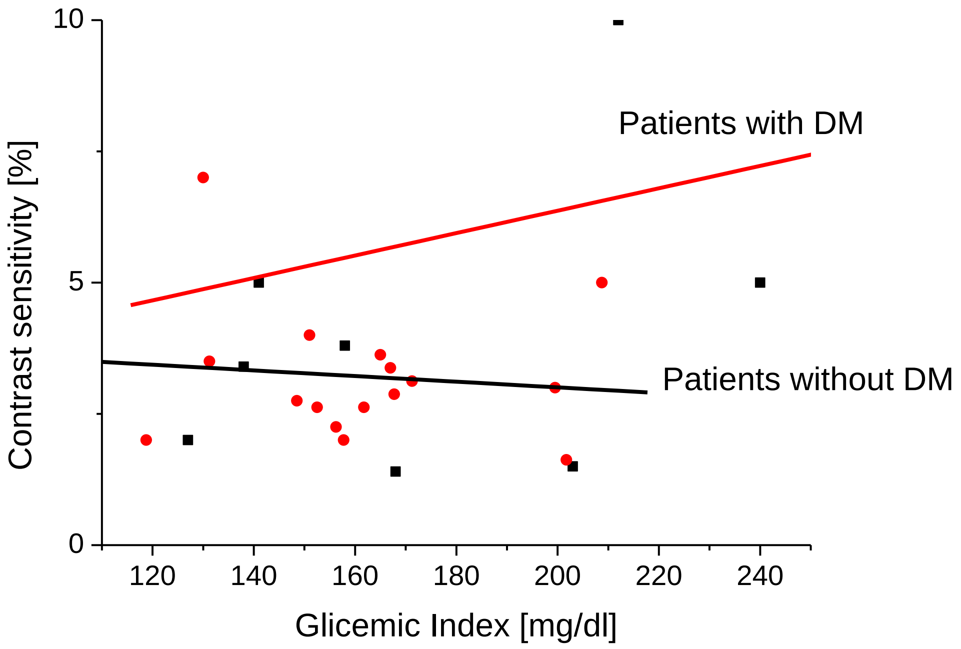

Fig. 3. Contrast sensitivity variation in correlation with glycemic index variation for both types of eyes.

To assess the influence of glycemic index (GI) variation on retinal thickness in the para-macular area (see Figure 2), data from the SD-OCT image (Table 3 and Table 4) were used for the four sectors: nasal, inferior, superior and temporal.

Table 3. Variation of retinal thickness with GI for patients with diabetic retinopathy

Age	Day, time	glycemic index	RIGHT EYE thickness (μm)					LEFT EYE thickness (μm)				
			N. PARA	I. PARA	S. PARA	T. PARA	mean thick-ness	N. PARA	I. PARA	S. PARA	T. PARA	mean thick ness
63	09:00	177	299	303	300	289	298	289	298	273	268	282
	12:00	193	302	304	304	291	300	291	295	278	278	286
	15:00	142	302	305	298	292	299	293	300	278	282	288
	18:00	158	299	302	302	289	298	291	296	279	279	286
68	09:00	104	299	288	302	284	293	306	299	298	289	298
	12:00	149	291	280	295	277	286	300	297	294	282	293
	15:00	242	292	280	296	273	285	302	297	294	283	294
	18:00	68	290	281	295	273	285	300	294	292	283	292
65	09:00	111	348	343	346	342	345	348	344	351	338	345
	12:00	95	348	337	338	336	340	348	339	346	337	343
	15:00	104	349	344	346	334	343	348	347	350	341	347
	18:00	196	352	348	349	341	348	349	344	346	334	343
65	09:00	245	319	316	316	309	315	333	324	320	313	323
	12:00	179	318	314	314	307	313	332	324	322	312	323
	15:00	118	317	313	314	308	313	330	323	319	309	320
	18:00	271	316	311	311	303	310	333	326	324	311	324
63	09:00	91	294	364	306	353	329	478	479	379	478	454
	12:00	126	375	369	388	415	387	449	493	391	448	445
	15:00	104	380	390	391	400	390	493	553	365	432	461
	18:00	190	392	393	398	436	405	416	463	347	404	408
65	09:00	254	311	298	319	309	309	302	304	305	283	299
	12:00	219	312	309	319	310	313	267	288	293	268	279
	15:00	243	316	317	322	313	317	261	306	303	284	289
	18:00	185	316	318	322	312	317	305	305	302	283	299
53	09:00	186	325	315	309	306	314	315	308	300	302	306
	12:00	250	322	311	312	305	313	315	310	313	298	309
	15:00	185	318	308	311	301	310	313	306	311	297	307
	18:00	199	320	310	310	302	311	313	308	315	302	310

Table 3. Variation of retinal thickness with GI for patients without diabetes mellitus

age	day time	glycemic index	RIGHT EYE thickness (μm)					LEFT EYE thickness (μm)				
			N. PARA	I. PARA	S. PARA	T. PARA	mean thickness	N. PARA	I. PARA	S. PARA	T. PARA	mean thickness
79	09:00	186	320	312	313	303	312	324	313	318	305	315
	12:00	115	316	310	309	298	308	326	315	320	306	317
	15:00	144	318	312	312	303	311	327	315	320	308	318
	18:00	146	318	314	311	300	311	327	317	323	310	319
66	09:00	180	267	306	303	286	291	301	289	302	277	292
	12:00	119	291	300	298	288	294	302	301	303	289	299
	15:00	210	290	302	301	294	297	301	302	300	285	297
	18:00	138	287	307	306	298	300	299	301	301	288	297
72	09:00	120	310	304	311	304	307	307	306	273	285	293
	12:00	198	310	304	311	297	306	296	293	294	285	292
	15:00	156	308	305	309	297	305	288	300	270	282	285
	18:00	171	310	305	311	305	308	296	300	296	297	297
78	09:00	133	312	314	315	307	312	305	302	309	298	304
	12:00	178	309	306	310	299	306	306	303	308	296	303
	15:00	196	309	306	310	297	306	305	301	310	299	304
	18:00	161	305	305	303	301	304	307	302	306	289	301
50	09:00	99	331	328	337	318	329	333	327	335	313	327
	12:00	123	331	328	334	320	328	342	335	348	329	339
	15:00	173	331	329	336	318	329	338	329	341	324	333
	18:00	236	327	329	328	317	325	334	326	338	322	330
74	09:00	121	288	280	294	286	287	289	288	302	279	290
	12:00	133	284	289	294	279	287	288	287	299	278	288
	15:00	120	283	286	290	277	284	288	288	301	281	290
	18:00	151	285	288	293	277	286	289	289	301	281	290

The processing of the data included in Tables 2 and 3 resulted in the following graphical dependencies:

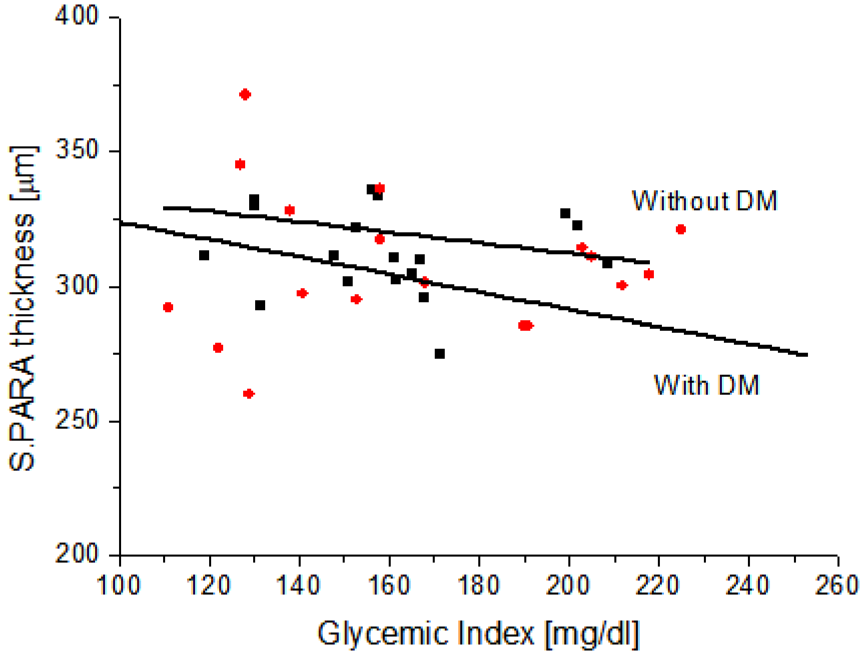

Fig. 4. Variation of retinal thickness
in the lower para-foveolar area.

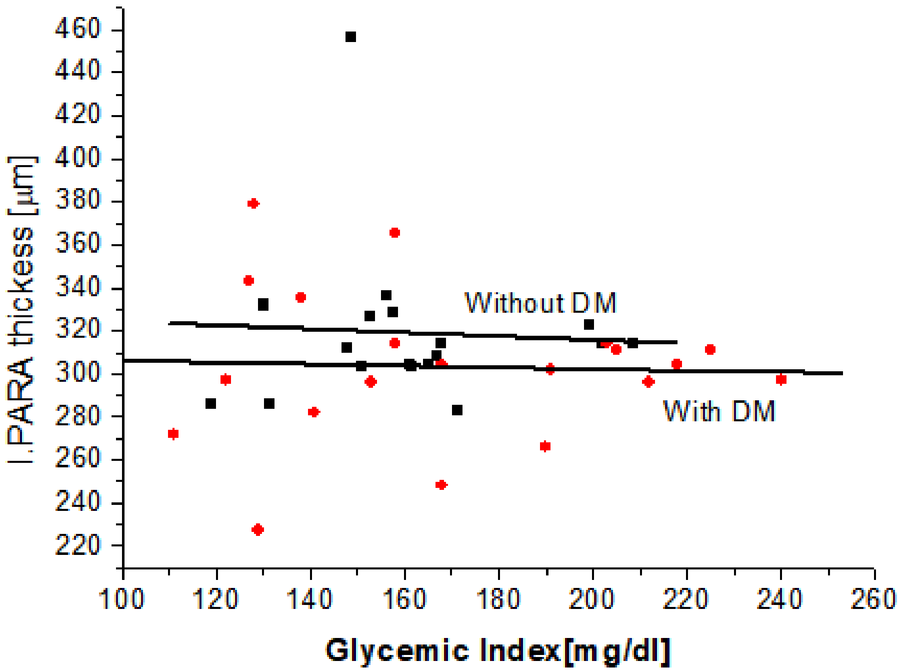

Fig. 5. Variation of retinal thickness
in the upper para-foveolar area.

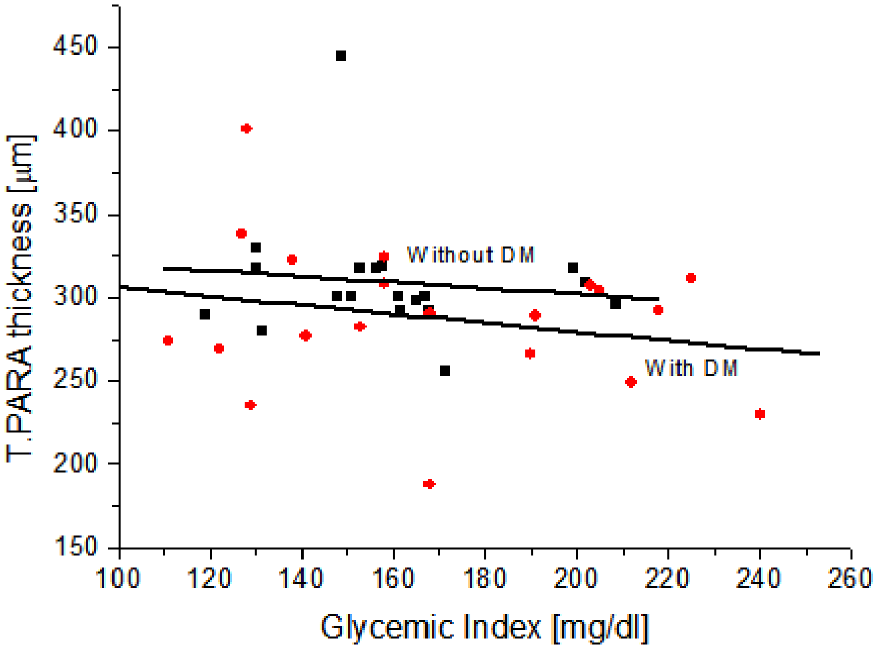

Fig. 6. Changing the thickness of the retina
in the area nasal para-foveolar.

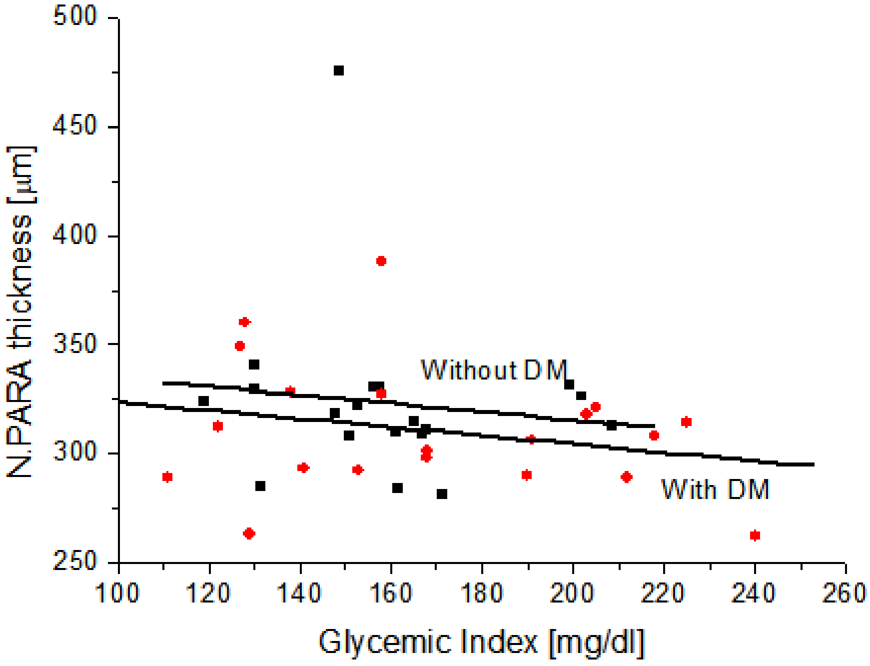

Fig. 7. Variation of retinal thickness
in the area temporal para-foveolar.

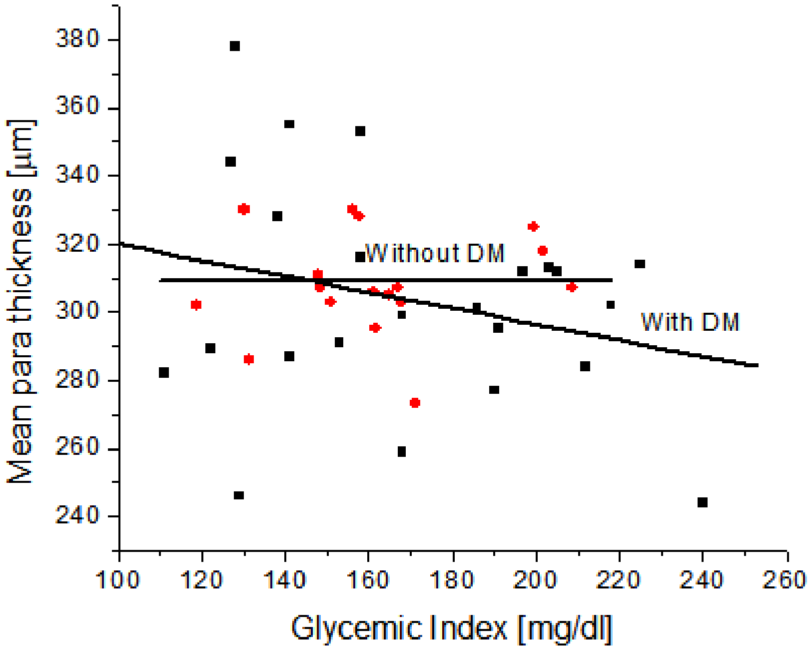

Fig. 8. The variation in the mean thickness of the retina in the para-foveolar area.

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 353µm in the nasal retina, respectively; the macular thickness is approximately 270µm [18]; visual acuity decreased along with the macular thickness [19]. Moreover, the density of photoreceptors decreased the more the glucose level increased. [20]. Other efficient investigation and evaluation methods in diagnosis and treatment are presented in following papers [19- 24].

Starting from the paper [14, 25], 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. [25, 26], there are situations in which the inferior limit can't be well demarcated on the OCT image from the Retinal pigmentation epithelium (RPE). Other 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 [5]. This has not been as frequent in the patients without DM.

For patients in both groups, there was no direct correlation of retinal thickness values in the parafoveolar area with age or between males and females. It can be appreciated that for the same age, the retina has a thickness predominantly over 300 μm in males, while in women it is predominantly below 290 μm.

At group level, a (generally significant) decrease in the thickness of the retina with increased blood glucose is observed for all parafovolateral regions, while the mean retinal thickness for patients without diabetes increases with the rise in the glycemic index.

For the 23 patients with diabetic retinopathy, for which data were collected from 33 eyes, one can differentiate into three age groups: group A (under 65), group B (between 65 and 70 years) and group C (over 70 years). Group B consists of 63.6% of the eyes, the others being equally divided between groups A and C. It is noted that all eyes in group A do not show variations in the mean retinal thickness greater than 5 μm, which is the measurement error of the device Cirrus. For group B, 12 eyes in 21 (i.e. 57.1%) show variations of less than 5 μm, while for group C, 66.7% of the eyes do not exceed a 5 μm variation in the mean thickness of the retina. It is possible that the variations in the thickness of the retina with the glycemic index variations will be relevant for that age range between the onset of vision problems caused by diabetes (the retina with some structural inertia) and the one in which visual problems are associated with both diabetes and with macular degeneration. Also, the lack of significant variation in retinal thickness is associated with the type of treatment followed by the patient, being even more evident in insulin-dependent patients. For the 19 patients without diabetes, for which data from 28 eyes were recorded, a differentiation can be made in the following age groups: group A (under 60 years), group B (between 60 and 75 years) and group C (over 75 years). Group B consists of 53.3% of the investigated eyes, the remainder being approximately equally divided among the other groups. By doing the same analysis of the retinal thickness variation below 5 μm, it is found that for the eyes of the group B the percentage of those little or not affected by the glycemic index variation is 60%, roughly the same as those in group B of the patients affected by diabetic retinopathy. For group B, small variations and large variations in retinal thickness in the parafoveolar area are equally common, while for patients included in group C, it is characteristic of the same inertia of the retina relative to blood glucose.

5. Conclusions

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

Therefore, CS increases with increasing of GI for patients with DM and decreases slowly for patients from control group.

For both groups, the retinal thickness decreases with increasing of GI within para, nasal and temporal foveolar areas. For inferior foveolar area de variation of the retinal thickness isn’t remarkable.

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. Also the study will continue with analyze of peri-foveolar areas.

R E F E R E N C E S

[1] Tamayo, T et al. **2014**, *Diabetes in Europe: an update.* Diabetes Res ClinPract, 103(2): pp. 206-17.

[2] Nathan, DM& D.E.R. Group **2014**, *The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview*. Diabetes care, 37(1): pp. 9-16.

[3] Kerner, W & Brückel, J **2014**, *Definition, classification and diagnosis of diabetes mellitus,* Experimental and Clinical Endocrinology & Diabetes, 122(07): pp. 384-6.

[4] Liu, Z, Kocaoglu, OP&Miller **2016**, *3D Imaging of Retinal Pigment Epithelial Cells in the Living Human Retina3D Imaging of RPE Cells in Living Human Retina*. Investigative Ophthalmology & Visual Science, 57(9): pp. OCT533-OCT543.

[5] Moraru, D et al. 2018, *Incursion in a Contrast Sensitivity Changes Related to Nonproliferative Diabetic Retinopathy,* Journal of International Scientific Publications, Materials, Methods & Technologies, ISSN 1314-7269, Volume 12: pp. 310-325.

[6] Cunha-Vaz, J&Coscas, G **2010**, *Diagnosis of macular edema*. Ophthalmologica, 224 Suppl 1: pp. 2-7.

[7] Drexler, W et al. **2001**, *Ultrahigh-resolution ophthalmic optical coherence tomography.* Nat Med, 7(4): pp. 502-7.

[8] Wojtkowski, M et al. **2004**, *Ophthalmic imaging by spectral optical coherence tomography.* Am JOphthalmol, 138(3): pp. 412-9.

[9] Sikorski, BL et al. **2013**, *The diagnostic function of OCT in diabetic maculopathy.* Mediators Inflamm, pp. 434-560.

[10] Sterian, PE. **2000**, *Fotonica*. Printech.

[11] Gavrilova ML, Gervasi O, Kumar V, Laganà A, Lee HP, Mun Y, Tan CJ, Taniar D, editors. **2005**, *Computational Science and Its Applications–ICCSA **2005***: International Conference, Singapore, May 9-12, **2005**: Proceedings. Springer-Verlag Berlin Heidelberg.

[12] Popescu, D.G. and Sterian, P., **2013**. Photonic crystal fiber mode characterization with multipole method. *UPB Sci. Bull., A Series*, *75*, pp. 205-215.

[13] Popescu, I.I. et al. **2010**, The Photon Wave Function and the Fresnel Formulas. *Romanian Reports in Physics*, *62*(2), pp. 360-368.

[14] Iordache, D.A., Sterian, P.E. and Tunaru, I., **2013**~~,~~. Charge coupled devices as particle detectors. *Advances in High Energy Physics*, *2013*.

[15] Adhi, M, et al. **2012**, *Macular Thickness by Age and Gender in Healthy Eyes Using Spectral Domain Optical Coherence Tomography*. PLoS One, 7(5), e37638.

[16] Goebel, W&Kretzchmar-Gross, T **2002**, *Retinal thickness in diabetic retinopathy: a study using optical coherence tomography (OCT).* Retina. The Journal of Retinal and Vitreous Diseases, 22(6):pp. 759-67.

[17] Chan, A et al. **2006**, *Normal Macular Thickness Measurements in Healthy Eyes Using Stratus Optical Coherence Tomography.* Arch Ophthalmol, 124(2): pp. 193–8.

[18] Chalam, KV et al. **2012**, *Retinal Thickness in People with Diabetes and Minimal or No Diabetic Retinopathy: Heidelberg Spectralis Optical Coherence Tomography*. Investigative Ophthalmology & Visual Science, 53(13): pp. 8154–61.

[19] Kakinoki, M et al. **2012**, *Comparison of Macular Thickness in Diabetic Macular Edema Using Spectral-Domain Optical Coherence Tomography and Time-Domain Optical Coherence Tomography*. Journal of Ophthalmology, Article ID 959721, pp. 1-5.

[20] Gupta, P et al. **2013**, *Determinants of Macular Thickness Using Spectral Domain Optical Coherence Tomography in Healthy Eyes: The Singapore Chinese Eye Study*. Investigative Ophthalmology & Visual Science, 54(13): pp. 7968-76.

[21] Fara, S. et al. **2012**~~,~~. New results in optical modelling of quantum well solar cells. *International Journal of Photoenergy*, 2012.

[22] Porumb, G.G. et al. **2001**, *Infrared radiometer with digital signal processing for medical applications.* In ROMOPTO **2000**: Sixth Conference on Optics, International Society for Optics and Photonics, Vol. 4430.

[23] Popescu, D. **2012**. *FDTD analysis of photonic crystals with square and hexagonal symmetry*. Journal of Advanced Research in Physics. Jan 24; 2(2).

[24] Okamoto, F. et al. **2000**, *Refractive changes in diabetic patients during intensive glycaemic control.* British Journal of Ophthalmology, Oct 1;84(10): pp 1097-102.

[25] Saxena, S. et al **2014**, *Photoreceptor Inner Segment Ellipsoid Band Integrity on SD-OCT*. Clinical Ophthalmology, Dove Press Journal, (8): pp. 2507-22.

[26] Hardin, J et al **2015**, *Factors Affecting Cirrus-HD OCT Optic Disk Scan Quality: A Review With Case Examples.* Journal of Ophthalmology, volume 2015, Article ID 746150.