STUDY OF THE INFLUENCE OF DIURNAL GLYCEMIA VARIATIONS IN THE HUMAN RETINA THICKNESS IN DIABETIC RETINOPATHY, THROUGH COMPARISON BETWEEN PARA-FOVEOLAR AND PERI-FOVEOLAR ZONES

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The paper aims to find possible relationship between variability of retinal thickness within para-foveolar and peri-foveolar zones to glycemic level in non-proliferative diabetic retinopathy (mild, medium and severe forms. The assessment of retinal thickness was made by using SD-OCT (Spectral Domain – Optical Coherence Tomography), during daytime, and by using comparison between para-foveolar and peri-foveolar zones. For some aspects, both para-foveolar and peri-foveolar zones have the same kind of thickness variations with glycemia diurnal variations, for both study groups considered. In the same time, variations are more visible for patients having diabetic retinopathy (DR) than those without diabetes mellitus (DM).

Keywords: optical coherence tomography, diabetes mellitus, diabetic retinopathy, retinal thickness, para-foveolar, peri-foveolar

1. Introduction

Optical Coherence Tomography (OCT) has emerged during last decade as an important tool for the evaluation of retinal layers, in order to visualize, to identify and to monitor more precisely different retinal diseases. One of them is retinopathy, who became the subject of this study.

Optical Coherence Tomography is a non-invasive imaging method, having high resolution, which not implies utilization of optical ionizing radiation and which offers in-time images of in vivo tissues. This method drifts from lower coherence interferometry. Theoretical basics of OCT were established by two mathematicians (D. Huang and M.R. Lee) and this work was presented in [1].

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The main parts of an OCT are as following: light source, scanner and detections systems. The NIR light beam reaches the splitter mirror; from this one beam is going to the probe, the other one to the reference mirror. The two beams, on their return ways, overlap and create interference image. This investigation method has the capacity to deliver tissues images with high depth resolution, histologic visible. OCT is of interest to ophthalmology, to dermatology, to dentine imaging or, using catheter, to internal organs.

Specialized papers indicate the following OCT methods [2]: frequency domain (FD-OCT), time domain (TD-OCT) and spectral domain (SD-OCT). The last one could be of two types: based on a spectrometer (SB-OCT) or having laser with controlled frequency (SS-OCT). The swept-source version proves to be the fastest OCT methods which offers enough clarity of in vivo images.

For both spectral-domain methods it is a limitation for coherence length for interference who is decreasing with increasing the emitting spectral length. The advantage of this method consists in N times greater sensitivity (N being the number of spectral windows in OCT) and in superiority regarding acquisition data rates (a much better signal/noise ratio).

In short time after the first OCT utilization, the number of researches in this field increased very much, therefore in 2009 were published in Web of Science, each day, 5 articles on the average [3]. Many authors have compiled and inventory of the field of using OCT, highlighting its advantages compared to other bioimaging methods or the versatility of the system and its continued development. [4] [3].

Within an article published in Review of Optometry [5], is underlined the idea of using OCT during DR evaluation and monitoring, instead of fluorescence (FA). OCT allows ophthalmologists to evaluate retinal microvascular system more detailed than traditional method. Retinal vascularization evaluation is an important investigation of diabetic patients monitoring. FA becomes more and more demanding when advanced diabetes stages, because the weakness of intravenous access they have. Because this reason, OCT as non-invasive method is an optimal monitoring investigation, offering a better visualisation of retinal micro-vascularisation for patients with DR. Images provided by OCT (on an 8mm x 8mm area) contain optic nerve head (ONH), macula and posterior pole during one single investigation.

Diabetes Mellitus (DM) has become one of the most prevalent health worldwide problems during last years. Type 2 of DM as the most common form of DM typically occurs in adult patients, meanwhile Type 1 diabetes typically occurs in young patients.

If in 2013 the estimated number was 382 million people suffering from DM and 415 million in 2015, this number could rise to 592 million in 2035, or 642 million in 2040 [6]. In recognition with this estimation, at European level was

developed a strategy based mainly on prevention and control of this chronic disease (arisen from The Joint Action on Chronic Diseases and Promoting Healthy Ageing Across the Life Cycle). [7]

The evidences shown that for Romania in 2015 the percentage was 8.5 from entire population and the prognosis shows that this will be around 13.7 in 2040, which means that Romania will be among seven most European countries affected on long term. In the same time, the estimated average diabetes-associated expenditure per adult person with diabetes in Romania in 2015 was €860, the lowest at Europe level.

It's known that DM is the cause of diabetic retinopathy (DR) which is the major vision-threatening nowadays (around 30%). That's why early detection and regular investigations of ocular complications of DM is important in order to decrease its negative impact on patients view, to avoid eyesight losing or at least to obtain a slower DR evolution.

DR appears along more or less years, through multiple retinal blood vessels deteriorations, followed in 2.6% cases by blindness. DR consists mainly in micro-aneurisms, in lack of capillarity perfusion and in some ischemia. This disease can be present under two versions: proliferative (PDR) and non-proliferative (NPDR). For this study we included only patients with non-proliferative diabetic retinopathy. NPDR appears when retinal blood vessels become fragile and allow fluids to leave for their exterior. In this way the ophthalmologists could observe on various devices (on OCT images clearer and more detailed) some signs as haemorrhages, micro-aneurisms, exudates, sometimes inter-retinal micro-vascularisation anomalies. PDR is installed when new and abnormal blood vessels appear in different retinal sectors, who is easily followed by eyesight loss. [8]

2. Methods

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

This study is based on OCT images resulted from investigation of 24 patients with DR and 19 patients without DM as control group. The patients had variable glycemic index (GI) values during daytime, at 9.00, 12.00, 15.00 and 18.00 o'clock. Initial group contained almost 80 patients, but many of them have been excluded because they couldn't participate to entire investigation process having other medical issues or their results on OCT had a score below 4/10, the limit established for at least a medium relevance for our study aims. Some works [9] recommended 4 to 7/10 score for a better SD-OCT scanning and over 8/10 score for a high quality.

For this study was used for OCT scanning Cirrus^{TM} HD-OCT model from Carl Zeiss Meditec, Inc., class II (acc. 21 CFR 886.1570). This model is a computing device which takes and analyses cross-sectional tomograms of anterior and posterior ocular structures (including cornea, retina, optic nerve head layers, macula and optic disc). During data acquisition we tried to avoid those factors who can have an important influence in optic disc scan quality as patients-dependent factors, operator-dependent factors and device-dependent factors, in according with Harding J.S.'s article [10], and also different other factors who can be involved in medical scientific investigations [11].

3. Results and discussions

Following the same steps in collecting and interpretation of data as we did for para-foveolar zones [12, 13], here there are some of the data for peri-foveolar zones (nasal, superior, inferior, and temporal).

Table 1

Variation of retinal thickness with GI for patients with diabetic retinopathy

Age (years)	Day time	Glycemic index (mg/dl)	Retinal thickness (μm)				
			Peri-nasal sector	Peri-inferior sector	Peri-superior sector	Peri-temporal sector	Mean value
63	09:00	177	283	172	253	194	225
	12:00	193	282	247	256	239	256
	15:00	142	282	248	251	239	255
	18:00	158	275	244	252	229	251
72	09:00	130	287	264	276	274	275
	12:00	126	290	262	282	282	279
	15:00	106	287	269	277	270	276
	18:00	124	291	264	276	277	277
85	09:00	98	260	196	250	209	229
	12:00	160	253	192	262	207	228
	15:00	162	255	194	250	211	227
	18:00	96	249	214	195	182	210
66	09:00	207	288	262	268	250	267
	12:00	148	287	260	271	251	267
	15:00	127	285	255	274	253	267
	18:00	148	289	260	270	250	267
63	09:00	91	404	379	295	404	370

	12:00	126	393	376	291	309	342
	15:00	104	397	403	290	310	350
	18:00	190	370	397	291	310	342
92	09:00	100	264	248	249	240	250
	12:00	108	266	245	252	241	251
	15:00	208	266	250	249	242	252
	18:00	196	266	250	251	243	252
67	09:00	123	281	253	268	253	264
	12:00	91	278	253	271	255	264
	15:00	110	281	252	268	251	263
	18:00	118	280	253	270	252	264

Table 2

Variation of retinal thickness with GI for patients without diabetes mellitus

Age (years)	Day time	Glycemic index (mg/dl)	Retinal thickness (μm)				
			Peri-nasal sector	Peri-inferior sector	Peri-superior sector	Peri-temporal sector	Mean value
79	09:00	170	301	267	277	251	274
	12:00	109	301	267	275	253	274
	15:00	108	300	266	275	253	273
	18:00	134	302	270	278	261	278
79	09:00	186	285	260	268	255	267
	12:00	115	283	259	310	256	277
	15:00	144	285	259	268	257	267
	18:00	146	286	254	270	251	258
67	09:00	156	275	252	254	251	258
	12:00	193	277	256	257	240	257
	15:00	123	274	252	254	251	258
	18:00	132	275	251	257	249	258
66	09:00	137	271	228	252	237	247
	12:00	99	269	229	255	238	248
	15:00	94	269	228	257	238	248
	18:00	145	274	230	254	238	249
65	09:00	121	288	266	278	274	276
	12:00	124	288	268	278	274	277
	15:00	121	289	270	278	274	278
	18:00	154	289	262	282	277	278
74	09:00	121	268	257	243	245	253
	12:00	133	263	239	245	239	246
	15:00	120	264	245	249	239	249
	18:00	151	264	246	251	243	251
62	09:00	167	274	258	258	253	261
	12:00	133	279	257	265	256	264

	15:00	174	281	252	268	257	264
	18:00	197	278	255	248	250	258

The processing of the data included as examples in Tables 1 and Table 2 resulted in graphical dependencies shown in Fig. 1 to Fig. 6 :

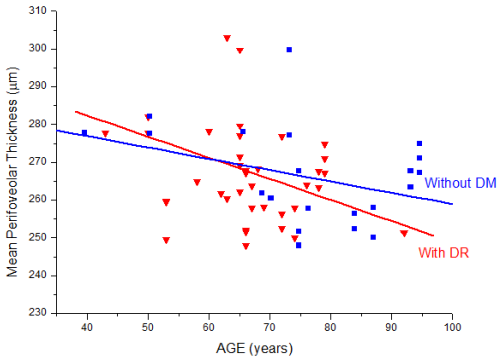


Fig. 1. Variation of peri-foveolar mean thickness with age for both study groups

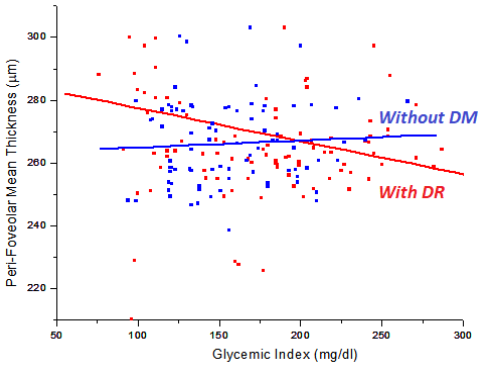
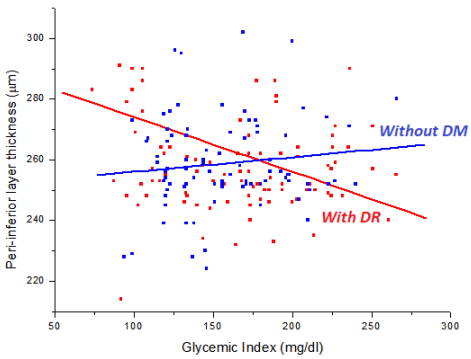


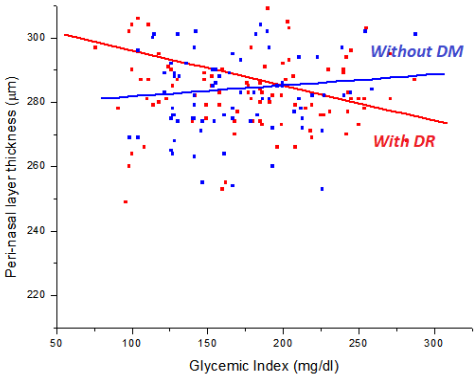
Fig. 2. Variation of peri-foveolar mean thickness with GI for both study groups

One aspect of the study results is regarding the dependence of retinal thickness within peri-foveolar zone with age (Fig. 1); for both groups was observed a decreasing of mean thickness with age, but this is more obvious for patients having diabetic retinopathy.

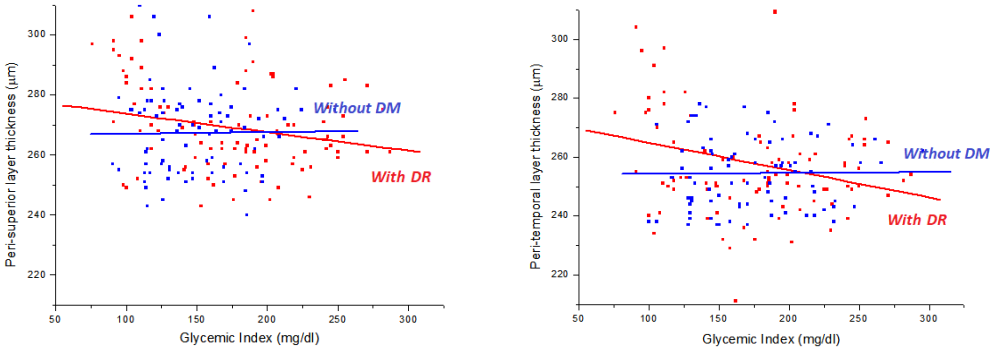
The data analyze indicate (Fig. 2) that the mean retinal thickness for peri-foveolar zones has a decreasing rate with increasing of glycemic index for patients with DR, but for those without diabetes mellitus the rate is so slowly increased that we can consider that it's not variable.



a)



b)



c) d)

Fig. 3. Variation of peri-foveolar thickness with GI
for both study groups and all sectors (a, b, c, d)

Observing the variation of retinal thickness with GI for all four peri-foveolar zones (Fig. 3) we can conclude that inferior zone shows the biggest drop, but also for the other three zone the decrease is considerable for patients with DR. For patients from control group there is a substantial increase for inferior and nasal zones, but very little for superior and temporal zones.

We have got an interesting perspective on these data, by using Origin 6.0 as tool, by comparative study between para and peri-foveolar zones, for both groups. Putting together all the data we have for para – foveolar and peri – foveolar zones we firstly concluded that both of them present a decreasing of the mean thickness with age almost with the same ratio (Fig. 4). For patients with DR the thickness has greater values for para-foveolar zone than peri-foveolar zone; for patients without DM is contrary, the thickness being greater for peri-foveolar zone than para-foveolar zone. It seems that DR, in time, affects less retinal layers thickness around foveola than at the border of macula.

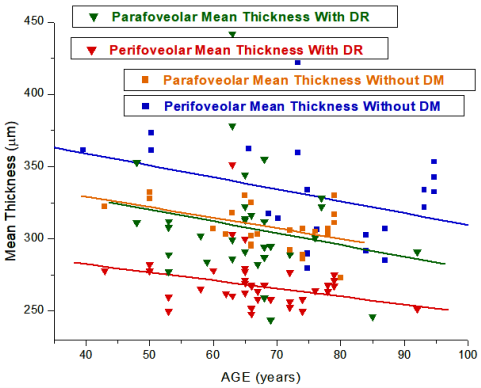
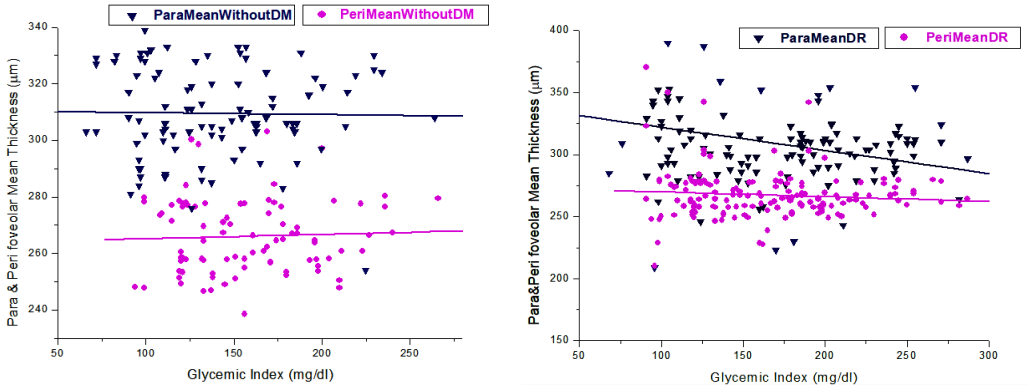


Fig. 4. Variation of para-foveolar and
peri-foveolar mean thickness with age for both study groups

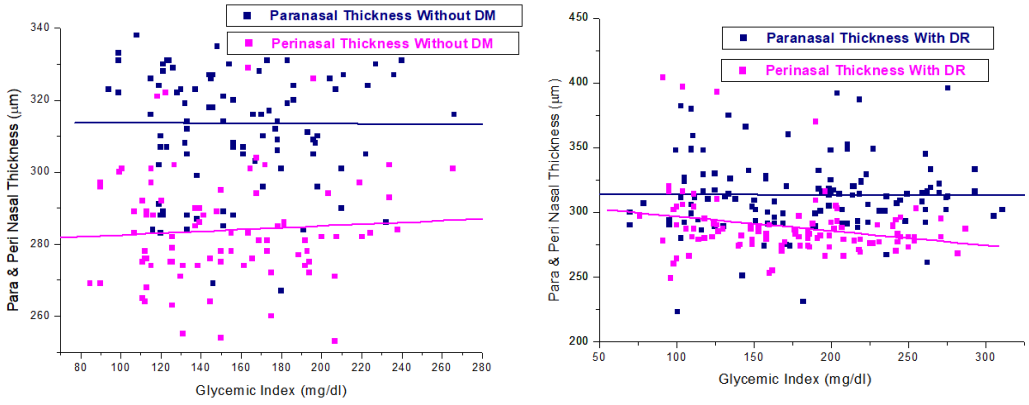
Taking the comparative analyze step-by-step we observed that retinal thickness variation with GI is obvious for patients with DR even is about the mean values or the sectorial values.



a) b)

Fig. 5. Variation of para-foveolar (a) and peri-foveolar
(b) mean thickness with glycemic index for both study groups

The most significant variation (decreasing in this case) of mean retinal thickness with increasing GI is for para-foveolar zone for patients with DR. The peri-foveolar zone seems to not be influenced in thickness by GI variation for both types of patients; the same thing is for para-foveolar for patients without DM. (Fig. 5)



a) b)

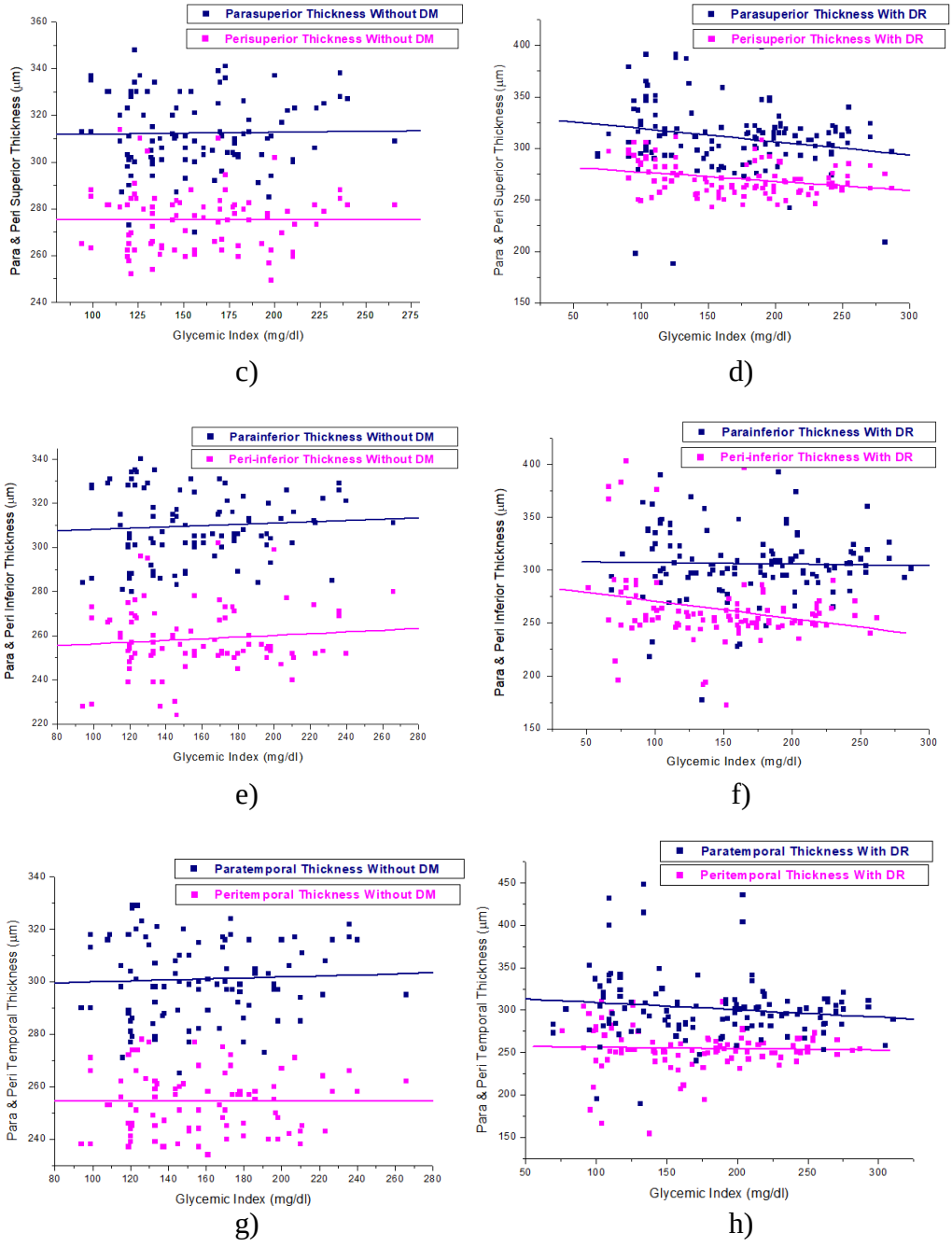


Fig. 6. Variation of para- and peri-nasal (a, b), para- and peri-superior (c, d), para- and peri-inferior (e, f), para- and peri-temporal (g, h) thickness with glycemic index for both study groups

If for the patients with DR the retinal thickness of different sectors is variable (mainly is decreasing) with glycemic index, for the patients from control

group the retinal thickness is almost constant, except peri-nasal and inferior sectors where could be observe a very slowly increasing with GI increasing (Fig. 6). Also, for this second group the values for retinal thickness are distributed almost evenly between 220 μm and 340 μm. But for the main study group all the values are concentrated on the approximative lines. This aspect could be interpreted as a trend for retinal thickness behavior for those patients affected by non-proliferative diabetic retinopathy.

4. Conclusions

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

Even the mean values for retinal thickness shown a pronounced decreasing for para-foveolar zones, the most important decreasing was observed in superior, inferior and nasal sectors for DR patients and peri-foveolar zone. In the main time, for patients without Diabetes Mellitus wasn't observed any significant increasing or decreasing of retinal thickness for para and peri-foveolar zones.

These variations could be explained, on one hand, by the effects of ELM disruptions due to fluid accumulation in this layer, and on the other hand even by photoreceptor damage. It's very probably that these processes could be irreversible for diabetic patients and so there are significant disruptions of retinal layers who leaded to seriously decreasing of layers thickness. It could be possible to make a correlation between this behavior and vascular endothelial growth factor (VEGF) who is considered a survival factor for retinal neurons. In 2010, J. Wang's team study [14] converged to the conclusion that Müller cell-derived VEGF plays an essential role in retinal inflammation, vascular lesions, and vascular leakage, these processes being derived from leukostasis process who is increased in diabetic retina and results in retinal vascular occlusion. Müller cells layer span the retina from pigment epithelium, being penetrated by light before photons activate photoreceptor cells. It can be acceptable that OCT doesn't offer information about each layer thickness, so decreasing of retinal thickness could be also the effect of progressive ganglion cells and astrocytes loss induced by diabetes [15] or the progressive modification of retinal pigment epithelium (RPE) for patients having RD. It still remains the questions regarding the differences between all 9 macula sectors given by OCT macula image.

This study stage requires to be followed by the same kind of analysis on data obtained using ImageJ for measuring the thickness of ellipsoid layer. A similar path has been taken in 2016, by B.D. Scoles's team [16] or W Dai's team [17].

R E F E R E N C E S

[1] *Huang D., Swanson E.A, Lin C.P, Schuman J.S., Stinson W.G., Chang W., Hee M.R., Flotte T., Gregory K., Puliafito C.A.* Optical coherence tomography. Science. 1991 Nov 22;254(5035):1178-81.

[2] *Podoleanu A.G.* Optical sources for optical coherence tomography (OCT). InLasers for Medical Applications 2013 (pp. 253-285).

[3] *Freitas A., Amaral M., Raele M.,* Optical coherence tomography: development and applications. InLaser pulse phenomena and applications 2010. InTech. Available: https://www.ipen.br/biblioteca/2010/17331.

[4] *Ogundiya A.O., Wushishi U.J., Babatunde O.,* Nat AP. IMPACT OF BUSINESS INTELLIGENCE (BI) TECHNOLOGIES ON COMPANIES .www.eng.ucy.ac.cy/cpitris/courses/ECE477/presentations/.../11-12.%20%20OCT.

[5] *Ferrucci S, Haynie JM.* OCT-A for AMD, Diabetes and Beyond: Imaging retinal and choroidal bloodflow can have a significant impact on how you diagnose and treat any number of ocular conditions. Review of Optometry. 2018 Sep 15;155(9):40-7.

[6] *Kumar B., Gupta S.K., Saxena R., Srivastava S.,* Current trends in the pharmacotherapy of diabetic retinopathy. Journal of postgraduate medicine. 2012 Apr. 1;58(2):132.

[7] *Richardson E., Zaletel J., Nolte E.,* National Diabetes Plans in Europe. World Health Organization 2016. 2016.

[8] *Amin J., Sharif M., Yasmin M.,* A review on recent developments for detection of diabetic retinopathy. Scientifica. 2016;2016.

[9] *Balasubramanian M., Bowd C., Vizzeri G., Weinreb R.N., Zangwill L.M.,* Effect of image quality on tissue thickness measurements obtained with spectral-domain optical coherence tomography. Optics express. 2009 Mar 2;17(5):4019.

[10] *Hardin J.S., Taibbi G., Nelson S.C., Chao D., Vizzeri G.,* Factors affecting Cirrus-HD OCT optic disc scan quality: a review with case examples. Journal of ophthalmology. 2015;2015.

[11] *Iliescu, F.S., Sterian, A.P., Barbarini, E., Avram, M. and Iliescu, C.,* Continuous separation of white blood cell from blood in a microfluidic device. UPB Scientific Bulletin, Series A, 71(4), pp.21-30, 2009.

[12] *Moraru D., Istrate S., Spulber C., Voinea L., Eniceicu C., Mihalcea R., Sterian P., Ciuluvica R., Careba I.,* Incursion in Contrast Sensitivity Changes Related to Non-proliferative Diabetic Retinopathy. Journal of International Scientific Publications, Materials, Methods and Technologies, ISSN 1314-7269, vol. 12, pp. 310-325, September 2018.

[13] *Moraru D., Spulber C., Istrate S., Eniceicu C.,* A Brief Study About the Influences of Glycemia Variations in a Non-proliferative Diabetic Retinopathy. Annals of the Academy of Romanian Scientists Series on Science and Technology and Information, ISSN 2066-8562, vol. 11, nr. 2, pp. 23-34, 2018.

[14] *Wang J., Xu X., Elliot M.H., Zhu M., Le Y.Z.,* Müller Cell-Derived VEGF is Essential for Diabetes-Induced Retinal Inflammation and Vascular Leakage. Diabetes Journals. 2010 Sept; 50:2297-2305.

[15] *Vujosevic S., Midena E.,* Retinal Layers Changes in Human Preclinical Early Clinical Diabetic Retinopathy Support Early Retinal Neuronal and Müller Cell Alteration. Hindawi Publishing Corporation, Journal of Diabetes Research, Volume 2013, Article ID 905058, 8 pages, http://dx.doi.org/10.1155/2013/905058

[16] *Scoles D., Flatter J.A., Cooper R.F., Langlo C.S., Robison S., Neitz M., Weinberg D.V., Pennesi M.E., Han D.P., Dubra A., Carroll J.,* Assessing photoreceptor structure associated

with ellipsoid zone disruptions visualized with optical coherence tomography. Retina (Philadelphia, Pa.). 2016 Jan;36(1):91.

[17] *Dai W., Tham Y.C., Cheung N., Yasuda M., Tan N.Y., Cheung C.Y., Wang J.J., Mitchell P., Sabanayagam C., Wong T.Y., Cheng C.Y.,* Macular thickness profile and diabetic retinopathy: the Singapore Epidemiology of Eye Diseases Study. British Journal of Ophthalmology. 2018 Aug 1;102(8):1072-6.