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Assessment of Macular and Choroidal Changes After Intravitreal Anti-VEGF Injections in Diabetic Patients with Diabetic Macular Edema

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Short title*:* Macular and Choroidal Changes After Anti-VEGF Injections

Abstract

Background: Diabetic retinopathy (DR) is a widely prevalent sequel of diabetes mellitus with multiple risk factors and predisposing conditions, it is a retinal vascular disorder characterized by many pathological changes and visible gross findings in the retina of the diabetic patients.

The purpose of the current study was to assess the macular and choroidal alterations using spectral domain optical coherence tomography (SD-OCT) imaging at baseline and one month after receiving intravitreal antivascular growth factor (anti-VEGF) (ranibizumab) therapy in patients who had diabetic macular edema (DME).

Methods: This was a prospective clinical study which was conducted on twenty eyes with type 2 diabetes with clinically significant macular edema (CSME). The intravitreal injection (IVI) of ranibizumab 0.3 mg was administered to the patients (0.05 mL). Prior to the injection and one month later, the central macular thickness, subfoveal choroidal thickness , choroidal thickness 500 m temporal and nasal to fovea were all assessed by SD-OCT.

Results: Postoperatively, the mean nasal, subfoveal and temporal choroidal thickness were 175.7±34.55, 185.6±29.13 and 183.9±34.62µm respectively. There was a statistically significant change in the best corrected visual acuity BCVA (p =0.04), the mean preoperative BCVA was 0.875±0.202 while the mean postoperative BCVA was 0.76 ± 0.22. The postoperative BCVA had a statistically significant (p= 0.03) negative correlation with the retinal thickness (r= -0.242), while it didn't have a significant correlation with the nasal, subfoveal and temporal choroidal thickness (p= 0.275, 0.248 and 0.343) respectively.

Conclusion: Injection of LUCENTIS® resulted in a decrease in choroidal thickness, which is a reflection of the impact LUCENTIS® had on the choroidal vasculature. This change was seen in all three areas. There was a substantial difference between the BCVA before injection and the BCVA one month after it, and this difference had a clear link to the thickness of the retina but not the thickness of the choroids.

Key words: Macular and Choroidal Changes - Intravitreal Anti-VEGF Injections - Diabetic Patients - Diabetic Macular Edema

INTRODUCTION:

Large numbers of people throughout the world are affected by diabetic retinopathy (DR), which manifests itself mostly as macular edema and proliferative retinopathy[1,2]. Microaneurysms and retinal capillary leaks are the main causes of diabetic macular edema (DME)[3].

The pathogenesis of DME has been linked to anomalies in the underlying choroidal vasculature as well as changes in the retinal vasculature that compromise the blood-retinal barrier (BRB)[3-5].

The swelling of the retina caused by diabetes is called diabetic macular edema (DME), and anti-vascular endothelial

growth factor (anti-VEGF) drugs are the standard treatment. Substantial evidence from several studies demonstrating enhanced optical and anatomical outcomes lends credence to this[6].

The choroid is a circulatory structure that aids the metabolism of the outer retina[7]. Insufficient choroidal blood volume and inadequate flow may be the result of a number of factors[8].

Choroidal maculopathy, which includes choriocapillaris obstruction, choroidal aneurysms , vascular degeneration, and neovascularization, may have a role in the DR pathogenesis[9].

Results from previous clinical investigations indicate that the severity of DR may be connected to the choroidal thickness, and that having DME is linked to much thinner than normal choroids. It's possible that the onset or advancement of the illness is responsible for these choroidal vascular abnormalities[3-5]. There may be long-term consequences or complications associated with the use of anti-VEGF drugs to decrease choroidal thickness in people with DR[10].

Improved depth imaging spectral-domain optical coherence tomography (EDI-OCT) imaging has allowed for better visualizations of the choroidal structures than was previously possible. Thus, choroidal thickness may be measured in a wide range of eye diseases[11].

Treatment for DME often entails intravitreal injections of anti-VEGF. Although anti-VEGF injections improved eyesight, multiple studies revealed a correlation with a thinned central retina[12]. Nonetheless, there is currently little evidence on the effects of anti-VEGF injections on the choroid in diabetics[13].

The purpose of this research was to use (SD-OCT) imaging before and after intravitreal antivascular growth factor (anti-VEGF) (ranibizumab) treatment to evaluate macular and choroidal changes in patients with diabetic macular edema (DME).

Patients and Methods

Subjects:

Twenty eyes of 20 participants with type 2 diabetes and clinically significant macular edema (CSME) were included in this prospective clinical study. All participants were recruited from the outpatient clinics of Benha University Hospital. Approval for the study was obtained from the local ethics committee and informed consent forms, which were in compliance with the requirements of the Declaration of Helsinki, were signed by all participants. Full ophthalmological clinical examination and (SD-OCT) imaging were used to evaluate CSME. According to the Early Treatment diabetic retinopathy study (ETDRS) protocol, CSME was diagnosed when the central retinal thickness was more than 300 m. The intravitreal injection (IVI) of ranibizumab 0.3 mg was administered to the patients (0.05 mL). Prior to the injection and one month later, the central macular thickness, 500 m temporal and nasal to fovea choroidal thickness, and subfoveal thickness were all assessed by SD-OCT..

Inclusion criteria included:

- Patients with type 2 diabetes mellitus, who have CME (macular thickness > 300 µm)
- Well controlled on oral hypoglycemic drugs
- Age > 40 years
- Spherical equivalent (SE): ranges from -2 to +2

Exclusion criteria included the following:

-Vitreomacular traction syndrome -Previous anti-VEGF or intravitreal steroids therapy for DME within six months of the first visit

- Probable or known glaucoma

-Cataract

-Diabetic retinopathy with proliferation

-Previous laser treatment for the retina

-Previous vitrectomy with pars plana

-High myopia (spherical equivalent >-6.00) and patients with posterior staphyloma

-Patients with ischemic maculopathy

-Foveoschisis

-Age-related macular degeneration

-Other causes of macular edema.

Methods:

All participants were underwent to the following:

I- Preoperative work-up:

Full ophthalmological examination was done with emphasis on:

- Best corrected visual acuity (BCVA) was measured using **Snellen** chart with conversion to **logMAR** notation for statistical analysis.
- Refraction was done to all patients by (**Topcon Auto-refractometer RM 8900)** to exclude high myopia.
- Intra -ocular pressure (IOP) was measured by non-contact air puff tonometer
- Detailed fundus examination (The posterior segment was examined by indirect ophthalmoscopy or by slit lamp with non-contact lens).

Fluorescein Angiography (FA):

- After pupillary dilatation with Tropicamide 1% eye drops, a fluorescein angiogram was performed with Spectralis HRA2 from Heidelberg Engineering in Germany. Patients who had ischemic maculopathy or proliferative diabetic retinopathy (PDR) were not included in the study.

Optical Coherence Tomography (OCT):

- OCT was done using **(the RTVue XR Avanti, Optovue, inc., OCT)** after pupillary dilatation with Tropicamide 1% eyedrops and informing patient about the steps of the procedure.
- **Central retinal thickness (CRT) measurement protocol:** A 6×6 mm^2 area on the B-scan map were used to record the central retinal thickness . All OCT images that has signal strength index (SSI) below 6 were excluded from the current study.

Choroidal thickness (CT) measurement protocol:

1-line raster improved depth imaging scanning of 300 with 768 A-scans per frame and an average of 100 frames. Two observers measured the choroidal thickness (CT) using a manual measuring ruler, perpendicularly from the outside edge of the hyper-reflective RPE to the inner sclera sub-foveally, and at intervals of 500 m temporally and nasally to the fovea up to 1000 m **.**

II – Operative Procedures:

- The patient was informed about the operative procedure steps then prepared and draped with the proper operative outfit.
- The procedure was done under topical anesthesia and proper sterilizing measurements.
- 0.3 mg of LUCENTIS® in 0.05ml was injected (3.5mm from the lower temporal limbus in phakic patients and 3 mm in pseudophakic patients) intravitreally (in the lower temporal quadrant) by a 27 gauge needle**.**

III – Postoperative Examination:

All patients were examined post-operatively to exclude any complications, and the intra ocular pressure (IOP) was measured.

Postoperative medications were:

- Topical antibiotic eye drops every four hours.
- Topical Anti-Glaucomatous given if the IOP was found to be elevated.

All patients were followed up 1 month and the postoperative examination was done including a full ophthalmological examination with special emphasis on:

- Best corrected visual acuity (BCVA).
- IOP.
- Biomicroscopic examination of the anterior segment was done to exclude any changes or complications.
- Fundus examination was done to detect fundus changes after the injection.
- OCT: (1 month postoperative)
- OCT was done using (The RTVue XR Avanti, Optovue, inc., OCT), CRT and CT were measured following the same preoperative steps and technique.
- Changes in the central retinal (macular) thickness and choroidal thicknesses were detected by subtracting the pre-operative macular and choroidal thicknesses from the post-operative macular and choroidal thicknesses for every case.

Statistical Analysis

The program used was SPSS version 20. Quantitative data were analyzed using mean and standard deviation, while

frequency and percentage were used with qualitative data. Paired t test was used to compare before and after within the same group. Pearson correlation found relationship between variables. P value was considered significant if it was ≤ 0.05.

RESULTS:

Twenty eyes of 20 patients from both sexes were included, undergoing intravitreal injection of LUCENTIS® for diabetic macular edema. The data was collected, tabulated and analyzed as follow:

The mean age of the studied cases was 57.3±8.71 years with a range from (44-79) years. The studied cases included 5 males (25%) and 15 females (75%). The study included 15 right eyes (75%) and 5 left eyes (25%).

The mean preoperative IOP was 17.7±2.79 mmHg and ranged from 14 – 22 mmHg. The mean immediately postoperative IOP was 20.2±2.75 mmHg and ranged from 16–25 mmHg. There was statistically significant difference between the mean of preoperative and immediately postoperative IOP (P <0.001) . Although patients' IOP returned to normal values the next day after the operation.

The mean preoperative BCVA was 0.875±0.202with a range from 1.00 to 0.3. The mean postoperative BCVA was 0.76±0.22with a range from 1.00 to 0.2**.** The difference between preoperative and postoperative BCVA was statistically significant (table 1).

Table 1: Mean and standard deviation of the preoperative and one month postoperative BCVA:

	Preoperative BCVA	**1 month postoperative BCVA**
Range	1.00 – 0.3	1.00 – 0.2
Mean±SD	0.875±0.202	0.76±0.22
P	0.04*	

p: p value for paired-test *: statistically significant at p≤0.05

According to the change in the BCVA there were 12 cases with improved postoperative BCVA (60%), 8 cases with the same BCVA postoperative (40%).

Preoperative (CT) was measured using EDI-OCT and the mean subfoveal, nasal, and temporal CT measurements were 204.5±50.01µm, 194.8±48.06µm and 201.65±50.41µm respectively.

EDI-OCT was used to quantify postoperative CT, and the mean values for nasal, subfoveal, and temporal CT were determined 175.7±34.55µm, 185.6±39.39.13µm and 183.9±34.62µm respectively. Table (2), figure (1)

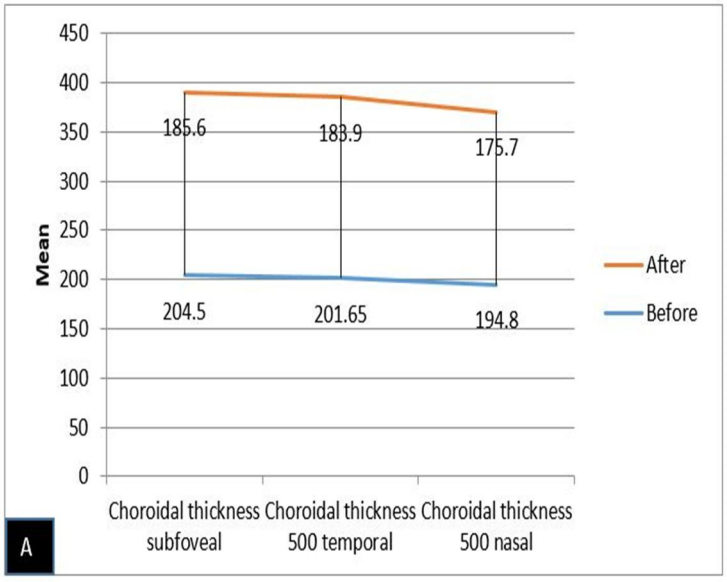
There was significant difference between the preoperative and the postoperative nasal, subfoveal and temporal CT (p: 0.007, 0.009 and 0.003) respectively.

Table 2: The mean and standard deviation of preoperative and one month postoperative choroidal thickness:

	Before		**After**		**Statistical test (Paired t)**	**P value**
	Mean	**SD**	**Mean**	**SD**		
Choroidal thickness subfoveal	204.5	50.01	185.6	39.13	2.89	0.009**
Choroidal thickness 500 temporal	201.65	50.41	183.9	34.62	3.45	0.003**
Choroidal thickness 500 nasal	194.8	48.06	175.7	34.55	3.02	0.007**

p: p value for paired t-test

*: statistically significant at p≤ 0.05



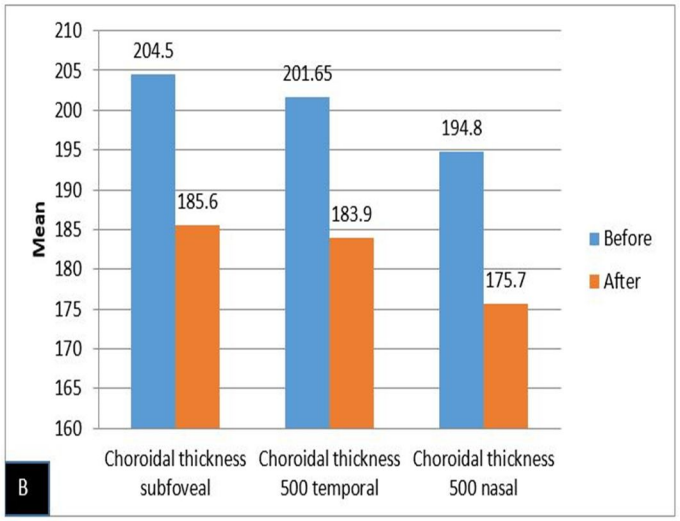


Figure 1: A and B: Comparison between the mean preoperative and one-month postoperative choroidal thickness (CT).

The choroidal thickness was reduced after injection of LUCENTIS® and the mean differences between the two measurements were (18.9±10.88µm) subfoveal, (17.75±15.79µm) temporal to the fovea and (19.10±13.51µm) nasal to the fovea. figure (2).

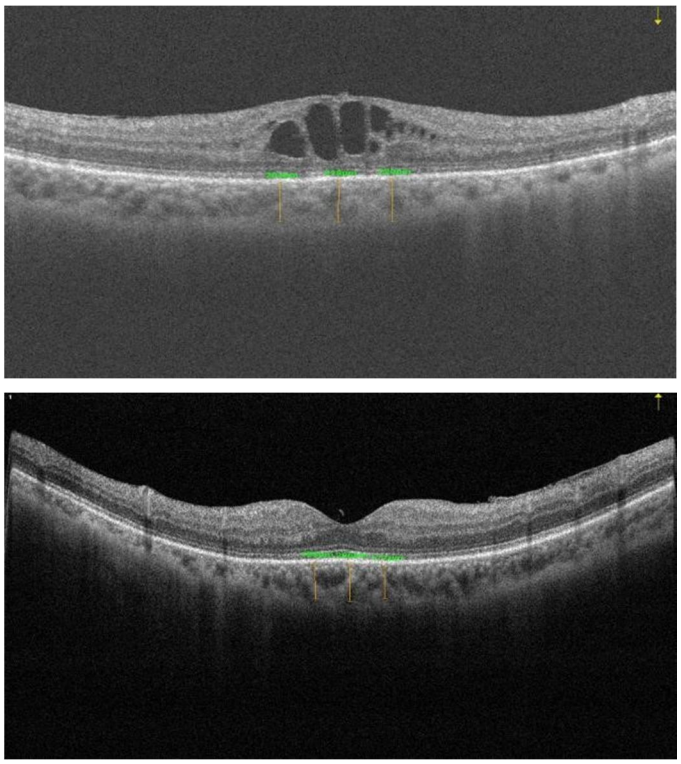


Figure 2 (A) Preoperative Gray scale EDI-OCT image with choroidal thickness measurements (B) Postoperative Gray scale EDI-OCT image with choroidal thickness measurements.

Preoperative central retinal thickness was measured and the mean thickness was 474.95±137.32µm with a range from 300µm to 879µm. One-month postoperative central retinal thickness was measured and the mean thickness was 387.3± 109.18µm with a range from 237µm to 635µm.There was statistically significant difference between preoperative and postoperative mean central retinal thickness. Table (3) .

Table 3: The mean and standard deviation of preoperative and one month postoperative retinal foveal thickness.

Retinal foveal thickness	**Preoperative**	**1 month postoperative**	**P**
Range	300 – 879	237 - 635	0.011*
Mean ± SD	474.95±137.32	387.3±109.18	

p: p value for paired t-test

*: statistically significant at p≤0.05

The central retinal thickness was reduced after injection of LUCENTIS® and the mean difference between the two measurements was 87.65±28.14µm with a range from 4µm to 376µm.

Table (4) and figure (3) show the correlation between the difference in choroidal thickness (µm) and the difference in retinal thickness (µm) among the studied cases. There was a negative correlation but it was statistically insignificant (P=0.340) subfoveal,(P=0.240) temporal and (P=0.426) nasal.

Table 4: Correlation between the difference in choroidal thickness and the difference in retinal thickness among the studied cases:

CMT	**After**	
	R	**P**
Choroidal thickness subfoveal	-0.225	0.340
Choroidal thickness 500 temporal	-0.276	0.240
Choroidal thickness 500 nasal	-0.189	0.426

CMT: central macular thickness r: Pearson coefficient

*: statistically significant at p≤0.05

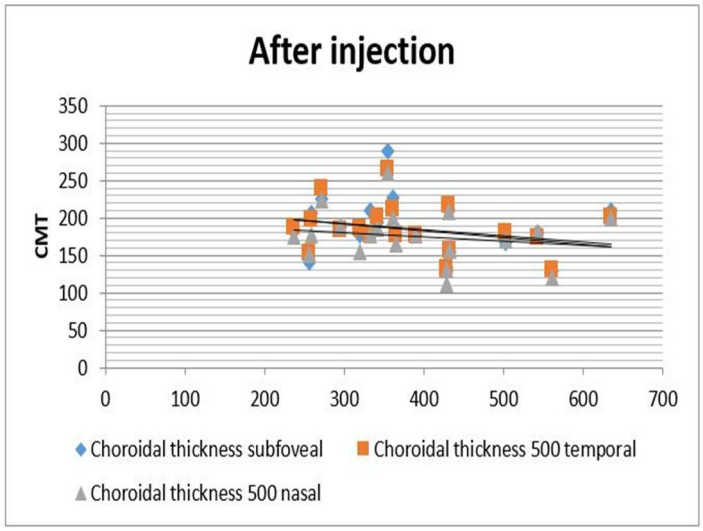


Figure 3: Correlation between the difference in choroidal thickness and the difference in retinal thickness among the studied cases.

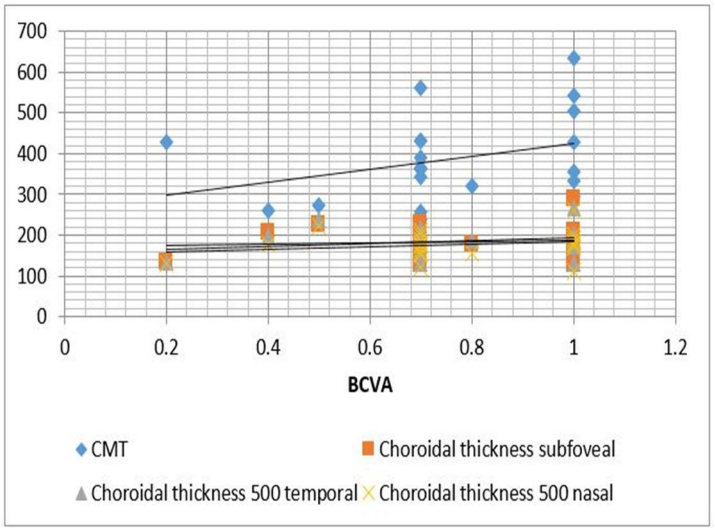


Figure 4: Correlation between the postoperative retinal thickness and postoperative choroidal thickness and the postoperative BCVA among the studied cases.

Table (5) and figure (4) show the correlation between the postoperative retinal thickness, the postoperative choroidal thickness and the postoperative BCVA among the studied cases. There was statistically significant (p=0.03) negative correlation between the postoperative retinal thickness and the postoperative BCVA (r=-0.242).

Table 5: Correlation between the postoperative retinal thickness, the postoperative choroidal thicknesses and the postoperative BCVA among the studied cases.

BCVA	**After**	
	r	**P**
CMT	-0.242	0.03*
Choroidal thickness subfoveal	-0.271	0.248
Choroidal thickness 500 temporal	-0.224	0.343
Choroidal thickness 500 nasal	-0.257	0.275

BCVA: best corrected visual acuity, CMT: central macular thickness

r: Pearson coefficient *: statistically significant at p≤0.05

Although the correlation between postoperative nasal, subfoveal, and temporal choroidal thickness and BCVA was negative (r=-0.257, -0.271, and -0.224), it was not statistically significant (p=0.275, 0.248 and 0.343) respectively.

DISCUSSION

Normal choroidal vasculature has an important function in the metabolic support of the outer retina[14]. Previous researches demonstrated that DR severity may be related to choroidal thickness, and a significant decrease in choroidal thickness than normal was seen in eyes with DME[14-15].

The anti-VEGF intravitreal injections are currently the most popular treatment for DME , that can improve visual acuity. Many previous studies indicated a correlation between improved VA & the reduction of the central retinal thickness[12]. However, few researches had studied the effect of intravitral anti-VEGF injections on the choroid in DME patients[16].

In the current study, the choroidal thickness was measured using the enhanced depth imaging approach. We concentrated on the central subfoveal choroidal thickness, 500 m temporal and 500 m nasal to the fovea to eliminate the anatomical variation, and we measured the choroid using the same guidelines from previous studies, i.e. perpendicularly from the outer edge of the hyper-reflective retinal pigment epithelium (RPE) to the inner sclera[17,18].

Numerous factors have an impact on choroidal thickness. When evaluating choroidal thickness, axial length (AL) and spherical equivalent (SE) which have been connected to significant changes in choroidal thickness, should be taken into account[19-20]. Regression analysis revealed that each diopter of myopia can cause reduction of CT by 6.205 mm[21]. To eliminate the effect of diopter on CT, we had excluded any patient with refractive error more than 6 D.

In our research, the postoperative choroidal thickness was shown to be significantly decreased one month after LUCENTIS® injection in the subfoveal area (P=0.009), 500 m temporal to fovea (P=0.003) and 500 m nasal to fovea (P=0.007).

Park et al.[16] also compared choroidal thickness before and after Anti-VEGF injection using EDI-OCT in 15 eyes. The results of our investigation are in good agreement with this study as well as Lee et al.[22], who reported that the choroidal thickness was decreased 1 month after intravitreal injection of Anti-VEGF in 31 eyes. The same conclusion was reinforced by a recent research by Lains et al.[23] on 50 eyes employing EDI-OCT, which found that DME eyes had decreased choroidal thickness after anti-VEGF injection

In our study 12 cases had improved postoperative BCVA (60 %), 8 cases had the same BCVA postoperative (40 %), and the mean preoperative BCVA was 0.875 0.202; the mean postoperative BCVA was 0.76 0.22 (P=0.04). This supports the beneficial effect of LUCENTIS ® injection on BCVA.

Guesspie et al.[24] evaluated BCVA before and one month after LUCENTIS® injection in 18 eyes and showed a substantial improvement in the postoperative BCVA. The results of our investigation are in excellent agreement with this study's findings as well as those of Park et al.[16], who reported a favorable visual outcome after intravitreal injection of LUCENTIS®.

We also investigated the impact of the postoperative choroidal and retinal thickness on the postoperative BCVA. Between the examined cases, there was a statistically significant (P=0.03) negative association (r=-0.242) between the postoperative decreased central retinal thickness and the postoperative BCVA. This finding was backed by other earlier publications[24,25,26].

Although there were negative association between the postoperative nasal, subfoveal, and temporal choroidal thickness and the postoperative BCVA (r=-0.257, -0.271, and -0.224, respectively), it was a statistically insignificant correlation (P= 0.275, 0.248, and 0.343). As a result, we found that the BCVA significantly improved in correlation to retinal thickness not to choroidal thickness.

Glenn et al.[27], also demonstrated marked decreased CT in DME patients after anti-VEGF injection, but without any significant correlation between this change in the CT and the improved visual acuity, which is in agreement with our study, so this finding may not be related to any functional or anatomical outcomes in eyes with DME.

These results could be explained as was mentioned above by the effect of LUCENTIS® on the choroidal vasculature[28]. Along with the findings of this study, more experimental data on choroidal vasculature and more accurate means of choroidal measurement as well as a longer follow up period should be studied to provide better explanations for the changes in CT in response to intravitreal injection of LUCENTIS®.

CONCLUSION: In eyes with DME, the effect of Anti-VEGF injection doesn't stop at the retina alone as it also has an effect on the choroidal circulation**.** Choroidal thickness measurements were significantly reduced after injection of LUCENTIS® and the BCVA significantly improved in correlation to retinal thickness not to choroidal thickness.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY

All data are included in this article.

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Conflict of Interest

Authors declare no conflicts of interest.

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Ethics declarations

Conflict of interest

Shimaa E. Mahmoud, Ahmed M. Saeed, Marwa A. Tabl.. all authors have no conflicts of interest that are directly relevant to the content of this review.

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REFERENCES:

1. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care, 2012; 35(3):pp.556-64.
2. Moss SE, Klein R, Klein BE. The 14-year incidence of visual loss in a diabetic population. Ophthalmology. 1998;vol.105(6),pp.998-1003.
3. Antonetti DA, Klein R, Grdner TW. Diabetic retinopathy. N Engl J Med.2012;366(13):1227-1239.
4. Silpa-Archa S, Maleki A, Roohipoor R. Analysis of three-dimensional choroidal volume with enhanced depth imaging findings in patients with birdshot retinochoroidopathy. Retina.2016;36(9):1758-1766.
5. Kim BY, Smith SD, Kaiser PK. Optical coherence tomographic patterns of diabetic macular edema. Am J Ophthamol.2006;142(3):405-412.
6. Li X, Dai H, Li X. Efficacy and safety of ranibizumab 0.5 mg in Chinese patients with visual impairment due to diabetic macular edema: results from the 12-month REFINE study. Graefes Arch Clin Ex Ophthalmol. 2019;257(3):529-541.
7. Korobelnik JF, Do DV, Schmidt-Erfurth U, Boyer DS, Holz FG, Heier JS. Intravitreal aflibercept for diabetic macular edema. Ophthalmology. 2014;121(11):2247-54.
8. Tan CS, Cheong KX, Lim LW, Li KZ. Topographic variation of choroidal and retinal thicknesses at the macula in healthy adults. Br J Ophthalmol. 2014;98(3):.339-44.
9. Cao J, McLeod S, Merges CA. Lutty GA. Choriocapillaris degeneration and related pathologic changes in human diabetic eyes. Arch Ophthalmol. 1998;16(5):589-97.
10. Shiragami C, Shiraga F, Matsuo T, Tsuchida Y, Ohtsuki H. Risk factors for diabetic choroidopathy in patients with diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol.2002;240(6):436-42.
11. Branchini L, Regatieri C, Adhi M, Flores-Moreno I, Manjunath V, Fujimoto JG. Effect of intravitreous anti-vascular endothelial growth factor therapy on choroidal thickness in neovascular age-related macular degeneration using spectral-domain optical coherence tomography. JAMA Ophthalmol.2013;131(5):693-4.
12. Branchini L, Regatieri C, Adhi M. Effect of intravitreous anti-vascular endothelial groeth factor therapy on choroidal thickness in neovascular age-related macular degeneration using spectral-domain optical coherence tomography. JAMA Ophthalmol. 2013;13(5):693-694.
13. Yiu G, Manjunath V, Chiu SJ, Farsiu S, Mahmoud TH. Effect of anti-vascular endothelial growth factor therapy on choroidal thickness in diabetic macular edema. Am J Ophthalmol.2014;158(4):745-51.
14. Querques G, Lattanzio R, Querques L, Del Turco C, Forte R, Pierro L, Souied EH. Enhanced depth imaging optical coherence tomography in type 2 diabetes. Invest Ophthalmol Vis Sci.2012;53(10):6017-24.
15. Ünsal E, Eltutar K, Zirtiloglu S, Dinçer N, Özdogan Erkul S, GÜngel H. Choroidal thickness in patients with

diabetic retinopathy. Clinical ophthalmology. 2014;8:637-42.

16. Park YU, Chung HY, Kim HY. Effects of Diabetic Retinopathy and Intravitreal Bevacizumab Injection on Choroidal Thickness in Diabetic Patients Journal of Korean Ophthalomolgical Society. 2013;54(10):1520-5.

17. Hee MR, Puliafito CA, Duker JS. Topography of diabetic macular edema with optical coherence tomography. Ophthalmology.1998;105:360-70.

18. Yiu GI, Pecen PA, Sarin NE, Chiu SI, Farsiu SU, Mruthyunjays PA. Characterization of the choroid-scleral junction and suprachoroidal layer in healthy individuals on enhanced-depth imaging optical coherence tomography .JAMA Ophthalmology. 2014;132(2):174-81.

19. Tan CS, Cheong KX. Macular choroidal thicknesses in healthy adults–relationship with ocular and demographic factors. Invest Ophthalmol Vis Sci. 2014;55(10):6452–6458.

20. Shin JW, Shin YU, Lee BR. Choroidal thickness and volume mapping by a six radial scan protocol on spectraldomain optical coherence tomography. Ophthalmology. 2012;119(5):1017–23.

21. Ho M, Liu DT, Chan VC. Choroidal thickness measurement in myopic eyes by enhanced depth optical coherence tomography. Ophthalmology. 2013;120(9):1909–1914.

22. Lee SH, Kim JA, Chung HY, Kim HY. Changes of Choroidal Thickness after Treatment for Diabetic Retinopathy. 2014;vol.41,pp.45.

23. Lains IN, Figueira JO, Santos AN. Choroidal thickness in diabetic retinopathy: The Influence of Antiangiogenic Therapy. Retina.2014;34(6):1199-206.

24. Guesspie QU, Martenielliе DO, Noci DE. Short term fluctuation of diabetic macular edema after intravitreal Ranibizumab injection.Retina.2009;29(9):1274-81.

25. Diabetic retinopathy clinical research network. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. Ophthalmology. 2007;114(3):525-36.

26. Keane PE, Alasil TA, Updike JA, Dustin LA, Walsh AL, Sadda SE. Relationship between optical coherence tomography retinal parameters and visual acuity in diabetic macular edema. Ophthalmology. 2010;117(12):2379-86.

27. Glenn YU, Manjunath VA, Stephanie CI, Farsiu SI, Mahmoud TA. Effect of Anti-Vascular Endothelial Growth Factor Therapy on Choroidal Thickness in Diabetic Macular Edema.2014;65:13.

28. Erkul SE, Kapran ZI, Uyar MO. Quantitative analysis of subfoveal choroidal thickness using enhanced depth imaging optical coherence tomography in normal eyes. International ophthalmology.2014;34(2):35-40.