Evaluation Of Choroidal Thickness Before and After Intravitreal Injection Of Anti Vascular endothelial growth factors for Treatment Of Diabetic Macular Edema using Optical Coherence Tomography

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Abstract

Background: The choroid is the vascular tissue supplying the outer retina.
Objectives: We are concerned with studying the changes in choroidal thickness related to anti-VEGF injection in diabetic patients.
Patients and Methods: This was a prospective cohort interventional study conducted at South Valley University Hospital, Ophthalmology department and included 40 eyes from 40 patients with diabetic macular edema. Inclusion criteria included adult phakic patients with diabetic macular edema receiving anti vascular endothelial growth factors injections without prior anti-VEGF therapy. All the patients underwent full eye examination , Refraction was done, uncorrected visual acuity, corrected visual acuity were estimated ,Injections were done only one injection every month for three months and the follow up was 6 months after the date of the first injection. OCT Measurements were performed before and after 6 monthes. OCT Measurements were done 3 times and the average was estimated.
Results: The mean decrease in nasal choroidal thickness was 14.4 (SD = 4.3, 95% CI = 13.02:15.78, p value = .000). The mean decrease in subfoveal choroidal thickness was 12.25(SD = 3.59, 95% CI = 11.1:13.4, p value = .000). The mean decrease in temporal choroidal thickness was 13.33 (SD = 4.2, 95% CI = 11.98:14.67, p value = .000).
Conclusion: The temporal, nasal, and subfoveal choroid showed a decrease in thickness after receiving anti-VEGF injections in DME patients. . Further studies are recommended to ascertain the relationship between diabetic retinopathy, anti-VEGF injections & choroidal thickness.

Keywords: Choroid; Diabetic Macular Edema; Anti-VEGF.
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Introduction

Diabetic macular edema (DME) is a critical eye condition that is considered a prevalent cause of diminution of vision in diabetics affected by diabetic retinopathy (DR) (**Yau et al., 2012**), with macular edema as well as proliferative retinopathy being the leading causes of the resultant visual impairment (**Moss et al., 1998**). Anti-vascular endothelial growth factor (anti-VEGF) drugs have found their way to become widely used in the treatment of diabetic macular edema (DME). A large research area proves them to improve visual and anatomic outcomes (**Korobelnik et al., 2014**).

The choroid is the vascular tissue supplying the outer retina (**Tan et al., 2014**). Decreased choroidal blood volume and compromised flow may result in the dysfunction as well as the necrosis of the photoreceptor cells (**Shiragami et al., 2002**).

To be able to visualize the choroid and assess choroidal thickness, Enhanced depth imaging using spectral domain optical coherence tomography (SD-OCT) is used (**Regatieri et al., 2012**). Choroidal thickness may be related to DR severity, and DME is associated with a significant decrease in choroidal thickness (**Branchini et al., 2013**).

Currently, intravitreal anti-VEGF injection is the most common treatment for DME. Several studies have demonstrated an association between anti-VEGF with decreased central retinal thickness (**You et al., 2014**). However, there is currently a lack of studies investigating the effect of anti-VEGF injections on the choroid in patients with diabetes. The purpose of the present study is to evaluate the effect of intravitreal anti-VEGF injections on choroidal thickness using SD-OCT in patients treated for DME.

Patients and methods

This was a prospective cohort interventional study conducted in Ophthalmology department, Qena University Hospital. It included patients who were examined and imaged in the outpatient clinic and were injected in the operating room between May and November of 2022. Our sample included 40 eyes from 40 patients with diabetic macular edema.

Inclusion criteria: Adult phakic patients with diabetic macular edema receiving anti vascular endothelial growth factors injections without prior anti-VEGF therapy. Exclusion criteria: pseudophakic patients, children and uncooperative patients with disturbed conscious level and patients with other causes of visual loss.

The study was performed according to the Declarations of Helsinki. Local ethics committee approval was obtained with the code being SVUMEDOPH0261223364. Patient consent was obtained from all patients and then they underwent full history taking and clinical examination. All the patients underwent Spectral Domain Optical Coherence Tomography (SD-OCT), visual acuity assessment, pupil reaction assessment, and fundus photography. Refraction was done, uncorrected visual acuity, and best corrected visual acuity were estimated.,Injections were done only one injection every month for three months and the follow up was 6 months after the date of

the first injection. OCT Measurements were performed before and after 6 monthes. OCT Measurements were done 3 times and the average was estimated.

Methods: The procedure was performed using topical anesthesia and under complete sterile conditions. 0.5 mg\0.05 ml ranibizumab is injected 4 mm from the limbus intravitreally (in the lower temporal quadrant) by a needle (27 gauge) once monthly for 3 months. For images to be included in the present study, they were taken as close to the fovea as possible (thinnest macular point), with the understanding that slight differences in positioning affect the measured thicknesses. Using the Spectralis linear measurement tool, two independent observers measured CT perpendicularly from the outer edge of the hyper-reflective RPE to the inner sclera at 500-mm intervals temporal and nasal to the fovea up to 1,000 mm, as well as subfoveal. Measurements were performed prior to treatment and at a 6-month follow-up. We repeated our measurements for each patient and took the mean of the repeated measurements. We defined choroidal thickness as the perpendicular distance between the outer border of the retinal pigment epithelium and the inner border of the sclera. Measurements were done 3 times and the average was estimated.

To achieve this study purpose, we evaluated and compared choroidal layer thickness changes using SD-OCT using OCT-Spectralis (Heidelberg Engineering GmbH 69121 Heidelberg / Germany, SN: TR-KT-2069, Manufactured 02/13) with the software Heidelberg Eye Explorer version 1.9.10.0 (**Pazos et al., 2017**), before starting intra-vitreal Ranibizumab injections and again after finishing six months.

The primary (main) outcome was the choroidal thickness pre- and 6 months postoperatively. The secondary outcomes included visual acuity using the logMAR scale (uncorrected visual acuity UCVA and best corrected visual acuity BCVA) and central foveal thickness. We also assessed the refraction of patients.

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS) software program (version 26). Qualitative variables were recorded as frequencies and percentages and were compared by Chi-square test. Quantitative measures were presented as means ± standard deviation (SD) and were compared by Student t-test. Regression correlation and analysis between different variables were performed as indicated. A P-value of < 0·05 was considered to be significant.

Results

Our study included 40 eyes of 40 patients with diabetic macular edema. 20 eyes (50%) were right & 20 eyes (50%) were left. 17 patients (42.5%) were males, and 23 patients (57.5%) were females. The mean age of the patients was 57.68 years (SD = 7.7, range = 47:73) (**Table.1** and **Fig.1 & 2**).

Table 1. Eyes of the Patients

Right	Left
20 (50%)	20 (50%)

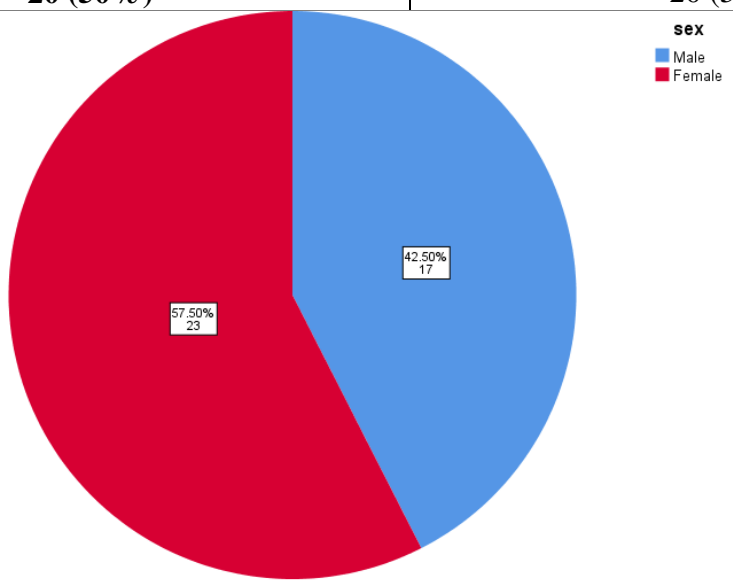

Fig.1. Pie Chart showing the sex distribution of patients.

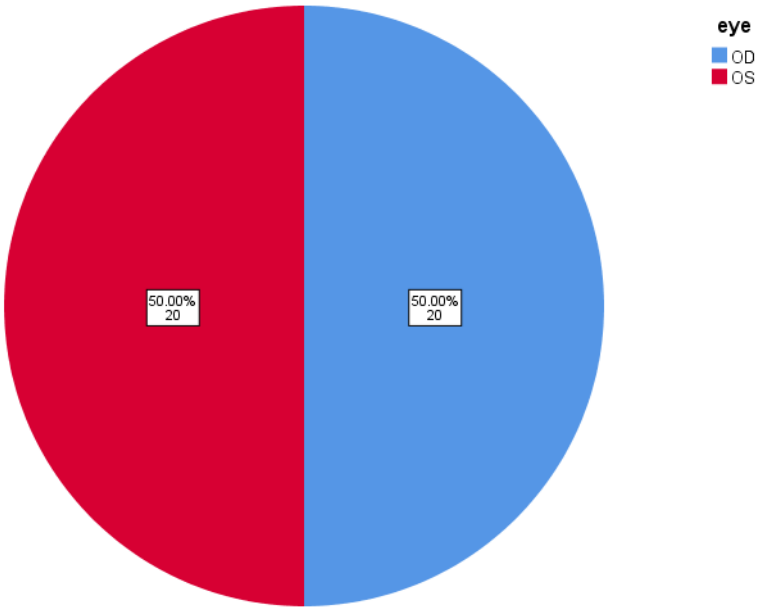

Fig.2. Pie Chart showing the eye of the patients.

The mean preoperative visual acuity on LogMar was 1.09 (SD = 0.21, range = 0.78:1.48) which improved to 1.01 postoperatively (SD = 0.32, range = 0.48:1.48) (**Table. 2**). The mean preoperative nasal choroidal thickness was 241 microns (SD = 9.7, range = 216:253), and postoperatively it decreased to 226 microns (SD = 12.4, range = 195:244). The mean preoperative subfoveal choroidal

thickness was 250 microns (SD = 9.6, range = 226:263) and postoperatively it decreased to 238 microns (SD = 11.5, range = 209:253). The preoperative temporal choroidal thickness was 246 microns (SD = 9.4, range = 221:257) and postoperatively, t decreased to 233 microns (SD = 12.4, range = 205:250) (**Table. 3**, and **Figs. 3-5**).

Table 2. Sex of the Patients

Male	Female
17 (42.5%)	23 (57.5%)

Table 3. Preoperative & Postoperative Visual Acuity on the LogMAR Scale. Mean (SD)

	Preoperative	Postoperative
Mean Visual Acuity	1.09 (0.21)	1.01 (0.32)

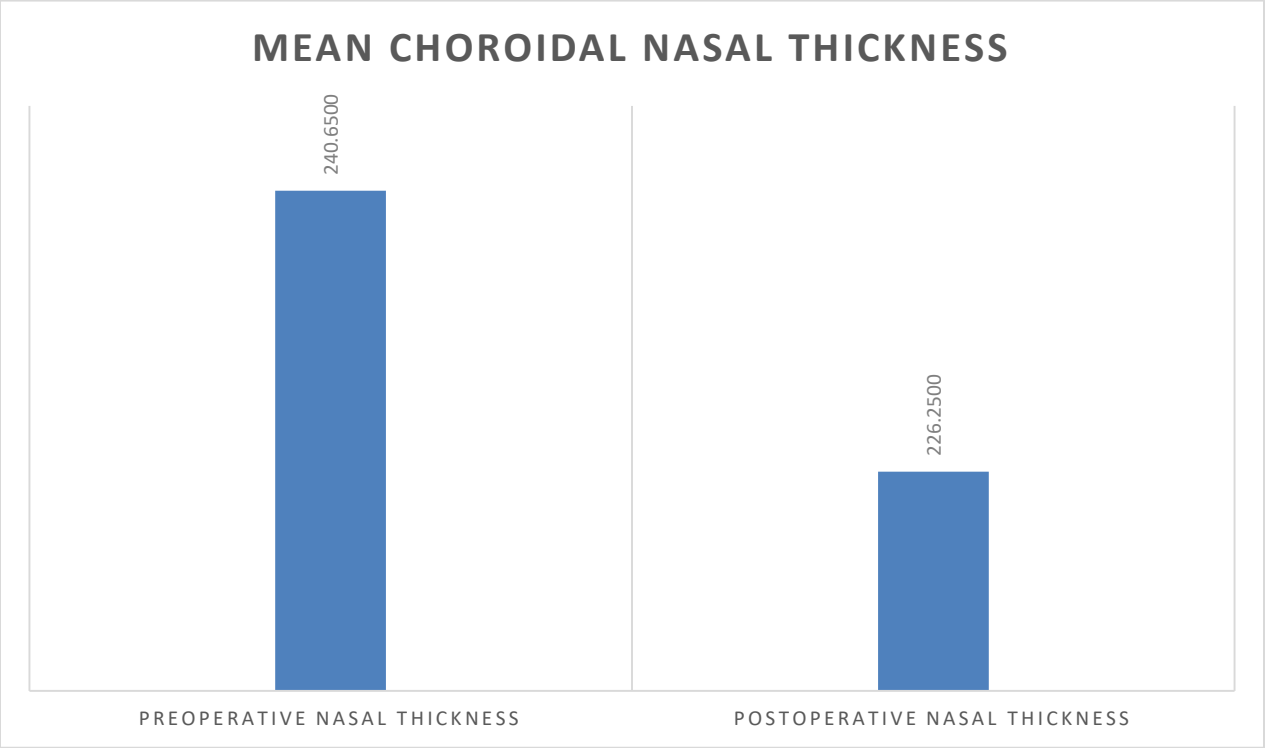

Fig. 3. Bar chart of Preoperative vs Postoperative Nasal Choroidal Thickness.

Using Paired samples t-test, the mean improvement in visual acuity was 0.08 (SD = 0.13, SEM = 0.02, 95% CI = 0.04:0.12, t = 3.8, df = 39, p = 0). The mean decrease in nasal choroidal thickness was 14.4 (SD = 4.3, SEM = 0.68, 95% CI = 13.02:15.78, t = 21.1, df = 39, p value = .000). The mean decrease in subfoveal choroidal thickness was 12.25(SD = 3.59, SEM = 0.57, 95% CI = 11.1:13.4, t = 21.6, df = 39, p value = .000). The mean decrease in temporal choroidal thickness was 13.33 (SD = 4.2, SEM = 0.67, 95% CI = 11.98:14.67, t = 19.97, df = 39, p value = .000) (**Table.4** and **Figs. 6, 7**).

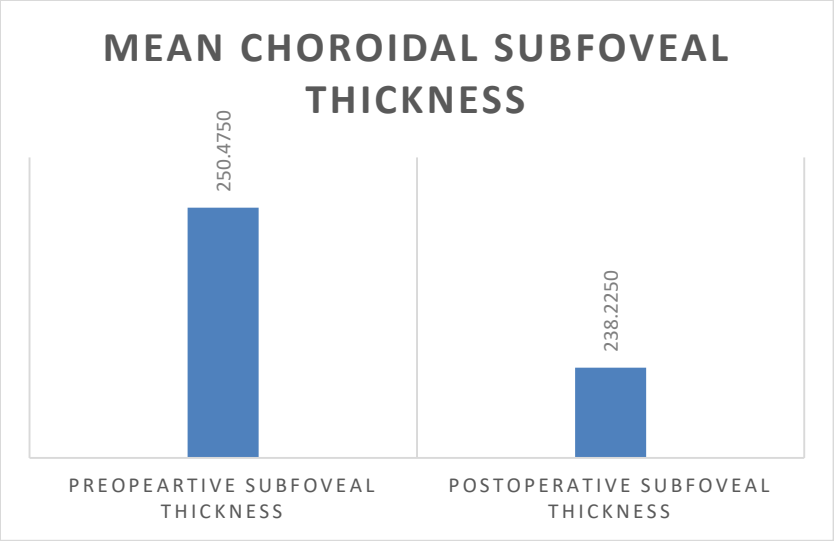

Fig. 4. Bar chart of Preoperative vs Postoperative Subfoveal Choroidal Thickness.

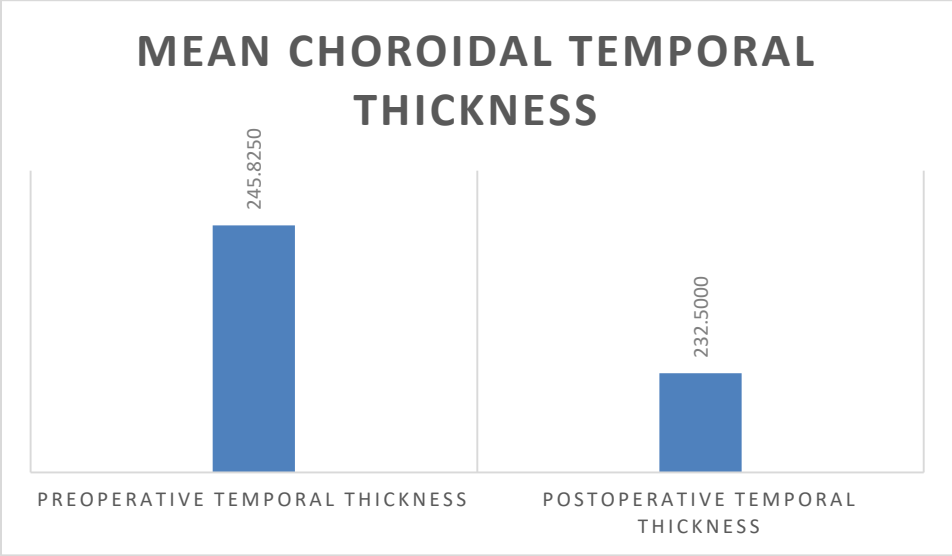

Fig.5. Bar chart of Preoperative vs Postoperative Temporal Choroidal Thickness.

Table 4. Preoperative & Postoperative Choroid Thickness Measurements, Mean (SD).

Variables	Preoperative	Postoperative	p
Nasal	241 (9.7)	226 (12.6)	.000
Subfoveal	250(9.4)	238 (11.5)	.000
Temporal	246 (9.6)	233 (12.4)	.000

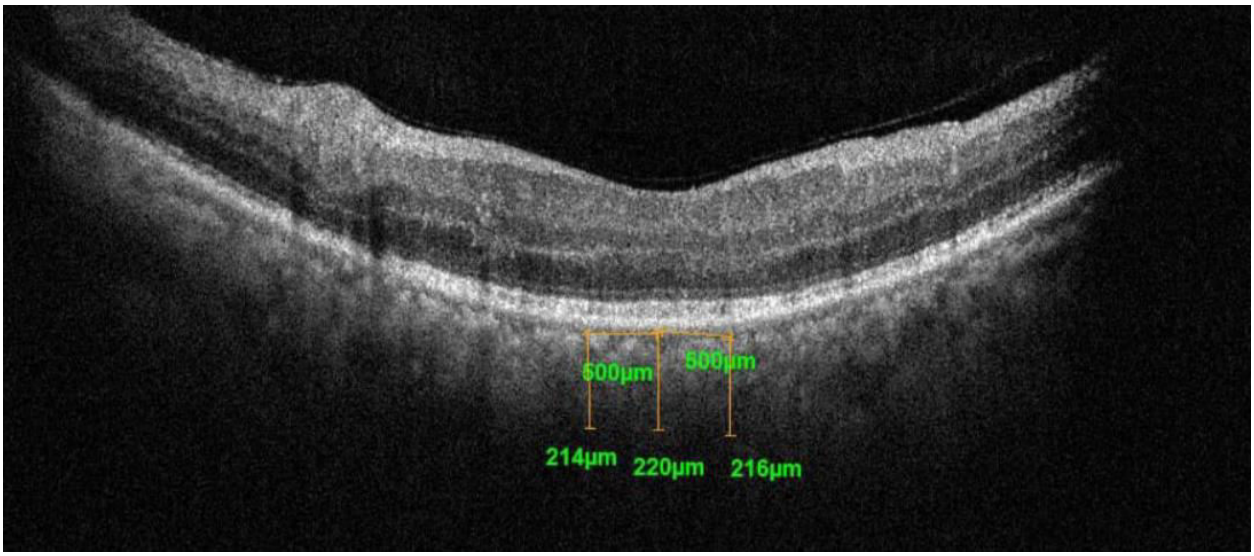

Fig. 6. Preoperative image of the right eye of a female patient.

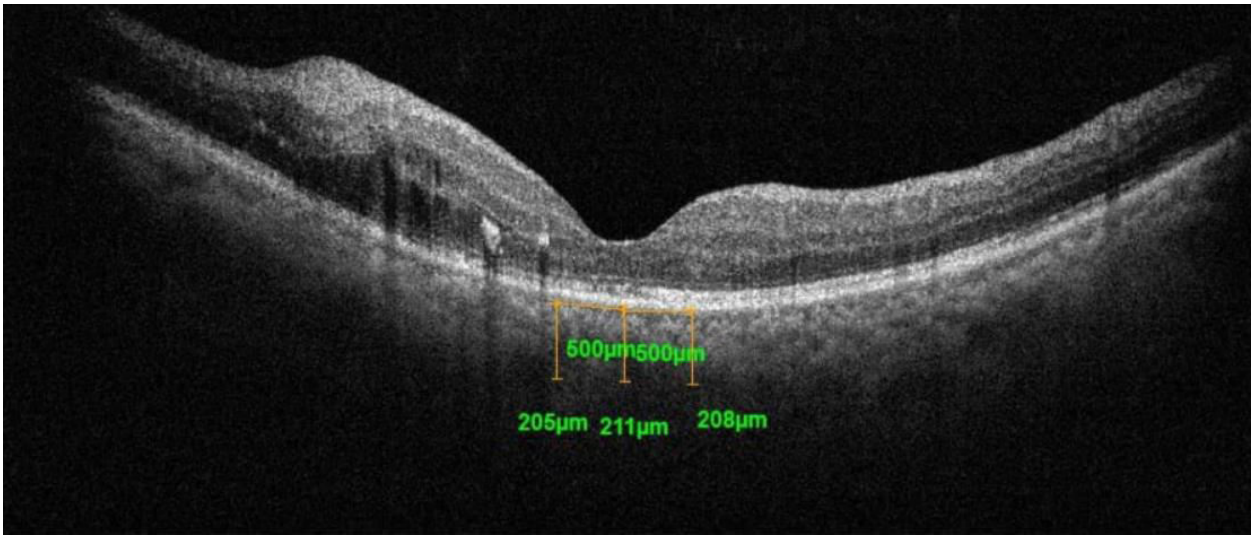

Fig.7. Postoperative image of the right eye of a female patient.

Discussion

The results of our study show that anti-VEGF injection affect the thickness of the choroid in eyes affected with diabetic retinopathy. The temporal, nasal, and subfoveal choroid showed a decrease in thickness post anti-VEGF injections and the results were statistically significant. The mean decrease in nasal choroidal thickness was 14.4 (SD = 4.3, 95% CI = 13.02:15.78, p = 0). The mean decrease in subfoveal choroidal thickness was 12.25 (SD = 3.59, 95% CI = 11.1:13.4, p = 0). The mean decrease in temporal choroidal thickness was 13.33 (SD = 4.2, 95% CI = 11.98:14.67, p = 0).

Wang et al. (2020), who examined 1347 patients, found that in early diabetic retinopathy, the choroid tends to increase in thickness in the early stages of diabetic

retinopathy, but decrease as diabetic retinopathy progressed along. This goes along with a meta-analysis performed by **Endo et al. (2020)** which included 17 studies comparing 3016 non-diabetic eyes to 1197 diabetic eyes and found that subfoveal choroidal thickness is lower in diabetic eyes. **Lains et al.(2018)** also found that patients with proliferative diabetic retinopathy had thinner central choroidal thickness than controls.

Wang et al.(2018) found that not only the choroid, but also the retinal pigment epithelium and outer retinal layers were significantly decreased in volume in diabetic retinopathy compared to controls in different regions of the retina. **Regatieri et al.(2012)** found that the average choroidal thickness in the temporal, nasal, and subfoveal areas was lower in NPDR patients than in normal patients, and lower in DME patients than in NPDR patients, and lower in PDR patients than in DME patients. **Unsal et al.(2014)** found a similar finding.

Rayess et al.(2015) had a similar sample size to ours, with 53 eyes, and found that diabetic eyes with a thicker subfoveal choroid thickness responded better to anti-VEGF treatment in terms of BCVA. The exact mechanism for the changes in choroid is interesting, especially given that even in patients with diabetes without diabetic retinopathy, **Ferreira et al.(2018)** found that the choroidal thickness is significantly more than non-diabetic patients by 6.16-24.27 μm. **Xu et al.(2013)** demonstrated a similar finding.

However, a few studies found that choroidal thickness increases as diabetic retinopathy increases in severity (**Rewbury et al., 2016**). **Endo et al.(2018)** resorted to dividing the choroid into its layers and found that the total and outer choroid thicknesses in mild to moderate NPDR patients were significantly thinner than normal controls. They also found that the choroidal outer layer thickness of the severe NPDR patients was significantly thicker than normal controls.

Treatment of diabetic retinopathy and diabetic macular edema can also affect choroidal thickness. **Ohara et al.(2018)** found that PRP causes a decrease in the choroidal thickness, which was persistent, even 6 months after treatment. **Endo et al.(2018)** in the DM treatment group, who received continuous systemic medication treatments including oral hypoglycemic agents with/without subcutaneous insulin therapy for DM there were no significant differences from the control group regarding choroidal layer thicknesses in all stages of DR.

These findings prove that the choroidal thickness suffers a decrease in all areas after anti-VEGF injection. It is not known if that decrease is due to pathological process of the diabetic retinopathy itself or if it's related to the anti-VEGF injection on the vascular endothelium. Further research is warranted to compare both groups of patients and conclude a follow up of patients using OCT to determine which of the two groups would suffer a greater decrease in choroidal thickness.

Our study is limited by a relatively low sample size, but its strength is a low p value ($p = .000$). Further studies are

recommended in order to ascertain the relationship between diabetic retinopathy & choroidal thickness.

Conclusion

We examined 40 eyes of 40 patients with diabetic retinopathy who received anti-VEGF injections before and 6 months after the procedure. OCT was examined to measure the choroidal thickness in the temporal, nasal, and subfoveal areas. The temporal, nasal, and subfoveal choroid showed a decrease in thickness after receiving anti-VEGF injections in DME patients. The mean decrease in nasal choroidal thickness was 14.4 (SD = 4.3, 95% CI = 13.02:15.78, p value = .000). The mean decrease in subfoveal choroidal thickness was 12.25(SD = 3.59, 95% CI = 11.1:13.4, p value = .000). The mean decrease in temporal choroidal thickness was 13.33(SD = 4.2, 95% CI = 11.98:14.67, p value = .000). Our sample size was limited but our results were statistically significant. Further studies are recommended in order to ascertain the relationship between diabetic retinopathy, anti-VEGF injections & choroidal thickness.

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