Al-Azhar International Medical Journal

Volume 4 | Issue 5 Article 12

2023
Section: Ophthalmology

Assessment of retinal ganglion cell complex thickness in diabetic patients before and after intravitreal injection of anti-VEGF agents by OCT

Mahmoud AbdAlhaleem Rabie
Department of Ophthalmology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt.

Ahmed Mohammed Sobhy
Department of Ophthalmology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt.

Ahmed Mustafa Mahmoud Mohammed
Department of Ophthalmology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt., am8293669@gmail.com

How to Cite This Article

Rabie, Mahmoud AbdAlhaleem; Sobhy, Ahmed Mohammed; and Mohammed, Ahmed Mustafa Mahmoud (2023) "Assessment of retinal ganglion cell complex thickness in diabetic patients before and after intravitreal injection of anti-VEGF agents by OCT," *Al-Azhar International Medical Journal*: Vol. 4: Iss. 5, Article 12.
DOI: https://doi.org/10.58675/2682-339X.1802

ORIGINAL ARTICLE

Assessment of Retinal Ganglion Cell Complex Thickness in Diabetic Patients Before and After Intravitreal Injection of Anti-VEGF Agents by OCT

Mahmoud AbdAlhaleem Rabie, Ahmed Mohammed Sobhy, Ahmed Mustafa Mahmoud Mohammed*

Department of Ophthalmology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt

Abstract

Purpose: **Compare retinal ganglion cell complex thickness in diabetic macular edoema studied cases before and after receiving an intravitreal injection of ranibizumab by spectral domain optical coherence tomography scans.**

Methods: **Prospective interventional study on 30 eyes with diabetic macular edema were imaged by spectral domain optical coherence tomography (SD-OCT) before receiving Ranibizumab intravitreal injection and one month after injection. Thickness changes in retinal ganglion cell complex after one month follow-up period were quantitatively analyzed and correlated.**

Results: **There was a statistical significant decrease in average retinal ganglion cell complex thickness in addition to the superior and inferior ganglion cell thickness after ranibizumab injection (P value < 0.001, <0.001 and < 0.001). Correlation between ganglion cell complex thickness values and duration of diabetes mellitus shows no statistical significant relation.**

Conclusion: **Intravitreal ranibizumab injection cause significant reduction in the Average, superior and inferior thickness of the retinal ganglion cell layer in diabetic patients along one month follow-up period, with negative correlation between the duration of diabetes and ganglion cell complex thickness parameters. Additional research with a larger sample, longer follow-up, and more injections is necessary.**

Keywords: Diabetic macular edema, Ganglion cell complex thickness, Intravitreal ranibizumab injection, SD-OCT

1. Introduction

Diabetic retinopathy is leading reason for blindness in studied cases aged twenty to seventy, and it is usually associated with period of diabetes mellitus.[1]

Retinal ganglion cells are first to be impacted and have greatest apoptosis rate. Even so, there is rising rate of apoptosis in the outer nuclear layer (photoreceptors) and retinal pigment epithelium.[2]

The macular region contains over fifty percent of all retinal ganglion cells and is propably the ideal region to identify ganglion cell loss.[3]

It is also realized that retinal ganglion cell analysis is not only limited to glaucoma but also applicable in several neurological and retinal conditions.[3]

Diabetes-related neuroretinal damage causes functional abnormalities like chromatic discrimination, contrast sensitivity, and dark adaptation, which can be discovered by electrophysiological researches in diabetic studied cases with diabetes for less than 2 years.[4]

Use of spectral domain optical coherence tomography allows for high-resolution measurements of individual layer thicknesses, indicating that thinning of inner retina is primarily caused by the loss of retinal ganglion cells.[5]

There are many therapy modalities in diabetic retinopathy. These contain retinal photocoagulation, intraocular injection of pharmacological agent and vitreoretinal surgery. One of the commonly used pharmacological agents which are injected

Accepted 4 December 2022.
Available online 30 November 2023

* Corresponding author at: Department of Ophthalmology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt.
E-mail address: am8293669@gmail.com (A.M. Mahmoud Mohammed).

https://doi.org/10.58675/2682-339X.1802

intravitreally in cases of diabetic macular edema are the anti-Vascular Endothelial Growth Factor (anti-VGEF) such as Aflibercept, Bevacizumab (avastin), ranibizumab (lucentis) intravitreally.[6]

In research, the impact of the intravitreal injection of Ranibizumab on ganglion cell complex is being evaluated by spectral domain optical coherence tomography in diabetic studied cases.

2. Patients and methods

This is a prospective interventional study that will be performed on 30 eyes with diabetic macular edema undergoing SD- OCT Ganglion cell thickness scanning before and after receiving Intraocular Ranibizumab (lucentis) Injection. Patients were seen in Beni-Suef ophthalmology Hospital outpatient clinic.

2.1. Inclusion criteria

Studied cases in years old group of forty: seventy, patients with clear media and visual axis confirmed by anterior segment examination using the slit lamp, patients with fundus picture of non-prolifrative diabetic Retinopathy confirmed by indirect ophthalmoscopy and studied cases with diabetic macular edema diagnosed by SD-OCT and showing central foveal thickness more than 200 μm seen in retinal thickness map.

2.2. Exclusion criteria

Previous retinalsurgeries or laser treatment, opacities of ocular media (which interfere with fundus examination) eg, corneal opacity or vitreous hemorrhage, eyes with proliferative diabetic retinopathy, retinal disorders other than diabetic retinopathy (such as glaucoma, macular degeneration, and retinal vein occlusion), eyes with ischemia or vitreomacular traction, patients with or having history of any optic neuropathies.

All included patients will be examined as follows: full history, including the patient's age, gender, and the length of their diabetes, Type of treatment, previous ocular surgery-interventions and previous laser treatment. Uncorrected and best corrected distant visual acuity using Snellen (decimal) visual acuity chart at a viewing distance of 6 m, Slit-lamp examination of anterior segment to exclude corneal abnormalities and significant cataract. Fundus examination using indirect ophthalmoscope and slit-lamp bio-microscopy, I.O.P measurement, With SD-OCT, retina's ganglion cell complex (GCC) thickness was measured, as was the retina's thickness map (Optovue, Inc.)

OCT is performed at 1st visit before intra-vitreal injection for estimating DME and ganglion cell thickness as baseline OCT map so it will be designated as the baseline visit and follow -up visits will be at 4 weeks after Intraocular injection of Ranibizumab (lucentis).

The OCT was performed as follows: Preparing the patient for the OCT exam by dilating his pupil by installing mydriatic eye drops in both eyes, registering the patient data (name, date of birth).

Select parameters to be examined (Retinal thickness map, GCC Thickness map). The patient sits centralized in front of the OCT machine resting his chin on the chin rest, tell the patient to follow the light to obtain perfect captures Press capture icon on the PC screen then print and analyze data. Average GCC thickness, superior, inferior, Global loss volume and Focal loss volume Percentage were measured and statistically analyzed.

2.3. The intraocular ranibizumab injection technique

2.3.1. Anaethesia

Topical proparacaine (use Betadine after waiting ten to 15 s).

2.3.2. Injection site

Usually inferotemporal Quadrant (3–3.5 mm for pseudo-phakes, 3.5–4 mm for phakic)from the limbus.

2.3.3. Technique of injection

Ensure you are in vitreous cavity and not the subretinal space by inserting the short 30 g needle into the injection site about halfway.

2.3.4. The injection dose

FDA-approved Ranibizumab (Lucentis) Ampoule (0.5 mg/0.05 ml), a medication for intraocular usage Wash the Betadine off thoroughly to prevent toxicity or eye discomfort in the patient. Optional: Place a topical antibiotic there and instruct the patient to apply it every three days.

2.4. Post-injection care

2.4.1. Follow up

Endophthalmitis and other intraocular injection-related complications, such as retinal tear or detachment, Increased IOP, optic nerve injury, cataract, endophthalmitis, bleeding (subconjunctival, vitreous hemorrhage), Endophthalmitis infection, vision loss resulting from any of the aforementioned causes, and eye loss (from a severe

infection), and loss of vision often take 4–6 weeks to appear.

2.4.2. Follow up after injection

All the patients were examined after 4 weeks after intraocular injection treatment. Examination involved including: Uncorrected and Best corrected visual acuity assessed by snellen (decimal) chart, slit-lamp anterior segment examination, slit-lamp bio-microscopy, I.O.P Air-Puff measurement, measurement of the GCC thickness and Retinal thickness Map by SDOCT to compare data with previous OCT scans to detect the difference between GCC thickness in the preinjection GCC thickness map and follow up GCC thickness map which was done after 1 month of injection and GCC thickness map which was done after injection then register them in a table.

3. Results

The current study was an interventional study conducted on 30 eyes from 30 individuals, to detect the potential alterations and variations induced by intravitreal injections of anti-VGEF (Ranibizumab) on retinal ganglion cell complex (GCC) thickness in studied cases with diabetic macular edema by comparing the GCC thickness before and after intravitreal Injections of anti VGEF using spectral domain O.C.T.

Table 1 demonstrates the baseline sociodemographic data of tested population. Participants were 12 (40%) females and 18 (60%) males. Their age was ranged from (36.0) to (71.0) years old, with average years old of (56.60 ± 10.78). The duration of diabetes Meletus was ranged from (7.50) to (30.0) years with an average duration of (16.90 ± 6.67) years.

Table 2 demonstrates the baseline BCVA and IOP among studied population data of the studied population. BCVA was ranged from (0.05) to (0.07) LogMar, with an average BCVA of (0.31 ± 0.12) LogMar. The IOP was ranged from (11.0) to (19.0) mmHg with an average IOP of (14.63 ± 2.84) mmHg (Table 3).

Superior GCC was ranged from (90.20) to (250.0) microns, with an average thickness of (144.66 ± 53.00) microns. Inferior GCC was ranged from (80.70) to (248.0) microns, with an average thickness of (146.32 ± 50.63) microns. Average GCC was ranged from (87.40) to (251.90) microns, with an average thickness of (143.86 ± 54.29) microns (Table 4).

Average GCC thickness before injection was ranged from (87.40) to (251.90) with an average thickness of (143.86 ± 54.29) while post-injection was ranged from (81.00) to (208.70) with an average thickness of (118.88 ± 44.07), P value < 0.001 (Table 5).

Reduction in inferior GCC thickness after injection was ranged from (26.23) to (14.15) with an average thickness reduction of (26.23 ± 14.149).

Table 1. Baseline sociodemographic data of tested population (sex, age and disease duration).

	Statistics
Sex, N (percent)	
Woman	20 (40%)
Man	18 (60%)
Age, (years)	
Mean ± SD	56.60 ± 10.78
Minimum – Maximum	36.0–71.0
Disease Duration, (years)	
Mean ± SD	16.90 ± 6.67
Minimum – Maximum	7.5–30.0

Table 2. The baseline BCVA and IOP among studied population.

	Preintravitreal
BCVA, (LogMar)	
Mean ± SD	0.31 ± 0.12
Minimum – Maximum	0.05–0.7
IOP, (mmHg)	
Mean ± SD	14.63 ± 2.84
Minimum – Maximum	11.0–19.0

Table 3. Baseline retinal ganglion cell complex (GCC) thickness before intravitreal injections of anti-vascular endothelial growth factor.

	Preintravitreal
Superior	
Mean ± SD	144.66 ± 53.00
Minimum – Maximum	90.20–250.0
Inferior	
Mean ± SD	146.32 ± 50.63
Minimum – Maximum	80.70–248.0
Average	
Mean ± SD	143.86 ± 54.29
Minimum – Maximum	87.40–251.90

Table 4. Comparing retinal ganglion cell complex (GCC) thickness before and after intravitreal injections of anti-vascular endothelial growth factor (ranibizumab).

	Preintravitreal	Postintravitreal	P value
Superior			
Mean ± SD	144.66 ± 53.00	119.24 ± 44.40	<0.001*
Minimum – Maximum	90.20–250.0	80.20–210.0	
Inferior			
Mean ± SD	146.32 ± 50.63	118.85 ± 44.23	<0.001*
Minimum – Maximum	80.70–248.0	81.0–208.20	
Average			
Mean ± SD	143.86 ± 54.29	118.88 ± 44.07	<0.001*
Minimum – Maximum	87.40–251.90	81.00–208.70	

Table 5. Variations[a] in retinal ganglion cell complex (GCC) thickness after as compared with before intravitreal injections of anti vascular endothelial growth factor (Ranibizumab).

	Postintravitreal
Superior	
Mean ± SD	23.78 ± 14.29
Minimum – Maximum	6.90–63.50
Inferior	
Mean ± SD	26.23 ± 14.15
Minimum – Maximum	5.00–66.00
Average	
Mean ± SD	23.52 ± 18.49
Minimum – Maximum	15.50–69.70

[a] Change was calculated as: (*before – after intravitreal injections*).

Table 6. Comparison of BCVA and IOP before and after intravitreal injections of anti vascular endothelial growth factor (Ranibizumab).

	Preintravitreal	Postintravitreal	*P* value
BCVA			
Mean ± SD	0.31 ± 0.20	0.38 ± 0.19	0.241
Minimum – Maximum	0.01–0.70	0.06–0.70	
IOP			
Mean ± SD	14.60 ± 2.87	14.63 ± 2.80	0.546
Minimum – Maximum	11.0–19.0	11.0–19.0	

Both BCVA and IOP increased slightly after intravitreal injections of anti-VGEF (Ranibizumab), but without statistically significant difference in both BCVA and IOP, *P* value < 0.001.

Reduction in average GCC thickness after injection was ranged from (15.50) to (69.70) with an average thickness reduction of (23.52 ± 18.49) (Table 6).

4. Discussion

Current imaging advancements have allowed analysis of structural variations in retinal layers in numerous retinal diseases. Spectral domain optical coherence tomography is useful tool for assessing retinal structural variations. Numerous researches have used OCT to examine GCC structural variations before and after intravitreal Ranibizumab injection in various diseases.[7]

Our findings showed that thickness of Ganglion cell complex, that consists of the three layers (Ganglion cell layer, Inner plexiform layer (IPL), and retinal nerve fibre layer RNFL), had changed. Average (*P* value < o.oo1), superior GCC (*P* = 0.000) and inferior GCC (*P* = 0.000). There was no variation in percentage of Global loss volume (GLV %) (*P* = 0.091) or Focal loss volume (FLV percent) (*P* = 0.200) along the 2 months follow up duration before and after Ranibizumab injection.

Beck *et al.*,[8] did a retrospective analysis involving 68 eyes of 43 individuals with age-related macular degeneration and SD-OCT pictures of those eyes. With a percentage loss of 15% in the injected eye and a reduction of 6% in the colleague non-injected eye, the study demonstrated a significant decrease in thickness of ganglion cell layer after follow-up period of around 24 months (*P* value = 0.01). Our results were consistent with those of **Beck *et al.*,**[8] however; their study was a retrospective study with a larger sample size 68 eyes of 43 patients compared to our study which investigated 30 eyes of 30 patients. In addition, Beck et al. investigated patient with AMD whereas we investigated patients with DME; also they had a longer follow-up period (24 months) than ours (2 months). The OCT machine used was Spectralis OCT which Segments the macular ganglion cell layer from other layers whereas in our study, we used RtVue OCT machine which analyses the ganglion cell complex with an isolated software specialized for GCC assessment, which might provide more reliability and reproducibility to the obtained data being more operator independent.

In 2012, **Nishimura *et al.*,**[9] discovered that the retinal ganglion cell function was not altered by repeated intra-vitreal Ranibizumab injection in patients of Age Related Macular Degeneration (AMD) in an attempt to assess safety of intra-vitreal Ranibizumab in the studied cases suffering from Age Related Macular Degeneration, the study done for 32 eyes of 32 studied cases before and after Ranibizumab injection 3 times at monthly intervals along 9 months with additional doses according to OCT follow-up done in retina unit of Iwate medical university hospital, using in their study SD-OCT, using also Focal macular ERG, Full Field cone ERG as functional indicator.[10]

We agree with **Ciloglu *et al.*,**[7] who showed that GCC (which includes GCL and IPL) in treated eyes vary considerably among baseline and various follow-up values. Before first injection, mean GCC thickness was 115.08 ± 16.72 μm, and after 3rd injection, it was 101.05 ± 12.67 μm. They discovered no variation in mean GCC thickness among treated and untreated eyes, however, macular thickness did vary among groups. Until 6th month of follow-up, we discovered no variation in mean GCC thickness among control and study groups. Even so, mean GCC thicknesses varied greatly among treated studied cases and controls in 2nd and 3rd months, however, this variation lost significance after 6th month, with rise in mean GCC thickness in treated studied cases. Following significant rise in mean macular thickness in 6th month, anti-VEGF therapy was initiated in control group studied cases, and we were unable to compare measurements for 9th month follow-up in study group.

Saad *et al.*,[11] showed that as regard the retinal thickness: Preoperative retinal thickness was assessed,

and the mean foveal thickness was 455.84 ± 127.29 μm and ranging from 267 μm to 773 μm. Three months postoperative retinal thickness was estimated, and the mean foveal thickness was 384.44 ± 111.887 μm with a range from 229 μm to 648 μm.

In a similar study of **Ebneter *et al.*,**[12] retrospective observational study done in university of Bern, while receiving intravitreal ranibizumab treatment in Switzerland, 33 eyes for 33 patients with diabetic macular edoema were photographed by spectral domain oct at monthly visits under the guidance of VA and SD-OCT.

Individual retinal layer thickness changes over a 1-year follow-up were quantitatively analyzed and interpreted. These thickness changes suggested reduction in thickness of all retinal layers especially inner retinal layers including GCC (P value < 0.05).

Nishimura *et al.*,[9] in an effort to assess safety of intra-vitreal Ranibizumab in the studied cases suffering from Age Related Macular Degeneration, it was observed that retinal ganglion cell function was not affected by repeated intravitreal Ranibizumab injection, the study done for 32 eyes of 32 studied cases before and after Ranibizumab injection 3 times at monthly intervals along 9 months with additional doses according to OCT follow up done in In addition to using SD-OCT, Focal macular ERG, and Full Field cone ERG as functional indicators, retina unit of Iwate Medical University Hospital collaborated with Spectralis, Heidelberg Engineering, Heidelberg, Germany on project.[9]

Collectively, we cannot ignore the neuro-protective effect of VEGF and take in consideration its effective role in survival of different retinal cells, as it may raise the question about the side effects of Anti-VEGF drug abuse. *Nevertheless,* the profile of Ranibizumab intravitreal injection in Diabetic Patients need to be further evaluated in a large multicenter Trial with a larger sample size and longer follow-up duration.

4.1. Conclusion

Ranibizumab Intravitrel Injection Significantly affects Average Ganglion cell complex thickness; also we found the same effect on the superior, inferior Ganglion cell thickness, so we should use intravitreal drug injection when there is a real need in patients of diabetic macular edema (Tables 4 and 6).

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declared that there were no conflicts of interest.

References

1. Wang H, Meng ZY, Li SG, Wang JJ, Sun J, Li HY. Macular evaluation of the retinal and choroidal vasculature changes in anterior ischemic optic neuropathy-a case control study. *BMC Ophthalmol*. 2018;18:1–3.
2. Sanes JR, Masland RH. The types of retinal ganglion cells: current status and implications for neuronal classification. *Annu Rev Neurosci*. 2019;38:221–246.
3. Schneider CL, Prentiss EK, Busza A, et al. Survival of retinal ganglion cells after damage to the occipital lobe in humans is activity dependent. *Proc Royal Soc B*. 2019;286: 20182733.
4. Hegazy AI, Zedan RH, Macky TA, Esmat SM. Retinal ganglion cell complex changes using spectral domain optical coherence tomography in diabetic patients without retinopathy. *Int J Ophthalmol*. 2017;10:427.
5. Muftuoglu IK, Ramkumar HL, Bartsch DU, Meshi A, Gaber R, Freeman WR. Quantative analysis of the inner retinal layer thicknesses in age-related macular degeneration using corrected optical coherence tomography segmentation. *Retina*. 2018;38:1478.
6. Mansour SE, Browning DJ, Wong K, FlynnJr HW, Bhavsar AR. The evolving treatment of diabetic retinopathy. *Clin Ophthalmol*. 2020;14:653.
7. Ciloglu E, Unal F, Dogan NC. Changes in the ganglion cell complex thickness after anti-VEGF treatment for diabetic macular edema. *Arq Bras Oftalmol*. 2020;83: 372–377.
8. Beck RW, Edwards AR, Aiello LP. Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. *Arch Ophthalmol*. 2009;127:245–251 (Chicago, Ill.: 1960).
9. Nishimura T, Machida S, Harada T, Kurosaka D. Retinal ganglion cell function after repeated Intravitreal injections of ranibizumab in patients with age-related macular degeneration. *Dovepress J*. 2012;6:1073–1082.
10. Sharma P, Mittal S. Nanotechnology: revolutionizing the delivery of drugs to treat age-related macular degeneration. *Expet Opin Drug Deliv*. 2021;18:1131–1149.
11. Saad Eldeen MAEM, Mostafa M, Khallaf ME. Study of the changes in choriodal thickness before and after intravitreal injection of ranibizumab in diabetic macular edema. *Al-Azhar Int Med J*. 2020;1:17–24.
12. Ebneter A, Wolf S, Abhishek J, Zinkernagel MS. Retinal layer response to Ranibizumab during treatment of diabetic macular edema. *Retina J*. 2016;3:1314–1323.