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ORIGINAL ARTICLE

Quantitative Assessment of Macular Thickness in Glaucomatous Human Eye Using Optical Coherence Tomography

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ABSTRACT

Background: *Glaucoma is the cause of thinning of the layer of nerve fibers in the macula. Therefore, an objective study is considered a necessary document to continue evaluating the thickness of the macula.*

Objectives: *To assess macular thickness by OCT in glaucomatous eyes in comparison to normal eyes and to identify the changes in the macula in glaucoma patients*

Patients and Methods: *The study included 181 eyes (69 normal eyes and 121 eyes with glaucoma), and each patient underwent a thorough ophthalmological examination and an OCT examination. All eyes were scanned to measure macular thickness using a 6x6 mm ETDRS map centered on the central disc in its middle. The macula was divided into 9 regions, including the central disc (1 mm), inner ring (3 mm), and outer ring (6 mm).*

Results: *The mean age was 42.1 years in the normal eyes group and 58.1 years in the glaucoma group. From a comparison of macular thickness between two groups in all regions except the central disc region, it was statistically significant less than (P = 0.05) with the same result among both genders. The difference in the layer of nerve fibers between glaucoma and the normal eye was greatest in the TOM area (27.11) microns and least in the central disc (4.32) microns.*

Conclusions: *Persistent macular thinning, which represents a marker for alternative status in detecting structural changes in the progression of glaucoma over time. The OCT device is considered a sensitive device in diagnosing, monitoring and treating glaucoma.*

Keywords: *glaucoma, macular thickening, ocular coherence tomography (OCT)*

1. INTRODUCTION

It is difficult to define glaucoma precisely, as it encompasses a diverse group of disorders. All forms of the disease have in common a potentially progressive and characteristic optic neuropathy which is associated with visual field loss as damage progresses, in which intraocular pressure is usually a key modifying factor. Glaucoma affects up to 2% of those over the age of 40 years globally, and up to 10% over the age of 80, 50% may be undiagnosed (1). The word glaucoma originally meant 'clouded' in Greek; as such, it may have referred either to a mature cataract or to corneal edema that might result from chronic elevated pressure. Today the term does not refer to a single disease entity, but rather to a group of diseases that differ in their clinical presentation, pathophysiology, and treatment. These diseases are grouped together because they share certain features, including cupping and atrophy of the optic nerve head, with attendant visual field loss and it is frequently related to the level of intraocular pressure (IOP) (2). Glucomas can be classified according to the etiology on basis of primary and secondary forms (3). There are different known risk factors that contribute to the development of glaucoma, it`s progression and extend include heredity, ethnicity, the size of the eye, systemic vascular disease, vasospastic disorders including migraine, and the size and shape of the optic cup (4). Pathophysiology of glaucoma is believed to be multifactorial. Multiple factors acting either on cell bodies or their axons are believed to lead to Retinal ganglion cell death. According to various theories, factors like elevated intraocular pressure (IOP) and vascular dysregulation primarily contribute to the initial insult during glaucomatous atrophy in the form of obstruction to axoplasmic flow within the RGC axons at the lamina cribrosa, altered optic nerve microcirculation at the level of lamina and changes in the laminar glial and connective tissue (5). Nerve fiber layer thinning has been shown to be the most sensitive indicator of glaucomatous damage, preceding both visual field loss and detectable changes in optic nerve appearance. In many cases visual field loss and characteristic changes in the optic nerve head appearance may not be detected even when up to 50 percent of the nerve fibers have been lost (6). Methods of evaluating macular thickness, such as ophthalmoscopy or stereoscopic biomicroscopy, are insensitive for detecting small changes in retinal thickness. However, current diagnostic instruments, such as

laser-generated slit lamp biomicroscopy, and the Heidelberg Retina Tomography, have been able to objectively assess macular thickness but fail to show intraregional structures. So after the advent of Optical Coherence Tomography (OCT) a precise cross-sectional imaging of the eye is possible (7-8). Optical Coherence Tomography is a noninvasive, noncontact, transpupillary imaging and provides quantitative, objective and reproducible assessment of nerve fiber layer thickness, which performs high-resolution, cross-sectional imaging of the ONH, RNFL and macula. It measures the intensity and echo time delay of back-scattered and back-reflected light from the scanned tissues (4, 6). The size and anatomical distribution of retinal ganglion cells varies throughout the posterior pole, approximately 50% of retinal ganglion cells are located in the macular region 4-5 mm from the center of the fovea with the peak density occurring 750 to 1100 µm from the foveal center where the cell density may be 4 to 6 cell body thick, although cell diameter distribution is variable (4). Macula scan displays two maps, centered on the macula, showing retinal thickness and volume, map regions within a 6×6 mm area centered on the fovea, as defined by the ETDRS. Three concentric circles divide each map into three zones: fovea 1mm, inner 3mm and outer macula 6 mm. The inner and outer zones are further divided into four quadrants by two diagonal lines. Thus, a total of nine areas [According to ETDRS map, It identifies the layers of the retina and determines macular thickness by measuring the distance between the inner limiting membrane (ILM) and the inner boundary of retinal pigment epithelium (RPE) in each of the 9 regions.] (Fovea, superior outer, superior inner, inferior outer, inferior inner, temporal outer, temporal inner, nasal outer, and nasal inner) are available for analysis (2, 10). Technique has been applied in the diagnosis of a variety of macular diseases and in the evaluation of the treatment effects. OCT assessment of peripapillary retinal nerve fiber layer thickness has been reported to differentiate normal from glaucomatous eyes. Macular thickness assessment may offer an alternative method of assessing retinal ganglion cell injury in glaucoma (2, 6, 8). Normal macular thickness is variable, two studies at approximately 175µm and one study at 210µm. The study done in Erbil city in 2012, the mean and STD of central foveal thickness (average thickness in 1000 µm diameter area) was 217±26µm (9).

2. METHODOLOGY

The study protocol was reviewed in advance and accepted by Research ethics committee of Hawler Medical University.

This was a cross sectional study conducted at Hawler Teaching Hospitals in Erbil city during a period of 6 months included 100 persons (normal persons and Patients with glaucoma in different age group of both gender who were consecutively attending to eye clinic in Hawler Teaching Hospital. The data were obtained by direct interview and examination of normal and glaucomatous patients after taking signed consent from all the patients.

We adopted convenient sampling technique and selected 100 individuals who were agreed to participate in the study and met the inclusion criteria.

During data collection the individual with one or more of the following was excluded from the study; history of ocular trauma, previous ophthalmic surgery or diseases (e.g. uveitis), macular edema due to (central retinal venous occlusion, cystoid macular edema, diabetic maculopathy and hypertensive retinopathy……etc), age related macular degeneration and congenital eye problem.

Ophthalmic examination:

A thorough ophthalmic examination was done for all patients; best-corrected visual acuity, slit-lamp biomicroscopy with 90-diopter lens, indirect ophthalmoscopy, fundus photography and OCT. Macula evaluated carefully by biomicroscopic fundus examination to determine the existence of any change in the Macula.

Instruments and equipments that are used included Snellen chart; for checking best visual acuity, autorefractometer; (Topcon KR8800, Japan) used for assessment of refractive errors. tonometry with applanation tonometry (Haag Streit, Bern, Switzerland), Pachymetery; of central corneal thickness (Nidek-up-1000-ultrasounic pachymeter), slit lamp biomicroscopy; (Topcon, Japan; model SL-3F) used for anterior and posterior segment examination with or without dilatation and with the aid of special ophthalmic lens, like Volk/Ocular Standard +90D, ocular maxifield +90d, ocular maxifield +78d and optical coherence tomography (OCT); (NIDEK Model RS 3000 NAVIS-EX) performed for all patient include in the study.

The medication used was Tropicamide (Tropamid) 1% eye drop for dilatation of the pupil.

Statistical Analysis and Data Management were performed using the statistical package for social sciences version 19 (SPSS19). Macular thickness in normal eye compared with macular thickness in glaucomatous eyes by Student's t-test with unequal variances. The correlation between macular thickness and visual acuity in glaucomatous eyes and normal eyes was assessed by Pearson's correlation analysis and the correlation coefficients were calculated. All statistical tests and analysess performed with level of signifciance of two tailed P. value pf ≤ 0.05.

3. RESULTS

Out of 100 persons, 181 eyes were included in this study, these eyes subdivided into 2 groups, 69 eyes from 40 normal persons; 21 (52.5%) males and 19 (47.5%) females whose age ranged between 20 and 73 years with a mean of 42.05 years, and 112 eyes belonged to 60 glaucomatous patients; 33 (55%) males and 27 (45%) females aged between 30-83 years with mean age of 58.05 years (**Table 1**). Out of the 60 patient (112 eyes) in glaucomatous group, 44 (73.3 %) were diagnosed incidentally and 16 (26.6%) were known to have glaucoma (**Table 2**).

Regarding the education of glaucomatous patient to their disease and awareness to the sequel of glaucoma in the future and their compliant to treatment, it appears that (71.7 %) were not aware about glaucoma, (75%) were compliant to treatment, (36.7 %) had family history of glaucoma and 40 % had history of (topical or systemic) steroid use, (**Table 3**).

Among the 112 eyes of the glucomatous patients, 33 (29.5%) were diagnosed as glucoma within 1 year, 65 (58%) eys were diagnosed within 1 – 5 years and 14 eyes (12.5%) diagnosed for more than 6 years. Distribution according to age groups revealed that duration of less than one year was more frequent, (36.4%), in patients aged (50-59) years. Those diagnosed within 1 – 5 years were more frequently distributed in the age group (60-69) years they were 20 (30.76%) eyes while the diagnosed glucoma at 6 years or more were more frequently distributted in those aged 70 years or older, they contributted for 6/14 (42.9%) eyes. The association between age and duration of glaucoma was statistically significant, (P. value = 0.019), (**Table 4**). The mean intraocular pressure (IOP) in the 112 eyes of the 60 glucoma patients was (18.42 ± 6.34 mmHg) in 60 (112 eyes) glaucomatous patient, however, patients who were using steroid had signifciantly higher IOP of (20.36 mmHg) compared to

17.21 mmHg among those who do not used steroids,, with a significant difference of 3.15 mmHg, (P. value = 0.010). Also IOP was lower by (2.86mmHg) in patients that compliant well to anti glaucoma treatment, where the mean IOP in these patients was 17.76 mmHg compared to 20.62 in those who were not compliant to anti glaucoma treatment, (P. value = 0.043), (**Table 5**). Out of 97 eyes in males; 37 (38.14%) of normal person and 60 (61.85%) eyes of glaucomatous patients. In females a total of and 84 eyes, 32 (38.09%) for normal person, 52 (61.9 %) for glaucomatous patients. The effect of glaucoma on gender (male and female), reveals that in both group the NFL become thinner and this was more in female than male, statistically significant in all sectors except the fovea, as shown in (**Table 6**). NFL become thinner in glaucomatous patients when compared with normal person in all 9 sectors of macular map (ETDRS), this difference in NFL was statistically significant in all sectors except in the fovea as shown in (**Table 7**). In total, the difference in NFL in different macula sectors between glaucoma and normal persons was the higher in TOM ,(27.11 µm) while in fovea it was the lower (4.32 µm), as demonstarted in (**Table 8**).

Table 1. Frequency Distribution by Gender

Variable		Statistics	Normal eyes	Glaucomatous eyes	
			No.	No.	Total
Age (year)		Mean	42.05	58.05	51.65
		Range	20-73	30 - 83	20 - 83
Gender	Male	n (%)	21 (52.5)	33 (55.0)	54 (54.0)
	Female	n (%)	19 (47.5)	27 (45.0)	46 (46.0)
Total		n (%)	(100.0) 40	60 (100.0)	100 (100.0)

Table 2. Frequency distribution by mode of diagnosis

Variable	No.	%
incidental	44	73.3
Glaucoma	16	26.6
Total	60	100

Table 3. Distribution of 60 glaucomatous patients according to their education, family history and history of steroid

Variable		No.	%
Compliant	Yes	45	75.0
	No	15	25.0
Awareness	Yes	17	28.3
	No	43	71.7
Family History	Yes	22	36.7
	No	38	63.3
History of steroid use	Yes	24	40.0
	No	36	60.0
Total		60	100.0

Table 4. Distribution of age groups by duration of glaucoma

Age (year)	Duration of glaucoma (year)					
	<1		1 - 5		>6	
	No.	%	No.	%	No.	%
30-39	4	12.1	4	6.2	4	28.6
40-49	8	24.2	10	15.4	0	0.0
50-59	12	36.4	18	27.7	2	14.3
60-69	5	15.2	20	30.8	2	14.3
≥ 70	4	12.1	13	20.0	6	42.9
Total	33	29.5	65	58.0	14	12.5

P. value = 0.019 (significant)

Table 5. Comparison of mean IOP according to steroid use and compliant of glaucoma patients (n=60)

Variable		No. of cases	IOP (mmHg)		P. value
			Mean	SD	
History of steroid	Yes	47	20.36	7.91	0.010 sig
	No	65	17.21	4.69	
	Total	112	18.42	6.34	
Compliant of treatment	Yes	86	17.76	4.84	0.043 sig
	No	26	20.62	9.60	
	Total	112	18.42	6.34	

sig: significant

Table 6. Mean values with standard deviations and mean differences in 9 sectors of macula in normal and glaucomatous males

sectors	Glaucoma (n=60)		Normal (n=37)		Mean difference (µm)	P. value
	Mean	SD	Mean	SD		
Fovea	259.18	36.55	261.89	14.58	2.71	0.669 ns
TIM	306.28	46.71	328.16	14.68	21.88	0.007 sig
SIM	315.65	49.83	340.54	14.02	24.89	0.004 sig
NIM	318.45	52.75	336.38	14.42	17.93	0.046 sig
IIM	319.18	40.03	334.81	16.64	15.63	0.026 sig
TOM	264.35	45.34	294.95	11.56	30.60	0.001 sig
SOM	282.53	27.17	299.38	11.99	16.85	0.001 sig
NOM	296.33	40.78	310.65	13.11	14.32	0.041 sig
IOM	278.62	31.94	293.76	12.76	15.14	0.007 sig

sig: significant , ns: not significant

Table 7. Mean values with standard deviations and mean differences in 9 sectors of macula in normal and glaucomatous females

sectors	Glaucoma (n=52)		Normal (n=32)		Mean difference (µm)	P. value
	Mean	SD	Mean	SD		
Fovea	249.69	51.34	255.88	16.87	6.19	0.512 ns
TIM	302.94	46.79	325.16	20.13	22.22	0.013 sig
SIM	316.87	46.35	345.25	16.89	28.38	0.001 sig
NIM	314.40	53.58	336.06	20.87	21.66	0.032 sig
IIM	311.33	49.36	338.25	14.19	26.92	0.004 sig
TOM	269.10	37.35	292.19	18.61	23.09	0.002 sig
SOM	283.67	25.86	300.47	12.67	16.8	0.001 sig
NOM	295.15	36.27	315.38	15.32	20.23	0.004 sig
IOM	277.00	33.29	296.44	17.19	19.44	0.003 sig

sig: significant , ns: not significant

Table 8. Mean values with standard deviations and mean differences in 9 sectors of macula in normal and glaucomatous patient.

Sectors	Glaucoma (n=112)		Normal (n=69)		Mean difference (µm)	P. value
	Mean	SD	Mean	SD		
Fovea	254.78	44.09	259.10	15.86	4.32	0.434 ns
TIM	304.73	46.56	326.77	17.36	22.04	<0.001 sig
SIM	316.21	48.03	342.72	15.48	26.51	<0.001 sig
NIM	316.57	52.93	336.23	17.57	19.66	0.003 sig
IIM	315.54	44.57	336.41	15.54	20.87	<0.001 sig
TOM	266.55	41.70	293.67	15.18	27.12	<0.001 sig
SOM	283.06	26.45	299.88	12.23	16.82	<0.001 sig
NOM	295.79	38.58	312.84	14.27	17.05	0.001 sig
IOM	277.87	32.44	295.00	14.92	17.13	<0.001 sig
sig: significant , ns: not significant						

4. DISCUSSION

Glaucoma is a complex multifactorial disorder characterized by a typical pattern of optic nerve damage and visual field loss that is usually but not always associated with elevated IOP, Accepted parameters for monitoring glaucoma include description &photography of optic disc appearance (cup-disc ratio), measurement of IOP and periodic threshold perimetry and advances in posterior segment imaging technology. Glaucoma is characterized by loss of retinal ganglion cells (RGCs) and their respective axons, which comprise the retinal nerve fiber layer (RNFL), RGC loss, cannot be seen on slit-lamp ophthalmic examination. Likewise, nerve fiber layer (NFL) bundle defects are difficult to detect on clinical examination (11-14). In this study, we provide the normative data for macular thickness that measured according to ETDRS map by using spectral OCT/SLO (NIDEK machine) in area of a 3.46-mm diameter, it reveals thicker values than previous studies which could be explained by race, ethnicity& type of OCT machine (greater variability among different type of OCT machine instruments or reproducibility) (15-18).

The NFL registered among different OCT instruments is variable, for both average and sector values. These discrepancies may be a direct result of greater resolution achieved by more recent (OCT) system, less movement by the patient, in addition to the fact that values

obtained by spectral domain OCT is higher than Time domain OCT. Therefore, clinician should be aware of these discrepancies when interpreting the OCT image from different OCT modality (11, 19). Macular thickness in normal group shows that, in inner ring TIM, NIM, IIM, SIM thicker respectively, while in outer ring TOM, IOM, SOM, NOM thicker respectively. So superior and inferior sectors of inner ring are thicker than superior and inferior sectors of outer ring (this consistent with the anatomical relationship of superior and inferior arcuate fiber that travel to optic disc), and NOM thicker than other sector of outer ring (this consistent with the anatomical correlation of converging of nerve fibers to optic disc)(20-22). In current study normal group, no difference between male and female in all macula sectors, this agree with the results of Hee et al (1998), Sanchez-Tocino et al (2002) and Chan et al (2005) (31). Many other studies (9, 10, 30-32) found that there is slight difference in male NFL thickness which was thicker. According to Zeimer et al's hypothesis (1998), quantitative detection of glaucomatous damage at the posterior pole by retinal thickness mapping may provide a unique method for the detection and monitoring of early glaucomatous tissue loss (22). This study was based on Zeimer et al hypothesis(1998), with the major objective of evaluating the association between macular thickness and glaucoma; in current study this association was significant in all sectors except the fovea, many previous studies (11,13,14,18,22-29) support this, (The fovea, the central region of the macula, is characterized by a high cone density and lack of ganglion cells) (14), but the macula has the highest density of ganglion cells, with a peak at 750 to 1100 microns from the foveal center and ganglion cell loss in glaucoma may result in a decrease in macular cellularity and macular thickness. (26). There was a study by Medeiros et al (2005) found that all macular parameters were decrease except NIM) (14).

The findings of the study revealed that the most affected sector was TOM, which supported by the result of Kotera et al (18) (2011) he mentioned that the greater nerve fiber loss was in the temporal sector, while Nakatani et al (2011) study (27) and also Nile et al (29) study (2012), whom concluded that the TOM had more loss in NFL thickness in his comparison between progressive and non-progressive glaucomatous loss.

5. CONCLUSIONS

There is progressive NFL thinning in macular regions and the most significant decrease is in temporal outer macula. Slight thinning in Fovea but not in significant amount. here is difference in NFL loss between male and female, which is more in female except in TOM. Hence we recommend that for every glaucomatous /or glaucoma suspect person, in routine practice we recommended OCT of macula and optic nerve. OCT could represent surrogate biomarker for detecting progressive glaucomatous structural change over time. However, further studies are needed to increase our knowledge in diagnosis, monitoring &treatment of glaucoma.

Ethical Approval:

All ethical issues were approved by the author. Data collection and patient's enrollment were in accordance with Declaration of Helsinki of World Medical Association, 2013 for the ethical principles of researches involving human. In addition, before examination, the aim of the study was explained for the patients and signed consent was taken from all patients.

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