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Retinal Fiber Layer and Macular Ganglion Cell Layer Thickness in Diabetic Patients

Maalej Afef [1*], Khallouli Asma[2], Bouguerra Chaker[3], Ajili Faida[4] and Rannen Riadh[2]

[1]*Department of Ophthalmology, Military Hospital of Tunis, Autoimmune Diseases Unit Research UR17DN02, Tunis Elmanar University, Tunisia*

[2]*Department of Ophthalmology, Military Hospital of Tunis, Tunis Elmanar University, Tunisia*

[3]*Department of Epidemiology and Preventive Medicine, Military Hospital of Tunis, Tunis Elmanar University, Tunisia*

[4]*Military Hospital of Tunis, Autoimmune Diseases Unit Research UR17DN02, Tunis Elmanar University, Tunisia*

[*]**Corresponding author:** Maalej Afef, Department of Ophthalmology, Military Hospital of Tunis, Tunis Elmanar University, Tunisia, Tel: +21698687900; E-mail: afefmaalej@yahoo.fr

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Abstract

Background: To compare the ganglion cell-inner plexiform layer (GCIPL) thickness and the retinal nerve fibre layer (RNFL) thickness between type 2 diabetic patient's eyes with and without diabetic retinopathy (DR) and normal eyes.

Methods: In this comparative case-control study two groups of 58 eyes were examined by SD-OCT with peri-papillary RNFL, and macular GCIPL assessment. The first group includes 58 eyes of type 2 diabetic patients (33 eyes without DR, 25 eyes with moderate DR, without diabetic macular edema), the second group included 58 eyes of non-diabetic, non-glaucomatous patients. We compared RNFL and GCIPL thicknesses among different groups. We evaluated the potential systemic risk factors for RNFL and GCIPL loss (HBA1C, the presence of DR, other vascular diseases).

Results: The two groups were matched concerning the age, gender and the intra-ocular pressure (IOP) level. A significant differences between the two groups was found for the average, superior and inferior RNFL thickness ($p<0.001$, $p=0.005$ and $p=0.01$ respectively). Concerning the GCIPL thickness, it was significantly less in the diabetic eyes ($p<0.001$), but no significant difference was noted between the diabetic patient's eyes without DR and the healthy controls in all quadrants for the RNFL and the GCIPL. Multivariate linear regression analysis concluded that the diabetic duration, the HbA1c were correlated to RNFL and GCIPL loss in diabetic patient's eyes and the presence of arterial hypertension as well as lipid disorders were found as risk factors in the non-diabetic group.

Conclusion: RNFL and GCIPL loss seems to be the earliest retinal changes in diabetic patients, and associated with diabetic duration and poor control. These results can explain the higher risk of primitive angle closure glaucoma in diabetic patients and confirm the neurodegeneration theory in DR's physiopathology.

Keywords: Diabetes; RNFL; GCIPL; Diabetic retinopathy; Neurodegeneration

Introduction

Diabetic retinopathy (DR) is a major complication of diabetes. Early diagnosis, monitoring, and suitable management of this ocular disease are primordial in order to reduce the rate of blindness in diabetic patients. The classic pathophysiology of DR postulated that it's primarily a vascular disease, in which changes in the retinal vessel endothelium cells leads to the blood–retina barrier breakdown and so an increase in the vascular permeability [1]. Recent researches have postulated that there is a neurodegenerative process that preceded vascular changes in diabetic patients with neuronal cell loss concerning especially retinal ganglion cells [2]. Is the micro vascular changes causes the retinal neuropathy, or neurodegeneration is the primary feature of chronic hyperglycemia or both mechanisms are simultaneous and independants?

Optical Coherence Tomography (OCT) is actually the most precise method to measure retinal thickness with high accuracy. It becomes an essential tool to assess macular and peripapillar retinal layers.

The purpose of this study was to measure the peripapillary retinal nerve fiber layer (RNFL) thickness and the ganglion cell-inner plexiform layer (GCIPL) with SD-OCT, in type 2 diabetic patients (with and without DR) and compare them to normal age and sex-matched controls. The correlation with systemic metabolic control was evaluated.

Materials and Methods

We included in this comparative case-control cross sectional study two groups: The first group enrolled 58 eyes of 29 type 2 diabetic patients (33 eyes without DR, 25 eyes with moderate DR), the second group included 58 eyes of 29 non-diabetic, non-glaucomatous healthy patients. The present study respected ethical standards of the Declaration of Helsinki. Informed consent was obtained from all patients before enrollment. 58 consecutive type 2 diabetic patients,

referred for a systematic exam of the retina between June and September 2018 were included in this study. The healthy patients were recruited in the same period and were matched to the first group for the mean age and the sex. The first group was divided to two subgroups: 33 eyes without any signs of DR on the fundus exam, 25 eyes with moderate DR.

Were excluded from the study, patients with Type I diabetes, diabetic macular edema diagnosed on the OCT macular scan (central subfield thickness>250 microns), epiretinal membrane, severe non proliferative and proliferative DR, refractive errors, pre-existing glaucoma or high intra-ocular pressure, eyes with intraocular inflammation, optic nerve or neurologic pathologies, previous ocular treatment (intra ocular injections, laser, surgery), the presence of media opacities impeding the OCT exam (cataracts, corneal opacities).

The treatment of diabetes in the first group was oral anti-diabetic medications for 21 patients and insulin in 8 patients.

A detailed Ophthalmological examination was performed in all eyes with best corrected visual acuity, slit lamp examination. The Intraocular pressure was recorded using the same air puff non-contact tonometry and was correlated to pachymetry. Indirect fundus ophthalmoscopy with a 78-diopter lens was performed. Optovue three dimensional SD-OCT was used for scanning in all eyes. OCT exam was performed by the same person (an experimented orthoptist) and only scans with high quality were included in this study.

After pupil dilatation, both eyes of all subjects underwent following scan:

- • Retinal fiber layer (RNFL) thickness.
- • Ganglion Cell Complex (GCC) thickness.

RNFL thickness was measured using the optic nerve head (ONH) protocol (3.45mm diameter circle centered on the ONH).

The main parameters analyzed on the OCT-scan were: average RNFL thickness, temporal, nasal, inferior and superior RNFL thickness.

In addition, the opto-Vue SD-OCT device is equipped with software that allowed the analysis of diffuse and focal gonglion cell complex (GCC) defects by calculating global loss volume (GLV) and focal loss volume (FLV), respectively.

Other systemic disorders were noted for the 2 groups. For diabetic patient's group, the metabolic control was assessed by glycosylated haemoglobin (HbA1c) level. For the control group we looked at lipid control and arterial tension level.

Statistical analysis

The analysis of the results was performed with the 22th version of SPSS software. Data were analyzed using mean and standard deviation for quantitative variables and frequencies and relative frequencies for categorical variables. Comparisons between groups were done using unpaired t test. For comparing categorical data, Chi 2 test was performed. p-value <0.05 was considered as statistically significant. The pearson correlation's coefficient evaluated the eventual correlation between two quantitative variables. Multivariate linear regression analysis was conducted in order to determine the risk factors of RNFL and GCIPL loss in diabetic and healthy patient's eyes.

Results

In this study, the RNFL, GCIPL thicknesses were compared between diabetic patients (with and without DR) and normal non-diabetic, non-glaucomatous healthy patients. All the factors which could influence the studied measures were evaluated and a correlation between these factors and the OCT data was searched.

The average age of patients was 54.4 years for the diabetic group and 54.9 years for the control group (p=0.59). The sex ratio and the main general characteristics of patients in both groups are resumed in the Table 1. The two groups were matched for the mean age, the sex ratio and the BCVA average (Table 1). Concerning the intra-ocular pressure (IOP), no statistical difference was notes between the two groups (p=0.20) (Table 1). Looking at the diabetic patient's eyes group, we noted that the mean duration of the disease was 5.4 ± 3.1 years for the eyes without DR and 11.8 ± 4.9 for the eyes with moderate DR, The duration of diabetes was statistically higher in the patients with DR (p<0.001) (Table 1). The BCVA was 0.0 ± 0.0 LogMAR in all groups.

	GROUP 1 (n=58)		GROUP 2 (n= 58)	P value
	Without DR(n=3)	With moderate DR(n= 25)		
Mean Age	55.1 ± 3.4	53.8 ± 5.6	54.9 ± 8.2	0.59
Sex Ratio	1.06	1.08	1	
BCVA (log Mar)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
IOP (mmhg)	15.2 ± 1.8	15.7 ± 2.1	14.9 ± 2.3	0.2
Duration of diabetes (years)	5.4 ± 3.1	11.8 ± 4.9		<0.001*
HbA1c (%)	7.8 % ± 1.2%	8.1% ± 1.4%		0.39*
Mean systolic Arterial tension (mmHg)	15.7 ± 2.6	16.2 ± 2.5	16.5 ± 2.3	0.08
Mean Diastolic Arterial tension	7.4 ± 2.3	7.8 ± 2.1	8.1 ± 1.9	0.28
Total Cholesterol level (g/l)	1.97 ± 0.8	1.99 ± 0.5	1.84 ± 0.4	0.14

TG level (g/l)	1.84 ± 0.2	1.94 ± 0.4	1.87 ± 0.3	0.47

Note: DR: Diabetic retinopathy; BCVA: best corrected visual acuity; HBA1c: glycosylated hemoglobin

*comparison between diabetic patients with DR and without DR

Table 1: General characteristics of patients in the two groups.

The mean HbA1c level was 7.8% ± 1.2%, 8.1% ± 1.4%, in no-DR group, and moderate DR group, respectively (p=0.39).

Other vascular disorders were noted for the two groups with arterial tension evaluation, Cholesterol, TG levels (Table 1).

The GCIPL and RNFL thickness measurements were tested for all diabetic and control eyes.

The mean RNFL thickness was maximum in superior quadrant in all the groups. The average RNFL thickness was 89.7 ± 10.5 µm and 99.7 ± 20.6 µm in diabetic patients and controls, respectively (P<0.001). No statistical difference was found for the average of RNFL thickness between the diabetic patients without DR and control eyes (p=0.41) (Table 2).

Moreover, the RNFL thickness was significantly thinner in diabetic patients compared to controls, in the superior and temporal quadrants (p=0.005, p=0.01 respectively) (Table 2). Comparison of control group with diabetic patients without DR showed no difference of RNFL thickness for all quadrants (Table 2).

The average GCIPL thickness was 82.7 ± 8.5 µm and 86.2 ± 8.5 µm in diabetic patients and controls, respectively (P<0.001). CCIPL thickness was thicker in normal eyes than that of diabetic subjects, but this difference was statistically significant only in the superior and inferior areas (p=0.005, p=0.01 respectively) (Table 2). The difference between DR (-) group and control wasn't significant for all GCIPL quadrants (Table 2).

FLV and GLV were significantly higher in diabetic patients versus normal eyes (p=0.005 and p=0.01 respectively). These indicators were lower in control eyes compared to diabetic's eyes without DR but the difference wasn't significant (Table 2).

	GROUP 1 (n=58)		**GROUP 2 (n= 58)**	**P value**	
	Without DR (n=3)	With moderate DR (n= 25)	Diabetics *Vs* control	DR (-) *Vs* control	
RNFL (µm)					
Average	89.7 ± 10.5	87.2 ± 12.4	99.7 ± 20.6	<0.001	0.41
Superior	112.3 ± 11.3	108.2 ± 9.7	115.6 ± 11.7	0.005	0.15
Nasal	72.6 ± 10.1	71.8 ± 9.6	72.9 ± 13.1	0.78	0.76
Inferior	114.2 ± 10.7	113.8 ± 10.5	119.2 ± 12.3	0.01	0.88
Temporal	64.5 ± 10.3	63.4 ± 10.4	64.8 ± 11.8	0.72	0.68
GCIPL (%m)					
Average	82.7 ± 8.5	80.6 ± 10.2	86.2 ± 8.5	<0.001	0.39
Superior	80.2 ± 9.4	79.5 ± 7.4	85.6 ± 8.6	0.005	0.71
Nasal	76.8 ± 7.9	74.7 ± 6.9	82.9 ± 7.9	0.78	0.29
Inferior	74.5 ± 9.6	73.8 ± 9.6	81.4 ± 7.8	0.01	0.78
Temporal	83.5 ± 8.5	81.4 ± 8.3	86.4 ± 9.8	0.72	0.35
FLV %	0.69 ± 0.81	0.70 ± 0.59	0.39 ± 0.34	0.002	0.95
GLV %	3.92 ± 2.67	4.01 ± 1.9	2.84 ± 1.59	0.001	0.88

Note: FLV: focal loss volume; GLV: global loss volume

Table 2: OCT parameters in the two groups.

The Pearson coefficient showed that the average RNFL thickness was directly correlated with the GCIPL thickness in diabetic and control patients (r=0.42 and r=0.53 respectively).

A statistically significant negative correlation between the duration of diabetes, the HBA1C level and both RNFL and GCIPL thicknesses in the diabetic group (with or without DR) was found (Table 3). For

the control group, the arterial hypertension and lipid disorders were found as risk factors for both RNFL (p=0.001 and p=0.003 respectively) and GCIPL thinning (p<0.001 and p=0.004 respectively).

Discussion

In this cross-sectional study using SD-OCT, we investigated the RNFL and GCIPL thickness values in asymptomatic type 2 diabetic patients with and without DR. Our results revealed a significant reduction of the mean GCIPL thickness and RNFL thickness in diabetic patients compared to a homogenous control group. The focal and global loss volumes were bigger in diabetic patient's eyes. We also noted that RNFL and GCIPL loss occurred in diabetic eyes without any sign of DR.

		Diabetes duration	HBA1C
RNFL thickness (average)			
DR (+)	Pearson correlation	-0.16	-0.19
	P value	0.02	0.001
DR (-)	Pearson correlation	-0.05	-0.01
	P value	0.04	0.03
GCIPL thickness (average)			
DR (+)	Pearson correlation	-0.17	-0.21
	P value	0.001	
DR (-)	Pearson correlation	-0.07	-0.09
	P value	0.02	0.01
Note: DR (+): eyes with diabetic retinopathy; DR (-): eyes without diabetic retinopathy			

Table 3: Correlation among diabetes duration, HbA1c value, RNFL thickness, and GCIPL thickness in diabetic patients.

Neuroretinal degeneration is confirmed and seems to occur in different optic nerve diseases, such as glaucoma [3]. Interestingly, GCIPL and RNFL thinning has been found in retinal illnesses, such as non-proliferative idiopathic macular telangiectasia [4].

In recent studies, it was reported that GCIPL and RNFL thickness values were markedly reduced in diabetic eyes without DR and the authors concluded that neuroretinal alterations may precede micro vascular abnormalities in diabetic eyes [5-8].

Molecular mechanisms involved in retinal neurodegeneration in diabetes are complex. The exact relationship between vascular DR and diabetic retinal neuropathy is not yet well known [6].

It's admitted that diabetes induces neural apoptosis of ganglion, amacrine, and Müller cells, as well as increased expression of glial fibrillary acidic protein in Müller cells, activation of microglia (possibly caused by chronic glutamate toxicity [9], inflammatory glial activation, and increased expression of other neurotrophic factors, including basic fibroblast growth factor and ciliary neurotrophic factor. Altered glutamate metabolisms have been noted recently in diabetic retinas [10].

Chronic hyperglycemia, even without clinically detectable microvascular complications, can lead to the impairment of retinal gonglion cell layer and so to a reduction of GCIPL and RNFL thicknesses. Objective assessment of GCC is important in DR as it will help in detection of inner retinal loss associated with the disease and help in developing neuroprotective therapeutic regimens [11].

Detecting early impairment of neurologic tissue in DR can allow a preventive rather than interventional approach in treatment and then a better visual prognosis for these patients.

In the present study, the RNFL thickness was significantly thinner in diabetic patients compared to controls, mainly in the superior and temporal quadrants. Current study is in accordance with other studies [12,13]

Superior RNFL loss in diabetic retina has been related to lower perfusion in superior retina and the ONH which may lead to greater ischemia and so to structural damage in the ganglion cells superiorly [13]

However, Takis et al. showed that the mean inferior sectorial RNFL thickness was significantly lower in diabetic patients with no or mild retinopathy compared to healthy eyes [14].

Significant GCC thinning was noted in eyes with no DR and with DR compared to control eyes mainly in superior and inferior areas. Exact mechanisms for inner retinal loss are not yet very clear but have been related to lower perfusion and higher metabolic demands of the inner retina which make it more vulnerable to the metabolic stress induced by hyperglycemia [15].

Van Dijk et al. showed that the thinning of inner retinal layers in the macula in diabetes type 1 is progressive over time and is related to disease duration but occurs independently of retinal vasculopathy [15].

We found that FLV and GLV were significantly higher in diabetic patients versus normal eyes.

The duration of diabetes affected negatively the RNFL and the GCIPL thickness in our diabetic patients. Arterial hypertension and lipid disorders seem to be a risk factor for neurodegeneration in healthy patients. These systemic diseases were rarely evaluated as reducing RNFL and GCIPL thicknesses in normal and diabetic patients.

The presence of a significant correlation between the GCIPL and RNFL average thicknesses and HbA1c level wasn't reported by many studies. We predict that for our patients the level of HBA1c was high because of the poor control of diabetes and it can explain the loss of RNFL and GCIPL. Oshitari T et al. showed a weak negative correlation between the two variables [16].

Sugimoto et al. found that glycemic control (HbA1c levels) affects RNFL within 4 months [17]. Sahin et al. showed that there is a mild negative correlation between HbA1c and average RNFL thickness, and concluded that thinning of RNFL might be related with increased rates of atherosclerosis in patients with type 2 DM [18].

Evre P et al. noted that HbA1c and diabetes mellitus duration were not associated with any of the studied ocular parameters, except for a moderate correlation between binocular RNFL symmetry percentage and DM duration [6].

The main limitations of the current study are related to the fact that it was a non randomised study. It was a cross-sectional, observational study design. Second, we did not have fundus fluorescein angiography,

which might show the earliest retinopathy findings that could not be noticed by routine fundus examination. It would be more interesting if we had OCT angiography examinations also.

One of the main clinical implications of the present study is the notification that the diabetic eyes without apparent retinopathy may have subtle inner retinal damage. Our constatations may indicate a relative predisposition of diabetic eyes to glaucomatous retinal disorders. Moreover, we can postulate that diabetes mellitus may make difficult to detect glaucomatous cells damage.

Conclusion

These data confirmed neuroretinal alterations are early in DR, preceding microvascular changes. RNFL loss might be the earliest structural change of retina in diabetic patients.

It warrants neuroprotective intervention to prevent chronic neurodegeneration. The SD-OCT may represent an indispensable tool for identifying early signs of neurodegeneration in diabetic eyes. It will help in monitoring the patient. Further studies are necessary to understand whether ganglion cell neuroretinal degeneration and microvascular damages are pathogenically linked and whether neuroretinal degeneration represents a target in diabetes treatment to prevent DR.

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