Original Article

Ophthalmology and Allied Sciences
Volume 3 Number 2, July - December 2017
DOI: http://dx.doi.org/10.21088/oas.2454.7816.3217.22

Analysis of Changes in Retinal Nerve Fiber Layer before Vascular Changes in Patients with Diabetes Using Optical Coherence Tomography

Sneha Murade[1], R.R. Naik[2], Nitish Arora[3]

[1]Resident [2]Professor and Head [3]Resident, Department of Ophthalmology, PDVVPF's Medical College and Hospital, Ahmednagar - 414111, Maharashtra, India.

Abstract

Aim: To detect retinal changes in patients with type 2 Diabetes prior to vascular signs without diabetic retinopathy or with mild non proliferative diabetic retinopathy. *Methods:* A cross-sectional study was performed in three groups: 1. Patients without diabetes (Group A), 2. Patients with type 2 diabetes without diabetic retinopathy (Group B), 3. Patients with diabetes with mild diabetic retinopathy (Group C). Analysis of retinal layers was performed using Topcon 3D OCT. Macular scans were analyzed with regard to: retinal nerve fiber layer thickness, central subfoveal retinal thickness and average macular thickness. *Results:* In total, 60 patients were included in this study, of which 16 (26.67%) were classified into control group (Group A), 28 (46.67%) classified as diabetic patients with no diabetic retinopathy (Group B) and 16 (26.67%) classified as mild diabetic retinopathy (Group C). Quantitative analysis with using Topcon 3D OCT showed that the mean retinal nerve fiber layer was thinner in diabetics without diabetic retinopathy group when compared to controls. Statistically significant reduction in average retinal thickness in mild diabetic retinopathy group compared to control. Also indicated reduction in retinal nerve fiber layer in diabetic without diabetic retinopathy and eyes with mild diabetic retinopathy, compared to controls. Both the results were statistically significant. *Conclusions:* Our study found reduction in thickness of retinal nerve fiber layer in patients with diabetes without diabetic retinopathy, which suggests neuroretinal changes before vascular signs of diabetic retinopathy.

Keywords: Diabetes Mellitus; Diabetic Retinopathy; OCT; Optical Coherence Tomography; Macula; Retina; Neuronal; Neurodegeneration.

Introduction

Diabetic retinopathy (DR) is one of the major causes of blindness in patients from 30 to 60 years of age. Inspite of the recent advances, current treatment with pharmacological measures and laser may not be enough in some patients for complete visual recovery.

DR is primarily a vascular disease, but recent studies have shown some degenerative and neuronal changes that occur before the appearance of actual microvascular changes in patients with diabetes mellitus (DM) [1,2]. Laboratory studies support the occurrence of neuronal alterations like apoptosis in early stages itself in cases of diabetes [3-6].

Optical coherence tomography (OCT) makes it easier the deep understanding and study of a large number of eye diseases [7-8]. New generation Spectral Domain-OCT allows detailed examination of all retinal layers and vessels, thereby facilitating the study of pathogenesis of each disease.

Clinically, authors have reported diminution in average central retinal or single cellular layer thickness in diabetic eyes, including both with and without clinical signs of DR compared to control groups (subjects with no DM) [1,2]. Others studies have shown decrease in the inner retinal thickness

Corresponding Author: Sneha Murade, Resident, Department of Ophthalmology, PDVVPF's Medical College and Hospital, Ahmednagar-414111, Maharashtra, India.
E-mail: snehamurade@gmail.com

Received on 14.02.2017, **Accepted on** 23.02.2017

at macula in diabetics with mild disease, which may be caused due to initial loss of ganglion cells in the pericentral areas followed by retinal nerve fiber layer (RNFL) thinning in the peripheral part of macula [5,6,9].

Aim

The goal of this study was to investigate neuroretinal changes prior to vascular signs in patients with type 2 diabetes without diabetic retinopathy or with mild non proliferative diabetic retinopathy.

Material and Method

A study was performed in three groups:

(Group A) - Patients without diabetes.

(Group B) - Patients with type 2 diabetes without diabetic retinopathy.

(Group C) - Patients with diabetes with mild diabetic retinopathy**.**

Patients were examined in the Department of Ophthalmology at DVVPF Medical College and Hospital.

Analysis of retinal layers was performed using Topcon 3D OCT.

Macular scans were analyzed with regard to:

- Retinal nerve fiber layer thickness,
- Central subfoveal retinal thickness
- Average macular thickness.

Control subjects did not have a diagnosis of diabetes, any ocular disease, or any other systemic disease. These subjects were randomly recruited from individuals accompanying patients visiting the Department of Ophthalmology.

The Inclusion Criteria

1. Individuals with type 2 DM and above the age of 40 years. (The choice of type 2 diabetes was due to its prevalence and importance of future projection)
2. Mild DR was considered as the presence of at least one micro aneurysm in the retina, but no other diabetic lesions.

The Exclusion Criteria

1. If they presented with a best corrected visual acuity less than 6/9.
2. When OCT images were of inadequate quality (signal strength below 7),
3. If DR equal or worse than moderate,
4. Lens opacity and other vision impairing diseases such as glaucoma, cataract, uveitis, or macular degeneration.

After informed consent was signed, all participants underwent the following examinations:

1. Visual Acuity (BCVA)

   Patients were evaluated with respect to best corrected visual acuity using the Snellen chart.

2. Slit Lamp Biomicroscopy

   To detect signs of Anterior segment complications include rubeosis iridis, neovascular, ghost cell, and hemolytic glaucoma, cataract, and corneal decompensation.

3. Ophthalmoscopy - Direct and 90D
4. Spectral - Domain Optical Coherence Tomography (SD-OCT) - The patients had pupil dilation by tropicamide and evaluation through spectral-domain optical coherence tomography (SD-OCT).

Only SD-OCT analysis was performed, centered on the fovea and repeated three times by the examiner. Only scans with signal strengths ≥7 and without artifact were included in the study.

- The results were reported as mean values with standard deviation. Data was statistically analyzed.
- An unpaired *t* -test was used to calculate the *p* value between the study and the control group.
- Values of *p* less than 0.05 were considered statistically significant.

Results

In total, 60 patients were included in this study, of which 16 (26.67%) were classified into control group (Group A), 28 (46.67%) classified as diabetic patients with no diabetic retinopathy (Group B) and 16 (26.67%) classified as mild diabetic retinopathy (Group C). Quantitative analysis using Topcon 3D OCT showed that the mean retinal nerve fiber layer was thinner in diabetics without diabetic retinopathy group when compared to controls.

Statistically significant reduction in average

retinal thickness in mild diabetic retinopathy group compared to control. Also indicated reduction in retinal nerve fiber layer in diabetics without diabetic retinopathy and eyes with mild diabetic retinopathy, compared to controls. Both the results were statistically significant.

Table 1: Demographic data of subjects included in the study

Parameters	Controls (16)	DM with no DR (28)	Mild DR (16)	p
Age (in years)	54 ± 10	59 ± 10	62 ± 11	0.01
Gender (m or f)	8:8	11:17	7:9	0.53
Glycaemia (mg/dl)	92.50 ± 9.19	167.33 ± 134.44	148.81 ± 70.72	0.01
HbA1c (in %)	-	7.55 ± 1.57	7.16 ± 1.22	0.10
Duration of DM (in years)	-	12 ± 7	12 ± 9	0.98

Table 2: Thickness measured by SD- OCT Mean thickness (μm)

Measure	Control (N = 16)	DM with no DR (N = 28)	Mild DR (N = 16)
RT	284.07 ± 13.40	279.02 ± 14.26	271.46 ± 26.23
CS	260.61 ± 24.15	245.46 ± 24.36	254.68 ± 46.90
RNFL	45.93 ± 24.60	30.41 ± 3.46	29.78 ± 5.57

Table 3: Standardized regression coefficients derived from multiple linear regression

Dependent variable:	Independent variable	Standartized coefficients	P
RT	Age	0.154	0.126
(R = 0.293, p = 0.012)	DR status	0.210	0.038
RNFL	Age	0.156	0.103
(R = 0.427, p < 0.001)	DR status	0.358	<0.001

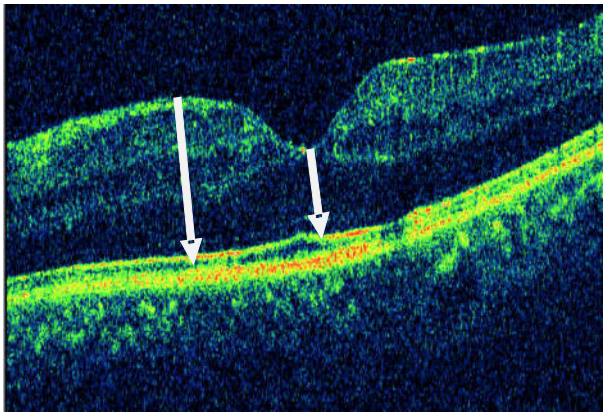

Fig. 1: Showing Central Subfoveal Thickness and Macular thickness on OCT

Analysis

In quantitative analysis the RT and RNFL were thinner in the group with DM with no DR when compared to controls ($p < 0.05$). Furthermore, RNFL was even thinner in patients with DR (Table 2). Test indicated a statistically significant reduction compared to controls ($p < 0.05$) in the following retinal layers: RT in mild DR group ($p = 0.032$); and RNFL in DM without DR or eyes with mild DR ($p < 0.001$).

The relationship between RNFL thickness and RT with variables with correlation (age and DR status). In Table 3, standardized coefficients of the explanatory variables are presented. These variables show that DR status is the most explanatory variable to thickness reduction.

Discussion

DR is the leading cause of mild to moderate visual impairment and blindness in the adult working population. It has been considered to be primarily a microvascular disorder [10]. However, recent publications proclaim that retinal neuronal degeneration can be detected before clinically detectable microvascular changes [1,2,4,11,12]. The hypothesis for the occurrence of neuronal degeneration before microvascular damage has been confirmed by electrophysiological studies [13,14]. Recent studies have proposed that diabetes also causes the loss of different types of retinal cells that include ganglion cells, bipolar cells, amacrine cells, horizontal cells and eventually affects photoreceptors [3,4,14,15]. Thus, clinically, various authors have reported a decrease in retinal thickness in diabetic eyes with or without clinical signs of DR when compared to normal subjects [1,2,12,16-18].

Vujosevic, Midena and Van Dijk et al. have shown a reduction in the inner retinal thickness in the region of macula in patients with mild DR. Van Dijk et al. postulated an initial GCL loss in the pericentral areas which was further followed by RNFL thinning in the peripheral part of macula [5]. In addition to this, Vujosevic and Midena found outer retina may not be affected at early stages of DM and concluded that automatic SD-OCT may be a useful tool to diagnose and monitor early changes in retina in DR patients.

The total macular thickness in diabetic eyes with no DR and mild DR was studied in our setting using CS and RT parameters and we found a significant decrease in the number of eyes with mild DR in RT ($P = 0.032$). These values matched the results of Biallosterski et al., who postulated that the mean RT in the pericentral area was decreased in patients with DR as compared to the healthy controls. Verma et al. also found that there was reduction in foveal thickness in patients with DM but there was no retinopathy when compared to healthy individuals [6].

RNFL thickness evaluation all quadrants with SD-OCT is considered to be a reliable parameter in patients of glaucoma. Herein, analysis disclosed reduction in RNFL both in patients with no DR and those with mild DR. Similar findings of decreased RNFL have been postulated by van Dijk et al. in patients with mild DR [1].

Strengths of our study included examination of both patients with DR or just DM and it also includes the objective analysis with the help of OCT software in addition to a subjective retinal measurement by two different experimented examiners.

A limitation of our investigation may be the poor intraclass correlation between examiners in some retinal layers. Apart from that, the difference in age between different groups was another limitation. Other drawback of our investigation was the uncertain onset of the DM, as type 2 DM patients may be affected by the disease for some time before the condition is diagnosed, but this fact would only underestimate the findings.

Conclusions

Our study found reduction in thickness of retinal nerve fiber layer in patients with diabetes without diabetic retinopathy, which suggests neuroretinal changes before vascular signs of diabetic retinopathy.

References

1. Van Dijk HW, Kok PH, Garvin M, Sonka M, Devries JH, Michels RP, et al. Selective loss of inner retinal layer thickness in type 1 diabetic patients with minimal diabetic retinopathy. Invest Ophthalmol Vis Sci. 2009;50:3404–9.
2. Biallosterski C, van Velthoven ME, Michels RP, Schlingemann RO, DeVries JH, Verbraak FD. Decreased optical coherence tomography-measured pericentral retinal thickness in patients with diabetes mellitus type 1 with minimal diabetic retinopathy. Br J Ophthalmol. 2007;2007(91):1135–8.
3. Abu El-Asrar AM, Dralands L, Missotten L, Geboes K. Expression of antiapoptotic and proapoptotic molecules in diabetic retinas. Eye (Lond). 2007;21:238–45.
4. Yang JH, Kwak HW, Kim TG, Han J, Moon SW, Yu SY. Retinal Neurodegeneration in Type II Diabetic Otsuka Long-Evans Tokushima Fatty Rats. Invest Ophthalmol Vis Sci. 2013;54:3844–51.
5. Van Dijk HW, Verbraak FD, Kok PH, Garvin MK, Sonka M, Lee K, et al. Decreased retinal ganglion cell layer thickness in patients with type 1diabetes. Invest Ophthalmol Vis Sci. 2010;51:3660–5.
6. Verma A, Raman R, Vaitheeswaran K, Pal SS, Laxmi G, Gupta M, et al. Does neuronal damage precede vascular damage in subjects with type 2 diabetes mellitus and having no clinical diabetic retinopathy? Ophthalmic Res. 2012;47:202–7.
7. Koh VT, Tham YC, Cheung CY, Wong WL, Baskaran M, Saw SM, et al. Determinants of ganglion cell-inner plexiform layer thickness measured by high-definition optical coherence tomography. Invest Ophthalmol Vis Sci. 2012;53:5853–9.
8. Mwanza JC, Durbin MK, Budenz DL, Girkin CA, Leung CK, Liebmann JM, et al. Profile and predictors of normal ganglion cell-inner plexiform layer thickness measured with frequency-domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2011;52:7872–9.
9. Wilkinson CP, Ferris 3rd FL, Klein RE, Lee PP, Agardh CD, Davis M, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003;110:1677–82.
10. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. N Engl J Med. 2012;366:1227–39.
11. Simó R, European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR), Hernández C. Neurodegeneration is an early event in diabetic retinopathy: therapeutic implications. Br J Ophthalmol. 2012;96:1285–90.
12. Vujosevic S, Midena E. Retinal layers changes in human preclinical and early clinical diabetic retinopathy support early retinal neuronal and

Muller cells alterations. J Diabetes Res. 2013;2013:905058.

13. Nilsson M, von Wendt G, Brautaset R, Wanger P, Martin L. Macular structure and function and the development of retinopathy in diabetes. Clin Exp Optom. 2012;95:306–10.
14. Nilsson M, von Wendt G, Wanger P, Martin L. Early detection of macular changes in patients with diabetes using Rarebit Fovea Test and optical coherence tomography. Br J Ophthalmol. 2007;91:1596–8.
15. Valverde AM, Miranda S, García-Ramírez M, González-Rodriguez Á, Hernández C, Simó R. Proapoptotic and survival signaling in the neuroretinal at early stages of diabetic retinopathy. Mol Vis. 2013;19:47–53.
16. Stem MS, Gardner TW. Neurodegeneration in the pathogenesis of diabetic retinopathy: molecular mechanisms and therapeutic implications. Curr Med Chem. 2013;20:3241–50.
17. Barber AJ, Gardner TW, Abcouwer SF. The significance of vascular and neural apoptosis to the pathology of diabetic retinopathy. Invest Ophthalmol Vis Sci. 2011;52:1156–63.
18. Gardner TW, Abcouwer SF, Barber AJ, Jackson GR. An integrated approach to diabetic retinopathy research. Arch Ophthalmol. 2011;129:230–5.