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Original Article

Comparison of Retinal Nerve Fiber Layer Thickness in Diabetic Patients with and without Diabetic Retinopathy and Healthy Individuals using Ocular Coherence Tomography

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Abstract

Objectives: Using Ocular Coherence Tomography, the study aimed to examine the RNFL thickness of type diabetics, patients with Diabetic Retinopathy, and healthy persons. **Methods:** 101 patients from the outside patient department and the Retina department of Tertiary Eye Care Hospital participated in this research. The cross-sectional study design was used. Non-probability consecutive sampling was utilized as the sampling technique. Patients were selected according to inclusion criteria. Visual Acuity was assessed using an (ETDRS) Early Treatment Diabetic Retinopathy Study Visual acuity chart at a distance of 6m. After the Ophthalmological Examination was done by a doctor, Ocular Coherence Tomography (Heidelberg Spectralis) was performed to assess RNFL thickness. The association between different types of diabetic retinopathy, Type-2 Diabetes, Normal Healthy, and retinal RNFL thickness was determined using a one-way ANOVA test. **Results:** The age range of the participants was between 40 and 69 years, with a mean of 55.68 ±10.437 years. 15.3% had diabetes for 1 to 5 years. 24% had Diabetes for 6 to 10 yea 19.9% had a Diabetes duration of 19.9%. The RNFL thickness was significantly decreased in type 2 diabetics, NPDR, and PDR as compared to normal Healthy individuals ($p<.001$). Age and duration of diabetes were closely correlated with the retinal nerve fiber layer ($p<0.001$). **Conclusion:** This study indicated that the (retinal nerve fiber layer) RNFL was considerably thinner in all quadrants of diabetic retinopathy (NPDR, PDR), type 2 diabetics, and healthy persons. Age and duration of diabetes were significantly correlated with average RNFL thickness.

Keywords: *Non-Proliferative; Diabetes Mellitus; Ocular Coherence Tomography; Proliferative Diabetic Retinopathy; Retinal Nerve Fiber Layer*

Introduction

Diabetes Mellitus is among the most common causes of vision loss.;it leads to diabetic retinopathy, resulting in significant vision loss in 5% of diabetics. Diabetic Retinopathy is one of the optic neuropathies distinct from Glaucoma; while having a thinner Retinal Nerve Fiber Layer, it lacks optic disc cupping. (Ramappa & Thomas, 2016)

Diabetes Mellitus is a constant health concern that affects all age groups, andgenders, both industrialized and developing nations, as well as rural and urban regions. (Meo *et al.*, 2016) In Pakistan, the prevalence of diabetic retinopathy among diabetics is 28.78%, of which 28.2% are VTDR. In 2010 among 285 million people with Diabetes, worldwide exhibited signs of DR, and one-fourth had vision-threatening Diabetic Retinopathy (VTDR), which includes severe Diabetic Macular Edema, NPDR, and PDR. (Mumtaz *et al.*, 2018)

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Diabetic retinopathy is the major factor responsible for visual loss world wide. In diabetic retinopathy, the eye's blood vessels become dilated and leaky, on the retina, aberrant new blood vessels grow, resulting in permanent vision loss. (Sohail, 2014) According to recent studies, there are not only vascular abnormalities in the early phases of diabetic retinopathy but also neuronal modifications, such as the death of retinal ganglion cells. (Oshitari, Hata & Yamamoto, 2008)

These two elements, vascular and neural anomalies, are taken into account while examining the pathophysiology of DR, and they provide insight into DR's development. (Barber *et al.,* 1998) Multiple studies have indicated that diabetics and NPDR patients have a weaker Retinal Nerve Fiber Layer compared to non-Diabetic patients. (Oshitari, 2006)

Multiple studies have shown that diabetics and NPDR patients have a thinner Retinal Nerve Fiber Layer than non-Diabetic patients. (Oshitari, 2006) Early stages of DR are distinguished by a reduction in the Retinal Nerve Fiber Layer's thickness. due to axonal degeneration and loss of retinal ganglion cells. This reduced RNFL thickness in DR patients is not reflected in early DR macular thickness due to increased vascular permeability, which masks the effect of neuronal damage. (Goebel & Kretzchmar 2002)

Patients with preclinical diabetic retinopathy have a much thinner nerve fiber layer compared to healthy persons. These neurodegenerative alterations resulting from preclinical diabetic retinopathy require additional study. (Mehboob *et al.,* 2019)

RNFL loss is the earliest change in diabetic retinopathy; neuronal modifications precede vascular abnormalities, hence RNFL thickness decreases before other structural changes occur in DR and diabetic patients. To test this Ocular Coherence Hypothesis that neural disorders precede vascular abnormalities: Tomography was used to determine the RNFL's thickness.

Methodology

Comparative cross-sectional research was carried out from July to December 2021 at a tertiary eye care hospital in Rawalpindi. This research included all patients having Diabetes, DR, and healthy individuals who were visiting an eye care hospital. This study was carried out in Rawalpindi's tertiary eye care hospital's OPD and Retina department. The Patients had detailed check-ups done by Optometrists and Ophthalmologists. The Total sample size was 101. (196 eyes of 101 patients). Among them 40 were healthy individuals, there were, 15 cases of PDR, 30 cases of NPDR, and 16 cases of Type 2 Diabetes. Under the supervision of prominent ophthalmologists, data was collected.

Out of 202 eyes, 196 were included because others did not meet inclusion criteria, so while analysing data others were excluded. Patients above the age of 40 years, Visual acuity better than 6/12 for healthy individuals, Non-proliferative Diabetic Retinopathy and Type 2 diabetics, and visual acuity worse than 6/12 for Proliferative diabetic retinopathy were included in the study. Individuals having any previous ocular surgery within one month. Patients having other pathologies affecting Retinal Nerve Fiber Layer thickness e.g., trauma, glaucoma, Hypertensive Retinopathy, and retinal dystrophies were excluded. Non-Probability Consecutive Sampling was done.

Every Patient that met the inclusion criteria in the Retina department and OPD of tertiary eye care hospital was taken as a sample. Every Patient got a full anterior and posterior segment examination, after all, preliminary examinations and informed consent, data was collected. Visual acuity was recorded using the ETDRS visual acuity Chart. Optical Coherence Tomography (OCT) was used to measure the thickness of the Retinal Nerve Fibre layer. The study was conducted after approval has been accorded by the hospital’s ethical committee. In descriptive statistics, frequency, the mean, and the standard deviation were utilized. The one-way ANOVA and independent T-test were employed for inferential statistics. To find out the mean difference in thickness and the association in all the cases. Data was collected after informed consent from the patient. Confidentiality was maintained. Ethical guidelines of the hospital were taken into consideration. Approval from IRB was sought before starting this research. The anonymity, autonomy, and privacy of patents were considered.

Results and Discussion

The research involved 196 eyes from 101 patients. The average age of responders was 55.68± 10.437 ranging from 40 to 70 years. Among 101 patients 62.2% (122) were female and 37.8 % (74) were male. 15.3% had diabetes for 1 to 5 years. Diabetes Duration has been classified into four categories which are presented in table 1. 80 eyes were of Healthy Individuals (40.8%), 60 were of NPDR (30.6%), 30 were of Type 2 diabetic (15.3%), 26 eyes were of PDR (13.3%).

To determine the association between Mean Retinal Nerve Fiber Layer Thickness and Diabetic Retinopathy (NPDR, PDR), Type 2 Diabetes, and Healthy Individuals One-Way ANOVA and Independent T-Test were performed. According to Tables 2 and 3, there was a statistically significant difference of $p<0.05$ between all groups.

The Normality of Age groups and duration of diabetes data were examined and found to be not normally distributed. To determine the association between the thickness of retinal nerve fiber duration of diabetes and age The Krushkal-Wallis Test was used, as shown in tables 4 and 5. A statistically significant ($p<0.05$).association was found between them.

Table 1. Frequency Distribution of Duration of Diabetes

Duration Of Diabetes	Frequency
0	80
1-5	30
6-10	47
11-15	39
Total	196

Table 2: Comparison of type of Diabetic retinopathy, Type 2 Diabetes and Healthy individuals with Mean RNFL thickness in all quadrants

Groups	N	Mean and S.D	p- values
NPDR mean RNFL Thickness	60	106.7±11.71	<.001
Type 2 Diabetes mean RNFL Thickness	30	93.43±3.61	<.001
PDR MEAN RNFLT Thickness	26	131.58±16.24	<.001
Healthy Mean RNFL Thickness	80	101.18±8.17	<.001

*n represents Patient Count, S.D. Standard Deviation, RNFL Retinal Nerve Fibre Layer Thickness, NPDR Non-Proliferative Diabetic Retinopathy, PDR Proliferative Diabetic Retinopathy

Table 3: One-way ANOVA Showing Comparison of RNFL Thickness among Healthy Individuals Type 2 Diabetics, PDR, and NPDR

		Mean diff.	*p*
NPDR Mean RNFL thickness	Type 2 Mean RNFL thickness	13.27	<.001
NPDR Mean RNFL thickness	PDR Mean RNFL thickness	-24.88	<.001
NPDR Mean RNFL thickness	Healthy Mean RNFL thickness	5.53	.012
Type 2 Mean RNFL thickness	PDR Mean RNFL thickness	-38.14	<.001
Type 2 Mean RNFL thickness	Healthy Mean RNFL thickness	-7.74	.003
PDR Mean RNFL thickness	Healthy Mean RNFL thickness	30.4	<.001

*n presents Number of Patients, NPDR Non-Proliferative Diabetic Retinopathy S.D Standard Deviation, RNFL Retinal Nerve Fiber Layer Thickness PDR Proliferative Diabetic Retinopathy, Type 2 Diabetes

Table 4: Comparison of Age Groups with Mean RNFL Thickness

Groups	N	**MEAN Ranks**	***p*-value**
40-50	63	93.9	<.001
61-70	70	72.25	
51-60	62	131.23	

Table 5: Comparison of Diabetes Duration with Mean RNFL Thickness Groups with Mean RNFL Thickness

Groups	N	**MEAN Ranks**	***p*-value**
0	80	85.83	<.001
6-10	46	106.24	
11-15	39	156.47	
1-5	30	41.82	

The most common complication of Diabetes Mellitus is diabetic retinopathy. And one of the foremost causes of visual impairment. Type 2 diabetics can prevent diabetic retinopathy by adhering to a healthy diet and an inactive lifestyle. This study concluded that RNFL thickness is significantly decreased (p<0.001) in all diabetic groups as compared to healthy individuals. The findings are congruent with those of Chen *et al.*, (2015), who found that RNFL thickness decreased in preclinical diabetic retinopathy (p=0.0003). Jia *et al*., 2020, revealed that patients without diabetic retinopathy had a lower RNFL thickness (p 0.0001), which is comparable to the findings.

The present study findings are in agreement with Mehboob Muhammad Afef *et al* 2019 which shows that RNFL thickness is significant in all quadrants between normal individuals and the diabetic population with Diabetic retinopathy. A previous study by De Faria, Russ & Costa, 2002 also concluded that thickness of RNFL is decreased in Type-1 Diabetics without retinopathy (p<0.0007) which are consistent with the study. A study by Dhasmana, Sah & Gupta, 2016 showed that reduced RNFL thickness was most prominently observed in superior, temporal, and nasal quadrants (p<0.001) which are parallel to the research. Ng *et al.,* 2016 in their research also displayed comparable results to the study in which thinness of the retinal fiber layer is noted in all quadrants.

A study by Araszkiewicz *et al*., in 2012 also showed a significant difference in all quadrants of in diabetic patients (p=0.002) which are similar to the study. In 2021, Ezhilvendhan *et al.,* (2021) discovered that in the diabetic population, the RNFL is significantly thinner than in the Normal group. Comparable results were shown by Sohn *et al.,* in 2015 according to the study in which thickness is reduced in diabetics but without DR as compared to control groups.

Karti *et al.,* 2017 in their study concluded that children with type 1 diabetes and no retinopathy experience loss of the retinal fiber layer, showing that neurodegeneration may occur without retinopathy. Lee *et al.* demonstrated in 2021 that the thickness of peripapillary retinal nerve fibers is reduced in diabetics, with comparable findings.

In 2017, Srinivasan *et al*., found that the nerve fiber layer thickness of the ganglion cell layer and did not differ substantially between diabetics with and without Diabetic Retinopathy and normal persons which shows contradicting results to the study.

Similarly, a 2017 study by Pekel *et al.,* demonstrated no statistically significant difference (p=0.32) in the thickness of RNFL between diabetic population without neuronal degeneration and the healthy population. They also demonstrated that binocular RNFL thickness asymmetry was more pronounced, and neuronal degenerations occur in diabetics without retinopathy. Researchers Marques *et al.* discovered no difference in RNFL reduction in thickness.

In the study the results are also in contrast with Dhasmana, Sah & Gupta, in 2016. They investigated that loss of RNFL occurs only in temporal and nasal areas with type-2 diabetic patients but without a further progression of retinopathy research explored found overall thinning of the nerve Fibre layer

Dhasmana, Sah & Gupta, (2016) also showed thinning was noted only in the superior region in type 1 Diabetics.

In their investigation of retinal and corneal degenerations in the early phases of diabetes, Srinivasan *et al.,* 2017 observed no statistically significant difference between diabetics and non-diabetics for RNFL.

Lim et al also showed similar results but in type 2 diabetics that RNFl thickness is decreased in all quadrants with and without retinopathy. However, which shows comparable results to the study. It is also compared to the age and duration of Diabetic with thickness of Retinal nerve Fibre layer (p=0.000) and found a significant association but the study Afef, Mehboob *et al*., and Sohn *et al*., stated no significant relationship of age (p= 0.623) which are independent of effect RNFL thickness with increasing age.

Srinivasan *et al.,* 2017 also found an association of age with mean retinal nerve fiber thickness (p=0.343), which contradicts to the study's results. Afef *et al* showed that there was an inverse relation with diabetes duration as ad retinopathy progresses further there is a loss of RNFL thickness.

As Diabetic Retinopathy is followed by changes in retina vasculature it results in endothelial and pericytes loss which ultimately leads to micro aneurysms, hemorrhages, and neovascularization and neurodegeneration are considered a key factor in the early stages of Diabetic retinopathy. As the duration of Diabetes increases it also causes changes in the nerve fiber layer. (Gardner *et al*., 2002).

Conclusion:

This study concluded that RNFL thickness decreases in diabetes mellitus patients, lesser than in healthy individuals, showing it as an early marker of diseases. This study also shows the association of RNFL thickness with age, with increasing age thickness decreases. With increased diabetes duration thickness decreases.

Conflict of Interests

The authors declare that they have no conflict of interests.

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References

Afef, M., Asma, K., Chaker, B., Faida, A., & Riadh, R. (2019). Retinal fiber layer and macular ganglion cell layer thickness in diabetic patients. *J Clin Exp Ophthalmol*, *10*(785), 2.

Araszkiewicz, A., Zozulinska-Ziolkiewicz, D., Meller, M., Bernardczyk-Meller, J., Pilacinski, S., Rogowicz-Frontczak, A., ... & Wierusz-Wysocka, B. (2012). Neurodegeneration of the retina in type 1 diabetic patients. *Pol Arch Med Wewn*, *122*(10), 464-470.

Barber, A. J., Lieth, E., Khin, S. A., Antonetti, D. A., Buchanan, A. G., & Gardner, T. W. (1998). Neural apoptosis in the retina during experimental and human diabetes. Early onset and effect of insulin. *The Journal of clinical investigation*, *102*(4), 783-791.

Chen, X., Nie, C., Gong, Y., Zhang, Y., Jin, X., Wei, S., & Zhang, M. (2015). Peripapillary retinal nerve fiber layer changes in preclinical diabetic retinopathy: a meta-analysis. *PloS one*, *10*(5), e0125919. https://doi.org/10.1371/journal.pone.0125919

De Faria, J. L., Russ, H., & Costa, V. P. (2002). Retinal nerve fibre layer loss in patients with type 1 diabetes mellitus without retinopathy. *British Journal of Ophthalmology*, *86*(7), 725-728. http://dx.doi.org/10.1136/bjo.86.7.725

Dhasmana, R., Sah, S., & Gupta, N. (2016). Study of retinal nerve fibre layer thickness in patients with diabetes mellitus using fourier domain optical coherence tomography. *Journal of clinical and diagnostic research: JCDR*, *10*(7), NC05. https://doi/10.7860/JCDR/2016/19097.8107

Ezhilvendhan, K., Shenoy, A., Rajeshkannan, R., Balachandrachari, S., & Sathiyamoorthy, A. (2021). Evaluation of macular thickness, retinal nerve fiber layer and ganglion cell layer thickness in patients among type 2 diabetes mellitus using optical coherence tomography. *Journal of Pharmacy & Bioallied Sciences*, *13*(Suppl 2), S1055. https://doi/10.4103/jpbs.jpbs_165_21

Gardner, T. W., Antonetti, D. A., Barber, A. J., LaNoue, K. F., Levison, S. W., & Penn State Retina Research Group. (2002). Diabetic retinopathy: more than meets the eye. *Survey of ophthalmology*, *47*, S253-S262. https://doi.org/10.1016/S0039-6257(02)00387-9

Goebel, W., & Kretzchmar-Gross, T. (2002). Retinal thickness in diabetic retinopathy: a study using optical coherence tomography (OCT). *Retina*, *22*(6), 759-767.

Jia X., Zhong, Z., Bao, T., Wang, S., Jiang, T., Zhang, Y., ... & Zhu, X. (2020). Evaluation of early retinal nerve injury in type 2 diabetes patients without diabetic retinopathy. *Frontiers in Endocrinology*, *11*, 475672. https://doi.org/10.3389/fendo.2020.475672

Karti, O., Nalbantoglu, O., Abali, S., Ayhan, Z., Tunc, S., Kusbeci, T., & Ozkan, B. (2017). Retinal ganglion cell loss in children with type 1 diabetes mellitus without diabetic retinopathy. *Ophthalmic Surgery, Lasers and Imaging Retina*, *48*(6), 473-477. https://doi.org/10.3928/23258160-20170601-05

Lee, M. W., Lee, W. H., Ryu, C. K., Lee, Y. M., Lee, Y. H., & Kim, J. Y. (2021). Peripapillary retinal nerve fiber layer and microvasculature in prolonged type 2 diabetes patients without clinical diabetic retinopathy. *Investigative Ophthalmology & Visual Science*, *62*(2), 9-9. https://doi.org/10.1167/iovs.62.2.9

Lim, H. B., Shin, Y. I., Lee, M. W., Park, G. S., & Kim, J. Y. (2019). Longitudinal changes in the peripapillary retinal nerve fiber layer thickness of patients with type 2 diabetes. JAMA ophthalmology, 137(10), 1125-1132.

Marques, I. P., Alves, D., Santos, T., Mendes, L., Santos, A. R., Lobo, C., ... & Cunha-Vaz, J. (2019). Multimodal imaging of the initial stages of diabetic retinopathy: different disease pathways in different patients. *Diabetes*, *68*(3), 648-653. https://doi.org/10.2337/db18-1077

Mehboob, M. A., Amin, Z. A., & Islam, Q. U. (2019). Comparison of retinal nerve fiber layer thickness between normal population and patients with diabetes mellitus using optical coherence tomography. *Pakistan journal of medical sciences*, *35*(1), 29. https://doi/10.12669/pjms.35.1.65

Meo, S. A., Zia, I., Bukhari, I. A., & Arain, S. A. (2016). Type 2 diabetes mellitus in Pakistan: Current prevalence and future forecast. *JPMA. The Journal of the Pakistan Medical Association*, *66*(12), 1637-1642.

Mumtaz, S. N., Fahim, M. F., Arslan, M., Shaikh, S. A., Kazi, U., & Memon, M. S. (2018). Prevalence of diabetic retinopathy in Pakistan; A systematic review. *Pakistan journal of medical sciences*, *34*(2), 493. https://doi/10.12669/pjms.342.13819

Ng, D. S., Chiang, P. P., Tan, G., Cheung, C. G., Cheng, C. Y., Ngung, C. Y., ... & Ikram, M. K. (2016). Retinal ganglion cell neuronal damage in diabetes and diabetic retinopathy. *Clinical & experimental ophthalmology*, *44*(4), 243-250. https://doi.org/10.1111/ceo.12724

Oshitari, T. (2006). Non-viral gene therapy for diabetic retinopathy. *Drug development research*, *67*(11), 835-841. https://doi.org/10.1002/ddr.20157

Oshitari, T., Hata, N., & Yamamoto, S. (2008). Endoplasmic reticulum stress and diabetic retinopathy. *Vascular Health and Risk Management*, *4*(1), 115-122.

Pekel, E., Tufaner, G., Kaya, H., Kaşıkçı, A., Deda, G., & Pekel, G. (2017). Assessment of optic disc and ganglion cell layer in diabetes mellitus type 2. *Medicine*, *96*(29). https://doi/10.1097/MD.0000000000007556

Ramappa, R., & Thomas, R. K. (2016). Changes of Macular and Retinal Nerve Fiber Layer Thickness Measured by Optical Coherence Tomography in Diabetic Patients with and without Diabetic Retinopathy. *International Journal of Scientific Study*, *3*(12), 27-33.

Sohail, M. (2014). Prevalence of Diabetic Retinopathy among Type? 2 Diabetes Patients in Pakistan? Vision Registry. *Pakistan Journal of Ophthalmology*, *30*(4).

Sohn, E. H., van Dijk, H. W., Jiao, C., Kok, P. H., Jeong, W., Demirkaya, N., ... & Abràmoff, M. D. (2016). Retinal neurodegeneration may precede microvascular changes characteristic of diabetic retinopathy in diabetes mellitus. *Proceedings of the National Academy of Sciences*, *113*(19), E2655-E2664. https://doi.org/10.1073/pnas.1522014113

Srinivasan, S., Dehghani, C., Pritchard, N., Edwards, K., Russell, A. W., Malik, R. A., & Efron, N. (2017). Corneal and retinal neuronal degeneration in early stages of diabetic retinopathy. *Investigative ophthalmology & visual science*, *58*(14), 6365-6373. https://doi.org/10.1167/iovs.17-22736