



Original Research Article

A study to show retinal neurodegeneration association with peripheral nerve conduction in diabetic (Type-II) patients

S P Singh¹, Brijesh Singh Yadav^{1,*}, K J Singh¹, Aparajita Chaudhary¹, Vinod Kumar Singh¹

¹Dept. of Ophthalmology, (RIO, Prayagraj), MLN Medical College, Prayagraj, Uttar Pradesh, India



ARTICLE INFO

Article history:

Received 14-03-2020

Accepted 03-04-2020

Available online 16-06-2020

Keywords:

Diabetic retinopathy

Electrodiagnostic nerve conduction test

GC-IPL thickness

Peripheral neuropathy

ABSTRACT

Objectives: Aim of this study was to show the association between retinal neuro-degeneration with peripheral nerve conduction in diabetic (type-II) patients.

Materials and Methods: A total of 30 diabetic patients age ranging from 35-70 years with mild/moderate non proliferative diabetic retinopathy (NPDR) and 30 non diabetic control were studied at M.D. eye hospital Prayagraj R.I.O., Prayagraj. Spectral-Domain -OCT imaging was performed with the cirrus HD-OCT (Version 6.5.0.772; Carl Zeiss Meditec, Inc.), along with nerve conduction study test.

Results: Mean ganglion cell inner Plexiform thickness was assessed in diabetic patients with neuropathy (Group-A) and without neuropathy (Group-B) in eyes. The difference between mean thickness of these two groups was found to be significant at same level of significance and confidence interval ($t=4.61$, $p=0.014$). Both the significant difference indicate that diabetic patients with neuropathy (Group A), were associated with lower mean of “ganglion cell–inner Plexiform thickness” in both the eyes as compared to without neuropathy patients (Group B).

Conclusion: In this study we found a positive correlation between decrease in Ganglion cell-inner plexiform layer (GC-IPL) thickness and decrease peripheral nerve conduction in diabetic patients. Decrease in Ganglion cell-inner plexiform layer (GC -IPL) is predictive of early retinal neurodegeneration in diabetic patients, according to our study.

© 2020 Published by Innovative Publication. This is an open access article under the CC BY-NC license (<https://creativecommons.org/licenses/by-nc/4.0/>)

1. Introduction

Diabetic retinopathy is a chronic progressive disorder predominantly affecting the microscopic vessels of the retina.¹ The neuroretinal ganglion cell involvement occur before microvascular changes starts, which leads to thinning of GC-IPL and detected on OCT. Thinning of GC-IPL is an early sign of diabetic neurodegeneration and requires careful clinical evaluation.² Retinal neurodegeneration is described as a consequence of neural apoptosis, reactive gliosis, glutamate excitotoxicity, decrease in neuroprotective factors and impairment of the neurovascular coupling.³

Diabetic peripheral neuropathy (DPN) cannot be diagnosed alone by clinical tests and it is difficult to detect mild neuropathy in early DPN patients. For diagnosis, a combination of clinical symptoms, physical examination and electrodiagnostic findings are used. Electrodiagnostic tests include a NCS, which is very informative and specific. For assessing peripheral neuropathy, nerve conduction study test of peroneal motor nerve, posterior tibial motor nerve (conduction velocity, terminal latency) are used.²

DR is one of the three major microvascular complications of diabetes along with neuropathy and nephropathy. These are caused by microvascular disturbances and arise sequentially: First neuropathy occurs, followed by retinopathy and nephropathy respectively. Diabetic peripheral neuropathy has been observed in patients with impaired glucose tolerance test.⁴

* Corresponding author.

E-mail address: dr.brijmln@gmail.com (B. S. Yadav).

Moreover, neuronal damage in the distal segment of the peripheral nerves is associated with objective measurements of neuropathy, such as nerve conduction velocity (NCV). The normal range of terminal latency is 3.2 to 4.5 ms in both the peroneal motor and posterior tibial motor nerve.² The normal ranges of conduction velocity in the peroneal motor, the posterior tibial motor, and the sural sensory nerve are 43–62 m/s, 41–61 m/s and 34–49 m/s, respectively. The normal range of F-wave latency is 44.7 ± 4.7 ms in the peroneal motor and 44.9 ± 6.2 ms in the posterior tibial motor nerve. In diabetics, retinal neuroglial dysfunction occurs before ophthalmoscopically visible signs of retinopathy (i.e., vascular changes) are seen. This raises the possibility that NCV may be a biomarker of diabetes progression, including ocular complications, in the earlier stages.⁴

Aim of this study was to show the association between retinal neuro-degeneration with peripheral nerve conduction in diabetic (type-II) patients. In this study, we study the association between various parameters, including NCV, ophthalmoscope findings and measurement of retinal structure, in type 2 diabetics with early DR, in order to search for novel biomarkers of DR.

2. Material and Methods

This study was carried out during December 2018 to November 2019. Patients were enrolled at M.D. eye Hospital, Regional Institute of Ophthalmology Prayagraj. The study was conducted in accordance with the ethical standards which were approved by institutional ethics review board with informed consent obtained from all participants.

It is a cross sectional study. A total number of 30 diabetic patients and 30 non diabetic controls were enrolled consecutively. The patients were evaluated for mean retinal thickness (μm) of the parafoveal area within diameters 1-3 mm, GC- IPL thickness and nerve conduction study of DPN, CPN was analysed.

2.1. Investigations

All patients underwent general and ophthalmic evaluation which includes:

1. General Examination and required Investigations.
2. Visual acuity unaided.
3. Direct ophthalmoscopy, Indirect ophthalmoscopy for evaluation of fundus.
4. OCT for evaluation of central macular thickness.
5. Nerve conduction study.

2.2. The inclusion criteria

1. Known diabetics, age ranging from 35 to 70 years.

2. No sign of diabetic retinopathy or mild/moderate NPDR.

2.3. The exclusion criteria

1. Duration of diabetes >10 years.
2. Diagnosis of any peripheral neurologic disease except diabetes- related neuropathy, medication for peripheral neuropathy prior to the nerve conduction test.
3. Cardiovascular disease.
4. Clinically significant macular edema.
5. Previous diagnosis of glaucoma.
6. Ocular hypertension, uveitis other retinal disease, any history of retinal treatment.
7. Diagnosed case of moderate/severe or PDR.

Additionally, 35 -75 age matched patients were taken as control group without diabetes for comparison of ganglion cell –inner plexiform layer thickness.

Investigations like routine blood Investigation, urine examination, Fasting plasma glucose and 2hr post prandial glucose, lipid profile and HbA1c was advised and undertaken. Visual acuity was done by Snellen's chart. A detailed fundus examination was done by indirect ophthalmoscopy. NPDR and PDR were diagnosed by the presence of fundus findings.

Spectral-Domain -OCT imaging was performed with the cirrus HD-OCT (Software version 6.5.0.772; Carl Zeiss Meditec; Inc.) We analyzed the mean retinal thickness (μm) of the parafoveal area within diameters 1–3 mm and the GC-IPL thickness in 6 macular regions was analyzed using Cirrus HD-OCT (Carl Zeiss Meditec). A color-coded macular thickness map, i.e., the macular cube (512×128 scan) was obtained with Cirrus HD OCT. The diameters of the circular areas were 1, 3 and 6 mm. The built-in algorithms of the Cirrus HD-OCT software (version 6.5.0.772) are capable of automatically identifying the outer boundary of the macular RNFL and the outer boundary of the IPL. The difference between the RNFL and the IPL outer boundary segmentation yields the GC-IPL thickness.

The average, minimum, and 6-sectoral (superior temporal, superior, superior nasal, inferior nasal, inferior, and inferior temporal) GC-IPL thicknesses are measured in an elliptical annulus with a vertical outer diameter of 4.0 mm and horizontal diameter of 4.8 mm. In this study, the average CC-IPL thickness of 6 sectors was used for statistical analysis. Nerve conduction studies are used mainly for evaluation of paraesthesia (numbness, tingling, burning) and/or weakness of the arms and legs. The nerve conduction study consists of the following components

Motor NCS are performed by electrical stimulation of a peripheral nerve and recording from a muscle supplied by this nerve. The time it takes for the electrical impulse to travel from the stimulation to the recording site is measured. This value is called the latency and is measured

in milliseconds (ms). The size of the response – called the amplitude – is also measured. Motor amplitudes are measured in millivolts. By stimulating in two or more different locations along the same nerve, the NCV across different segments can be determined. Calculations are performed using the distance between the different stimulating electrodes and the difference in latencies. In general, different pathological processes result in changes in latencies, motor, and/or sensory amplitudes, or slowing of the conduction velocities to differing degrees.

3. Results

A cross sectional control study with 30 cases (60 eyes) and 30 controls (60 eyes) was done to study the GC-IPL thickness imaging by Cirrus HD OCT in diabetic patients, neuropathy by nerve conduction study test.

Relationships are considered significant if p value < 0.05 . The intergroup differences are analysed by the chi-square test statistics. The differences between groups are defined by z -test.

Table 1: Distribution of patients according to sex group

| Gender | Number | Percentage |
|--------|--------|------------|
| Male | 17 | 56.66% |
| Female | 13 | 43.33% |

Table 2: Distribution of patients in relation to retinopathy and neuropathy

| Diabetic patient | Number | Percentage |
|---------------------|--------|------------|
| Without retinopathy | 17 | 56.66% |
| With retinopathy | 13 | 43.33% |
| With no neuropathy | 9 | 30% |
| With neuropathy | 21 | 70% |

6 shows difference of mean “ganglion cell –inner Plexiform thickness” in diabetic patients with neuropathy (Group-A) and without neuropathy (Group-B) in both, left and right eyes. In right eye, mean Ganglion cell thickness was 67.44 ± 8.64 SD in Group A which was comparatively lower i.e. 82.2 ± 8.64 SD than Group B patients. This difference in mean was found to be statistically significant at 5% level of significance and 95% confidence interval ($t=3.28$, $p=0.0027$).

Similarly, in left eye mean “ganglion cell inner plexiform thickness” was 69.71 ± 11.56 SD in Group A and $81.78 \pm$ SD in Group B patients. The difference between means thickness of these two groups was found to be significant at same level of significance and confidence interval ($t=4.61$, $p=0.014$).

Both the significant difference indicate that diabetic patients with neuropathy (Group A), were associated with lower mean of “ganglion cell–inner Plexiform thickness” in both the eyes as compared to without neuropathy patients

(Group B).

4. Discussion

50% diabetic patients develop diabetic polyneuropathy (DPN) but only about 20% develop clinical features of neuropathy at the time of diabetes diagnosis, since it is often under diagnosed owing to adverse and vague symptoms. OCT finding of thinner ganglion cell-inner plexiform layer can be an early signs of diabetic neurodegeneration and requires careful clinical evaluation regarding diabetic neuropathy.⁵

Total 30 diabetic patients were studied between 35-75 years age group. Maximum 33% patients came in 35-45 years age group. The mean age in our study is 51.59 ± 11 years, which is slightly less that quoted by Jin A Choi et al.⁶ to be 55.7 years. Eduardo Buchele Rodrigues et al.^{3,7} studied that diabetic induced changes in neuroretina before retina vessels on 102 patients and mean age was found to be $58.67 (\pm 10.7)$ which is slightly higher than our study. Jay Chhablani et al.⁸ found mean age 57.5 years. P. Carpineto et al.⁹ 60.9 ± 8.3 years. Kiyoungkim et al.⁵ 63.61 ± 12.52 years.

In present study we found that mean average GC-IPL thickness of diabetic in right eye is 72.46 ± 10.43 , in left eye 73.36 ± 12.86 thinner than healthy controls mean average GC-IPL thickness in right eye is 82.73 ± 5.6 , in left eye 82.66 ± 5.9 . Higher proportion (56%) of cases with decreased GC-IPL thickness if found in right eyes as well as left eye (56.66%) in comparison to controls of both eyes (13.33% for both eyes) and this is found to be statistically significant ($p=0.00044$ and $p=0.00044$ respectively) at 5% level of significance and 95% confidence interval.

Jay Chhablani et al.⁸ conducted retrospective study on 62 subjects with diabetes. In this study average GC-IPL thickness and minimum GC-IPL thickness were significantly lower in diabetics than non-diabetic healthy control group (p value < 0.05). P Carpineto et al.⁹ in their study found that mean average GC-IPL thickness was $80 \pm 8.1 \mu\text{m}$ and $85 \pm 9.9 \mu\text{m}$ in diabetic patients and controls, respectively ($p=0.001$). Dorothy et al.¹⁰ conducted observational case-control study. In this study mean average GC-IPL thickness was 4.49 thinner (95% CI: 2.92 to 6.06) in diabetic then healthy controls.

In our study we found that in right eye mean GC-IPL (Ganglion cell-inner plexiform layer) thickness was 67.44 ± 8.64 SD with neuropathy which was comparatively lower i.e. 82.2 ± 8.64 SD without neuropathy patients. This difference in mean was found to be statistically highly significant at 5% level of significance and 95% confidence interval ($t=3.28$, $p=0.0027$). Similarly, in left eye mean GC-IPL (ganglion cell inner plexiform layer) thickness was 69.71 ± 11.56 SD in neuropathy patients and $81.78 \pm$ SD in without neuropathy patients. The difference between means thickness of these two groups was found to be significant

Table 3: Association of abnormal Ganglion cell-inner plexiform layer thickness and diabetes with neuropathy among cases

| Cases with Abnormal GC-IPL thickness | Diabetes with Neuropathy, no. & % | Diabetes without Neuropathy, no. & % | X2 P-value |
|--------------------------------------|-----------------------------------|--------------------------------------|-----------------------|
| Right eye | 15(71.42) | 2(22.22) | X2 =4.370 P =0.0366 |
| Left eye | 16(76.19) | 1(11.11) | X2 = 8.378 P = 0.0038 |

Table 4: Comparison of cases and controls with abnormal GC-IPL thickness

| Laterality | Cases with Abnormal average GC-IPL thickness, no & % | Control with Abnormal average GC-IPL thickness, no & % | Z & P values |
|------------|--|--|------------------------|
| Right eye | 17(56.66) | 4(13.33) | Z = 3.5187 P = 0.00044 |
| Left eye | 17(56.66) | 4(13.33) | Z = 3.5187 P = 0.00044 |

Table 5: Association of abnormal G.C. thickness and with neuropathy among controls

| Control with Abnormal GC-IPL thickness | Control with neuropathy no. & % | Control without neuropathy no. & % | X2, P value |
|--|---------------------------------|------------------------------------|-----------------------|
| Right eye | 1(20) | 3(12) | X2 = 0.231 P = 0.6310 |
| Left eye | 2(28.57) | 2(8.69) | X2 = 0.518 P = 0.4718 |

Table 6: Association of average Ganglion cell -inner plexiform thickness to peripheral neuropathy in diabetic patients

| Diabetic patients | Right eye Mean average ganglion cell- inner plexiform thickness | Left eye Mean average ganglion cell- innerplexiform thickness |
|-----------------------------|---|---|
| Group A(with neuropathy) | 69.7 ± 4.34 | 69.7 ± 11.56 |
| Group B(without neuropathy) | 82.2 ± 8.64 | 81.78 ± 11.64 |
| Unpaired t test | t = 3.28 p = 0.0027 | t = 4.16 p = 0.014 |

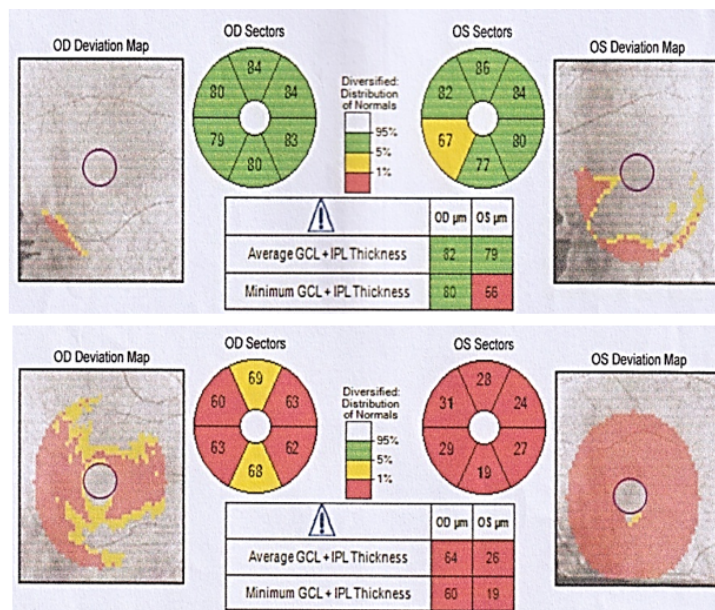


Fig. 1:

at same level of significance and confidence interval ($t=4.61$, $p=0.014$).

Kiyoung Kim, Seung-Young Yu et al.² evaluated GC-IPL (ganglion cell inner plexiform layer) in diabetic patients with definite neuropathy $75.2\pm 4.2\ \mu\text{m}$ and diabetic patients without neuropathy $82.0\pm 5.8\ \mu\text{m}$. There were significant differences between the no neuropathy vs neuropathy (82.0 ± 5.8 and 75.2 ± 4.2 , p value =0.005).

Kiyoung Kim et al.⁵ conducted retrospective cohort study. They selected 87 patients with type II diabetes. Change in mGCIPL thickness was related to baseline mGCIPL thickness ($r = -0.30$, $p = 0.005$). Study shows those patients who exhibit diabetic retinopathy progression had lower mGC-IPL ($p < 0.001$) thickness higher rate of change of mGC-IPL thickness ($p = 0.041$), and lower conduction velocity of peripheral nerve ($p < 0.001$) compared with those who exhibit no diabetic retinopathy progression

Sangeetha Srinivasan et al.¹¹ Studied association between full retinal thickness of macula with diabetic peripheral neuropathy in 2016, and found that in subjects with diabetic peripheral neuropathy, overall ($p=0.02$) retinal macular thickness significantly reduced. In the macula parafoveal (p value =0.004), superior (p value =0.01), Inferior (p value=0.002) was found significantly thinner in diabetic retinopathy.

A M Shahidi et al.¹² conducted a study on 105 individuals with type 2 diabetes with or without neuropathy. In this study a significant association was found between nerve fibre layer thickness and diabetic neuropathy cases (p value =0.03). In this study diabetic without neuropathy and no diabetic without neuropathy had no significant differences in nerve fibre layer thickness (p value = 0.78) also.

5. Conclusion

Majority of patients (33%) were in the age group of 35-45 years, 30% were of 46-55 years age group, 26.66% were in between 56-65 years and only 10% were more than 66 years. In this study population out of 30 patients, majority 56.66% were male while females were 43.33%. Among 30 patients, 56.66% were without diabetic retinopathy and 43.33% were with diabetic retinopathy. Majority of patients, 70% had neuropathy while only 30% patients were without neuropathy. In this study we found a positive correlation between decrease in Ganglion cell-inner plexiform layer (GC-IPL) thickness and decrease peripheral nerve conduction in diabetic patients. Decrease in Ganglion cell-inner plexiform layer (GC -IPL) is predictive of early retinal neurodegeneration in diabetic patients, according to our study.

Once Diabetic Retinopathy has started, its progression is predictable, leading to visual loss and blindness if undetected and/ or untreated. Thinning of GC-IPL is early sign of diabetic retinal neurodegeneration. Hence by careful clinical evaluation regarding retinopathy and peripheral

nerve symptoms, it can be detected earlier in type-2 diabetic patients and more strict diabetic control is recommended in hope of delaying future retinopathy.

6. Source of Funding

None.

7. Conflict of Interest

None.

References

1. Maurya RP. Diabetic retinopathy: My brief synopsis. *Ind J Clin Exp Ophthalmol.* 2015;1(4):189–190.
2. Kim K, Yu SY, Kwak HW, Kim ES. Retinal Neurodegeneration Associated With Peripheral Nerve Conduction and Autonomic Nerve Function in Diabetic Patients. *Am J Ophthalmol.* 2016;170:15–24.
3. Jonsson KB, Frydkjaer-Olsen U, Grauslund J. Vascular Changes and Neurodegeneration in the Early Stages of Diabetic Retinopathy: Which Comes First? *Ophthalm Res.* 2016;56(1):1–9.
4. Ito A, Kunikata H, Yasuda M, Sawada S, Kondo K, Satake C, et al. Hideki Katagiri, and Toru Nakazawa “the relationship between peripheral nerve conduction velocity and ophthalmological findings in type 2 diabetes patients with early diabetic retinopathy. *J Ophthalmol.* 2018;p. 2439691–2439691.
5. Kim K, Kim ES, Yu SY. Longitudinal Relationship Between Retinal Diabetic Neurodegeneration and Progression of Diabetic Retinopathy in Patients With Type 2 Diabetes. *Am J Ophthalmol.* 2018;196:165–72.
6. Choi JA, Kim HW, Kwon JW, Shim YS, Jee DH, Yun JS, et al. Seung - Hyun Ko “ Early inner retinal thinning and cardiovascular autonomic dysfunction in type 2 diabetes. *PLoS ONE*;12(3):174377.
7. Rodrigues EB, Urias FMMG, Penha E, Badaro. Eduardo Novais, Rodrigo Meirelles and Michel Eid Farah “Diabetes induces changes in neuroretina before retinal vessels : a spectral- domain optical coherence tomography study. *Int J Retina Vitreous.* 2015;doi:10.1186/s40942-015-0001-z.
8. Chhablani J, Sharma A, Goud A, Peguda HK, Rao HL. Viqar Unnisa Begum and Giulio Bartselli “ Neurodegeneration in Type 2 Diabetes :Evidence from spectral- domain optical coherence tomography. *Invest Ophthalmol Vis Sci.* 2015;56:6333–8.
9. Carpineto P, Toto, Aloia, Ciciarelli, Borrelli E, Vitacolonna D, et al. Neuroretinal alterations in the early stages of diabetic retinopathy in patients with type 2 diabetes mellitus. *Eye.* 2016;30(5):673–9.
10. Boptom DSN, Chiang PP, Tan G, Cheung CG, Cheng C–Y, Cheung CY, et al. Ecosse L Lamoureux Msc PhD and Mohammad K Ikram MD PhD “Retinal ganglion cell neuronal damage in diabetes and diabetic retinopathy. *Clin Exp Ophthalmol.* 2016;44:243–50.
11. Srinivasan S, Pritchard N, Vagenas D, Edwards K, Sampson GP, Russell AW, et al. Retinal tissue thickness is reduced in Diabetic peripheral neuropathy. *Curr Eye Res.* 2016;41(10):1359–66.
12. Shahidi AM, Sampson GP, Pritchard N, Edwards K, Vagenas D, Russell AW, et al. Retinal nerve fibre layer thinning associated with diabetic peripheral neuropathy. *Diabet Med.* 2012;29:106–11.

Author biography

S P Singh Professor

Brijesh Singh Yadav Junior Resident

K J Singh Professor and HOD

Aparajita Chaudhary Professor

Vinod Kumar Singh Lecturer

Cite this article: Singh SP, Yadav BS, Singh KJ, Chaudhary A, Singh VK. A study to show retinal neurodegeneration association with peripheral nerve conduction in diabetic (Type-II) patients. *Indian J Clin Exp Ophthalmol* 2020;6(2):159-164.