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Cross sectional case control study to establish the thickness of ganglion cell-inner plexiform (GC-IPL) layer thickness in type 2 diabetis (Type 2 DM) patients with diabetic retinopathy (DR) and compare with normal

Gopal S. Pillai[1], Manoj Prathapan[2,*]

[1]Associate Professor, [2]Assistant Professor, Dept. of Ophthalmology, Amrita School of Medicine, Amrita University, Ernakulam, Kerala

***Corresponding Author:**
Email: dr.manojprathapan@gmail.com

Abstract

Aim: Primary Objective: To evaluate the macular GC-IPL layer thickness in Type 2 DM patients with diabetic retinopathy(DR) and compare its thickness with normal eyes.

Secondary Objective: To identify any possible relationship between the GC-IPL thickness and grade of DR, duration of detected DM, age and gender of the patient.

Materials and Methods: Patients were recruited from the outpatient clinic of the Department of Ophthalmology at Amrita Institute of Medical Sciences, Kochi, Kerala, India

Inclusion criteria

1. Type 2 Diabetes with Mild Non Proliferative Diabetic Retinopathy (Mild NPDR) and Early Proliferative Diabetic Retinopath (Early PDR) without traction or vitreous hemorrhage (ETDRS classification)
2. Early proliferative diabetic retinopathy(PDR) was defined as presence of either neovascularisation of disc /elsewhere or preretinal hemorrhages or both (ETDRS)
3. Controls: Age-gender matched subjects free of ocular disease, diabetes, hypertension or other systemic diseases were recruited as controls from those who accompanied patients visiting the out patient clinic Statistically significant reduction of thickness of GC-IPL layer thickness between patients mild DR when compared to age matched controls (p=0.006).

Results

1. Statistically significant reduction of GC-IPL thickness was seen in early PDR compared to controls (p<0.001).
2. GC-IPL layer were thinner in patients with mild NPDR when compared to age matched controls.
3. Difference in thickness between GC-IPL thickness between mild NPDR and early PDR was not statistically significant.
4. There was no relationship between GC-IPL thickness and duration of detected DM, age and gender of the patient.

Conclusion

1. There was a statistically significant reduction of thickness of GC-IPL layer thickness between mild NPDR and Early PDR when compared to age matched controls. There was no significant difference between GC- IPL thickness between mild NPDR and early PDR.
2. These results support the concept that diabetes has an early neurodegenerative effect on the retina which occurs even before the vascular component of DR occurs.
3. This reduction of GC-IPL thickness changes do not cause vision loss, but only supports neurodegenerative theory.

Introduction

Its well recognized that DR is one of the leading cause for blindness. The two main theories accepted as the pathogenesis of DR are the micro-vascular theory and the neurodegenerative theory. Micro-vascular theory explains the clinically visible changes of DR like micro-aneurysms, capillary non-perfusion (CNP), hemorrhages, and hard exudates.[1-3] Many previous studies have shown reduction in thickness of ganglion cell complex early grade of DR. This neurodegenerative event usually remains unremarkable as patient remains to have good visual acuity, though detailed functional studies have shown reduced contrast dark adaptation and defective color vision in addition to electroretinogram(ERG) changes.

The neurodegenerative theory has been less extensively studied. Effort needs to be put to find out if early in the course of diabetes mellitus(DM), apoptosis of several neuronal cells including ganglion, amacrine, horizontal, Müller, and photoreceptor cells, happen side by or prior to the microvascular mechanism that's seen in DR. Recently it is found that these neurodegenerative changes result in macular thinning and which precede the onset of micro-vascular changes in DR.[8]

Optical Coherence Tomography (OCT) is a non-invasive diagnostic tool that works on principle of low coherence interferometry. Near infrared light creates an in vivo cross sectional view of the retina that is accurate to within at least 3 to 6 microns. There are 6 separate layers identifiable on OCT of the retina. Of these the layer of importance in this article is the GC-IPL layer. The technology of OCT has evolved greatly over time and now the time domain OCT is not used anymore. Spectral domain(SD-OCT) and swept source OCT are the once in clinical use now.

SD-OCT has better resolution and is more user friendly as image acquisition takes lesser time. 30-35% of retinal thickness in the macula region is contributed by ganglion cell complex. Reduction in the thickness of GC-IPL in known to occur in DM patients.

Approximately 50% of retinal ganglion cells are found in the macular region.

Hyperglycenia can induce damage to the neuroglial part of the retina. The other structures affected are the pericytes and retinal endothelial cells.

Ganglion cell apoptosis occurs in Type 2 DM patients. As Ganglion cells are predominantly see in macular area, its easier to identify reduction in ganglion cell layer in this part of the retina.

This reduction can be established by either looking at the full thickness of macula or by looking at GC-IPL comple thickness.

Ganglion cell layer alone cannot be differentiated by OCT. GC-IPL complex is seen and identified as a singles seperate layer and the thickness of this can be used as a substitute of ganglion cell layer thickness. Decrease in GCC(GCL+IPL) is not specific for DR. It is established to be decreased in Glaucoma and other causes of Optic atrophy. GCC thinning along with peripapilary RNFL thinning of superior and inferior quadrants are seen in glaucoma and GCC thinning along with peripapillary temporal or diffuse RNFL thinning is seen in Optic atrophy.

Reduced retinal thickness has been noticed in Type 1 Diabetic patients with mild DR and early proliferative diabetic retinopathy (PDR) compared to normal controls.[8] The purpose of the present study is to determine whether Type 2 DM like Type1 DM, also causes thinning of GC-IPL layer.

Eduardo et al has already demonstrated a reduction in thickness of GC-IPL layer in diabetics. Interestingly they also were able to find that reduction of GC-IPL not only occurs in mild DR patients but also in diabetic patients who don't have clinically detectable DR. I addition to reduction in GC-IPL thickness they also found there was a reduction of RNFL thickness associated in mild DR group when compared to age matched controls.[9] In our study also, we are also trying to find out what happens to the GCL-IPL thickness in mild NPDR and Early PDR when compared to age matched controls.

Materials and Methods

Patients were recruited from the outpatient clinic of the Department of Ophthalmology at Amrita Institute of Medical Sciences, Kochi, Kerala, India

Inclusion criteria

1. Type 2 Diabetes with Mild Non Proliferative Diabetic Retinopathy (Mild NPDR) and Early Proliferative Diabetic Retinopath (Early PDR) without traction or vitreous hemorrhage (ETDRS classification)
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3. Controls: Age-gender matched subjects free of ocular disease, diabetes, hypertension or other systemic diseases were recruited as controls from those who accompanied patients visiting the out patient clinic

Exclusion criteria

1. Refractive error of more than -8.00 DS and +5.00 DS in at least one eye.
2. Cataract patients were not included if OCT scan did not achieve signal strength 8 or more.
3. Patients who had macular edema were not included in study as this could lead to abnormal GC-IPL thickness.
4. Patients with other ocular condition like glaucoma or other causes of optic atrophy were again not included.
5. We excluded any patient who has undergone a previous intra ocular procedure like cataract surgery or intravitreal injections.

All included patients underwent thorough slit lamp stereo bio-microscopy, indirect fundoscopy and fundus fluorescein angiography and OCT (Cirrus Spectral domain OCT).

Duration of diabetes, Age and gender of the patient were noted on a questionnaire given to the patients at time of examination.

Spectral Domain OCT was used to get macular scan for GCC analysis which provided average GC-IPL thickness.

Statistical Analysis: Statistical analysis was performed. Mean age between diabetic patients with mild DR and early PDR and controls were done using Analysis of variance (ANOVA).

Grade of DR was compared to duration of Type 2 DM.

Average GCC-IPL layer thickness mild NPDR and Early PDR were compared to age matched controls.

Relationship between GC-IP layer thickness and the duration of DM, grade of DR, age and gender of patient were done using a multiple linear regression model.

Results

60 eyes of 30 patients with Type 2 DM were included. 32 eyes from 16 patients had mild DR and 28 eyes from 14 patients had early PDR.

DM duration was longer in patients with early PDR as compared to patients with mild NPDR, which is understood as the longer the duration of Type 2 DM the higher the chance of getting worse grade of DR and vision loss.

30 eyes of 15 individuals were taken as controls

There was no significant difference in age and gender between both patient groups and controls.

Table 1

Parameters	Controls (N=30)	Minimal DR (N=32)	Early PDR (N=28)
Age (yrs)	58+/-12	56+/-9	59+/-6
Gender (M:F)	16:14	19:13	17:11
Duration of DM (yrs)	NA	8+/-7	16+/-8

Statistically significant reduction of thickness of GC-IPL layer thickness between patients mild DR when compared to age matched controls (p=0.006).

Statistically significant reduction of GC-IPL thickness was seen in early PDR compared to controls (p<0.001).

GC-IPL layer were thinner in patients with mild NPDR and early PDR when compared to age matched controls.

Difference in thickness between GC-IPL thickness between mild NPDR and early PDR was not statistically significant.

Table 2: Values are the mean +/- standard deviation for all subjects in each group(p=0.006)

Parameters	Controls (N=30)	Minimal DR (N=32)	Early PDR (N=28)
GC-IPL layer thickness (mcm)	75.93+/-10.47	65.57+/-20.34	63.46+/-14.62

There was no significant association between duration of Type 2 DM, grade of DR status, age and gender of the patients.(Table 3) This could be because of inadequate number of participants.

Table 3

Parameters	P Value
Age	0.45
Diabetes Duration	0.47
DR status	0.65

Discussion

In our study we are finding a reduction in thickness of GCL-IPL layer at the macula in both mild NPDR and Early PDR when compared to age matched controls. This is in agreement to previous studies as well.

This reduction of the GC-IPL layer in patients with DR indicates an early neurodegenerative effect on the retina in diabetes, which occurs even though the vascular component of diabetic retinopathy remains minimal. Thus neurodegenerative changes including damage to the ganglion cells precede vascular changes by many years and significant loss of ganglion cells occur by the time mild diabetic retinopathy develops. It is interesting to note that the change in GC- IPL thickness between controls and mild diabetic retinopathy is much more than that between mild NPDR and early PDR. This means that most of the degeneration in neural elements is complete before vascular changes occur in diabetic retinopathy. It also means that, even with neurodegenerative process happening early in diabetics the vision threatening pathopysiological changes happen with vascular changes. Further research needs to be done to see if these neurodegenerative changes are a progressive process that happens in diabetic retinopathy and whether there is association to the level of diabetic control and other systemic factors like hypertension, lipid profile, coronary artery disease or use of systemic medication.

Further research need to be done to find out if there is a cause and effect relation between diabetic papillopathy and these neurodegenerative changes.

Previous studies, using identical methods, have already shown that ganglion cell thickness and RNFL thickness reduction occurs in Type 1 DM patients with mild DR when compared to age matched controls.[8] Our study is on Type 2 DM patients. Though the results are identical the pathogenesis of this thinning may not be similar. Type 1 DM patients have lower plasma insulin concentrations and higher blood glucose concentration from the beginning of the disease. Type 2 DM is characterized by initial hyperinsulinea which occurs as a consequence of insulin resistance. They will have relatively normal blood glucose level in the early stages of disease and as the disease gets more established even the production of insulin comes down due to inadequate secretion of insulin from Beta cells of pancreas. Insulin stimulates neuronal development and maintenance of retinal cells.

There was no significant association between duration of Type 2 DM, grade of DR status, age and gender of the patients. This could be due to inadequate sample size. The exact onset of Type 2 DM is very difficult to find out as blood glucose levels could be relatively normal in these stages as there is a compensatory hyperinsulinemia. This could be a confounding factor when it comes to finding the association between GC-IPL thickness and duration of DM. Also it is yet to find out if it's this hyperinsulinemia or the hyperglycemia that causes the neurodegeneration. But as previous studies have already shown these neurodegeneration in Type 1 DM patients, it would rather be the hyperglycemia that causes these changes.

The present study has some limitations

1. Small sample size
2. Study did not include severe and very severe diabetic retinopathy
3. Presence of undiagnosed diabetes in control subjects were not ruled our biochemically with

biochemical investigations like fasting blood sugars, postprandial blood sugars or HbA1c.

4. The study did not include a group who are diabetic, but without DR changes.
5. Type 2 DM is often sub-clinical. So some of the controls could have been actually having early DM and wrongly grouped in to controls as. The presence of undiagnosed diabetes would most likely lead to underestimation of the difference in retinal layer thickness between patients and control instead of overestimation.

The findings in this study provide further evidence for a neurodegenerative component in early DR. These findings of structural neuropathy may explain the neuroretinal functional deficits that are known in patients with diabetes who do not have evident vascular abnormality.

In summary, this study provides proof of concept that the inner retinal layers at the macula in type 2 diabetic patients with minimal DR and early PDR are thinner compared to normal controls. These results support the concept that DR includes a neurodegenerative component

Conclusion

There was a statistically significant reduction of thickness of GC-IPL layer thickness between mild NPDR and Early PDR when compared to age matched controls.

There was no significant difference between GC-IPL thickness between mild NPDR and early PDR.

These results support the concept that diabetes has an early neurodegenerative effect on the retina which occurs even before the vascular component of DR occurs.

These reduction of GC-IPL thickness changes do not cause vision loss, but only supports neurodegenerative theory.

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