

EVALUATION OF MACULAR THICKNESS IN TYPE -2 DIABETICS ON PIOGLITAZONE

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ABSTRACT

Thiazolidinediones are oral hypoglycemic drugs that have been recently used for patients of type 2 diabetes. Review of literature shows that their side effect of systemic fluid retention aggravates diabetic macular edema. This research work was designed to see the effect of Thiazolidinediones (Pioglitazone) on early diabetic retinopathy. Optical Coherence Tomography (OCT) was used to measure average and central foveal thickness. 122 consecutive eyes of metabolically stable Type 2 diabetes were taken up for study and followed for three months who fulfilled the exclusion criteria. Patients were divided in two groups. Group one included patients with no diabetic retinopathy. Group two included patient with mild / moderate retinopathy without macular edema. As group two was further randomized into two subgroups. First subgroup received standard systemic medical therapy for diabetes and second subgroup received 30mg Pioglitazone in addition to standard treatment. All subjects underwent complete ocular systemic examination including Optical Coherence Tomography (OCT) at baseline, 6 weeks and 3 months. In this study, there was increase in central foveal thickness and average cube thickness in both the subgroups on Pioglitazone. Pioglitazone therapy is related to statistically significant increase in macular thickness at three month follow up. Optical Coherence Tomography (OCT) is an important tool for picking up subclinical changes in macular thickness that do not reflect in visual acuity.

Key Words: Hypoglycemic, Diabetes, Macular edema, Retinopathy, OCT.

INTRODUCTION

At least 171 million people worldwide suffer from diabetes and this is estimated to be doubled by 2030 (WHO) (1.) Most common cause of visual impairment in diabetic retinopathy (DR) is because of macular edema.

Optical Coherence Tomography (OCT) is a new investigative tool for quantification and classifying macular edema. (2,3) By measuring thickness it aids in early detection of macular edema and also in serial follow ups of patients on treatment..

Hee et al. (4) showed that with OCT measurements in diabetics, the mean macular thickness was larger in all regions for eyes with Non Proliferative Diabetic Retinopathy (NPDR) or PDR compared with the normal eye. The difference was most significant in average and central foveal thickness.

The therapy for diabetes mellitus mainly includes Diet, exercise, life style and pharmacological management.

Rosiglitazone and Pioglitazone have been evaluated in clinical trial in patients of type-2 Diabetes mellitus. Both these drugs have a beneficiary role in diabetic retinopathy by reducing hyperglycemia it tends to lower the progression of diabetic retinopathy this is in contradiction to what its side effect of systemic fluid retention may have (systemic fluid retention can aggravate diabetic macular edema. Review of literature provided instances of aggravation of diabetic macular edema attributed to use of this class of medicine. (5,6,7,8,9,10.) This study was designed to see the effect of pioglitazone on early diabetic retinopathy.

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MATERIAL AND METHODS

A prospective study was conducted between Sept. 2009 to May 2010 on 122 consecutive eyes of 66 patients, who had metabolically stable Type 2 diabetes mellitus (DM) attending diabetic clinic run by Department of Medicine (who fulfilled exclusion criteria). Only those patients who completed their 3 months follow up were included. Exclusion criteria were: (1) Patients receiving Glitazones before enrolment into the study. (2) Any Intraocular surgery or recent pseudophakia (<3 months). (3) Any ocular disease (except early cataract). (4) Hazy ocular media that occluded Fundus imaging. (5) Hypertension with edema. The two groups were further randomized into two subgroups. First subgroup (Subgroup A) received the standard systemic medical therapy for diabetes. The second subgroup (Subgroup B) received 30mg of Pioglitazone in addition to standard treatment. A detailed history of all patients were taken. Ocular examination included Best Corrected Visual Activity (BCVA) on ETDRS Chart. Anterior segment examination and applanation tonometry was done. Fundus examination by 90 D lens central 50° fundus photography were taken. Fundus Fluorescein Angiography (FFA) was done, if required. Macula was studied by optical coherence Tomography using Cirrus HD - OCT (Carl Zeiss Meditec, Dubling CA) Scanning protocol was 512 x 128 combo, and the retinal thickness was measured in microns (μ). Retinal maps were analysed for all patients and average cube thickness and Central foveal retinal thickness was measured. Weight was measured. Patients were examined

for pedal edema, facial puffiness and chest crepitation. All patients were subjected to following baseline investigations: - Blood Pressure recording, Blood glycosylated Haemoglobin, Blood Haemoglobin level, Blood Urea, Serum Creatinine and Protein level. Fasting Lipid Profile, 24 hours urinary protein and ECG. All subjects were followed up at 6 and 12 weeks of therapy. All subjects underwent complete ocular & systemic examination including OCT on both visits.

The statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 15 statistical Analysis Software.

RESULTS

There were total of 66 patients (29 females and 37 males) with a mean age of 55.98 ± 7.88 years. Group wise distribution of all patients is given in Table 1.

The four groups did not differ significantly in all of the biochemical parameters, weight and both systolic and diastolic blood pressure at baseline.

In measuring retinal thickness of macula, at baseline average cube thickness ranged from 260.78 ± 15.29 to 266.7 At 6 week

interval the average cube thickness in different groups ranged from 260.70 ± 15.70 to 267.55 ± 8.74 . At 3 months the average cube thickness ranged from 261.33 ± 14.94 to 269.96 ± 10.47 . At 3 months there was a statistical significant difference among the groups. At 6 weeks, maximum change in foveal thickness was seen in group IB (Table 2 and Fig. 1).

At baseline mean central foveal thickness of macula was found to be maximum in Group IIB (254.83 ± 22.57) while the minimum was observed in Group IA (235.92 ± 18.22) showing a statistically difference among the groups ($P=0.0008$) at 6 weeks and 3 months too, the trend did not change (Table 3).

At baseline the central foveal thickness in NPDR group was significantly higher as compared to No DR group ($p=0.001$), however, there was no significant difference in change in central thickness in two groups at the end of 3 months ($p=0.430$) (Table-4).

Mean change in visual activity were not found to be significant statistically in different groups between baseline to 6 weeks and baseline to 3 months as shown in Table 5.

Table 1: Group wise distribution of all patients

| Group | Group IA | Group IB | Group IIA | Group IIB |
|-----------------|----------|----------|-----------|-----------|
| No. of Subjects | 19 | 18 | 15 | 14 |
| No. of Eyes | 38 | 33 | 27 | 24 |

Table 2: Change in average cube thickness in different groups at different time intervals

| SN | Group | Baseline vs 6 weeks | | | | Baseline Vs 3 months | | | | 6 weeks vs 3 months | | | |
|----|---------------|---------------------|------|-------|-------|----------------------|------|--------|--------|---------------------|------|-------|--------|
| | | Mean | SD | "t" | "p" | Mean | SD | "t" | "p" | Mean | SD | "t" | "p" |
| 1 | IA (n=38) | 0.18 | 1.23 | 0.925 | 0.361 | 0.68 | 2.16 | 1.955 | 0.058 | 0.5 | 1.67 | 1.843 | 0.073 |
| 2 | IB (n=33) | 1.7 | 3.1 | 3.147 | 0.004 | 4.39 | 3.18 | 7.934 | <0.001 | 2.7 | 2.2 | 7.04 | <0.001 |
| 3 | IIA (n=27) | 0.07 | 1.33 | 0.29 | 0.774 | 0.56 | 2.41 | 1.199 | 0.241 | 0.63 | 3.07 | 1.067 | 0.296 |
| 4 | IIB (n=24) | 0.92 | 2.36 | 1.905 | 0.069 | 4.33 | 1.58 | 13.446 | <0.001 | 3.42 | 1.98 | 8.469 | <0.001 |

Table 3: Mean Change in Central Foveal Thickness in different groups at different time intervals

| SN | Group | Baseline vs 6 weeks | | | | Baseline Vs 3 months | | | | 6 weeks vs 3 months | | | |
|----|---------------|---------------------|------|-------|-------|----------------------|------|--------|--------|---------------------|------|-------|--------|
| | | Mean | SD | "t" | "p" | Mean | SD | "t" | "p" | Mean | SD | "t" | "p" |
| 1 | IA (n=38) | 0.47 | 1.81 | 1.612 | 0.116 | 0.32 | 2.86 | 0.681 | 0.5 | -0.16 | 2.21 | 0.44 | 0.662 |
| 2 | IB (n=33) | 3.06 | 4.96 | 3.548 | 0.001 | 9 | 5.41 | 9.549 | <0.001 | 5.94 | 4.38 | 7.79 | <0.001 |
| 3 | IIA (n=27) | 0.41 | 3.57 | 0.594 | 0.558 | 1.56 | 4.27 | 1.892 | 0.07 | 1.15 | 3.19 | 1.867 | 0.073 |
| 4 | IIB (n=24) | 3 | 4.35 | 3.376 | 0.003 | 9.29 | 3.18 | 14.303 | <0.001 | 6.29 | 3.71 | 8.303 | <0.001 |

Table 4: Comparison of Central Thickness in NPDR and No DR Groups

| S.No. | Variable | No DR (n=71) | | NPDR (n=51) | | “t” | “p” |
|-------|-------------------------------|--------------|-------|-------------|-------|-------|-------|
| | | Mean | SD | Mean | SD | | |
| 1 | Central thickness at baseline | 237.35 | 18.50 | 250.98 | 27.41 | 3.279 | 0.001 |
| 2 | Changes in central thickness | 4.35 | 6.06 | 4.35 | 6.06 | 0.792 | 0.430 |

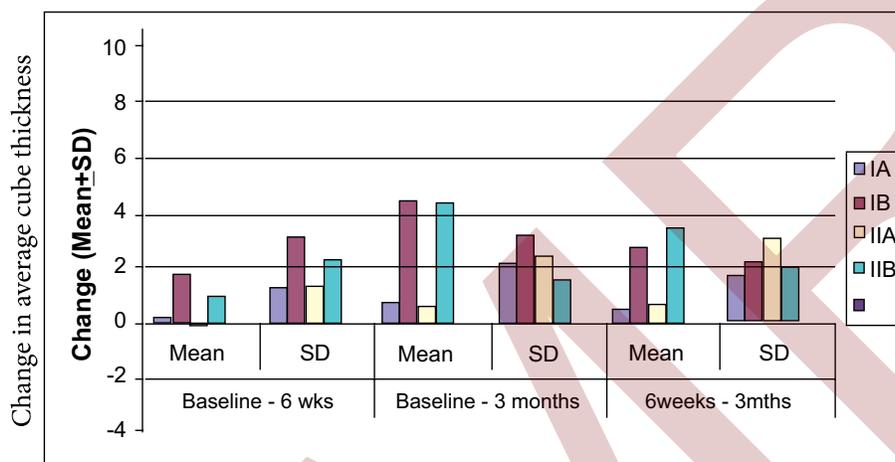


Table 5: Mean Visual Acuity in different groups at different time intervals

| SN | Group | Baseline Vs 6 weeks | | | | Baseline Vs 3 months | | | | 6 weeks Vs 3 months | | | |
|----|---------------|---------------------|------|-----|-----|----------------------|------|-----|-----|---------------------|------|-----|-----|
| | | Mean | SD | Min | Max | Mean | SD | Min | Max | Mean | SD | Min | Max |
| 1 | IA (n=38) | 0.15 | 0.13 | 0 | 0.4 | 0.15 | 0.13 | 0 | 0.4 | 0.17 | 0.12 | 0 | 0.4 |
| 2 | IB (n=33) | 0.13 | 0.13 | 0 | 0.4 | 0.13 | 0.13 | 0 | 0.4 | 0.13 | 0.13 | 0 | 0.4 |
| 3 | IIA (n=27) | 0.19 | 0.18 | 0 | 0.6 | 0.19 | 0.17 | 0 | 0.6 | 0.18 | 0.17 | 0 | 0.6 |
| 4 | IIB (n=24) | 0.13 | 0.13 | 0 | 0.6 | 0.13 | 0.13 | 0 | 0.6 | 0.13 | 0.13 | 0 | 0.6 |
| | ANOVA | 1.233 | | | | 1.112 | | | | 1.343 | | | |
| | “F” | 0.301 | | | | 0.347 | | | | 0.264 | | | |

DISCUSSION

This study was aimed at evaluating Pioglitazone as a risk factor for increase in macular thickness on OCT. It comprised of four groups (two experimental and two central groups) which were matched for age and sex. They were also comparable for biochemical parameters and duration of diabetes. All the four groups were matched for most of the confounding factors that could independently affect macular edema.

Optical Coherence Tomography (OCT) is a new investigative tool for in vivo imaging of the human retina which gives cross sectional information concerning retinal topography and tissue structure with a longitudinal resolution of less than 10 microns and is used clinically for quantification and classification of macular edema.2 None of the previous

studies (except 2 case reports) used OCT for measuring macular thickness. In this study, Spectral domain OCT was used to record baseline average cube thickness and central retinal thickness. Similar measurements were repeated at six weeks follow up and three months follow up for all subjects.

In the macular thickness assessment, central foveal thickness is the most important parameter11 because of its higher reproducibility and correlation with other measurements of the central macula. Also it is more directly related to the visual acuity, fovea having the most densely clustered cones. Next in line is the average macular thickness.

In this study, there was a statistically significant increase in central foveal thickness and average cube thickness in both the groups on Pioglitazone 30mg (Groups IB and IIB). Group

IB showed statistically significant difference even at 6 weeks of starting Pioglitazone. The increase in macular thickness detected in our study by OCT was subclinical which could be observed only on very sensitive tool like OCT.

Some of the previous studies have also Glitazone (5,6,7,8) induced fluid retention with worsening of Diabetic Macular edema and its spontaneous improvement on withdrawal of this group of drugs. There was some contradiction in the scientific literature (9). However these studies utilized a small number of subjects with retrospective data collection and varying study design with none being randomized or controlled. Moreover, OCT was not used to quantify macular thickness.

Our study also had its limitations. Most important being short follow up period of three months with a limited increase in thickness of macula due to short time to study the full effect of the drug. Secondly, we did not take subjects with advanced DR or those with macular edema which might have different response as compared to the selected population.

CONCLUSION

On the basis of our observation and analysis, we came to following conclusion:

1. Pioglitazone therapy is related to a statistically significant increase in macular thickness at three months of follows up, although this increase is subclinical in terms of visual acuity.
2. The average cube thickness and central foveral thickness was found to be significantly higher in the early non proliferative diabetic retinopathy group at baseline.
3. Implying that the ongoing diabetic retinopathy has an effect on retinal thickness.
4. OCT is an important tool in direct visualization of retina and picking up subclinical changes in macular thickness that do not reflect in visual acuity.

Although the number of patients and length of follow up in this preliminary study were limited it has demonstrated a significantly greater risk of developing increased

macular thickness in patients of type 2 diabetes mellitus on Pioglitazone therapy, with and without early diabetic retinopathy. So, patients on Pioglitazone therapy must be under regular supervision of an ophthalmologist to observe changes in macular thickness (macular edema).

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