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CLINICAL STUDY OF THE PREVALENCE OF PRE-CLINICAL MACULAR OEDEMA IN DIABETICS AS MEASURED BY OPTICAL COHERENCE TOMOGRAPHY(OCT) AND CORRELATION WITH HbA1c LEVELS

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ABSTRACT **Background:** Diabetic retinopathy is an important cause of preventable blindness. Early detection and initiation of treatment can prevent vision threatening complications of this disorder. Diabetic macular edema can be detected using Optical Coherence Tomography (OCT) prior to its clinical presentation. This study was done to detect preclinical macular edema on OCT prior to its clinical manifestation and its correlation with HbA1c (glycosylated haemoglobin) levels. **Methods:** A total of 400 eyes of 200 subjects with Diabetes mellitus having clinically normal macula were included in the study. The Central subfield Thickness (CST) and Total Macular Volume(TMV) were measured using Spectral domain OCT. The subjects were segregated into two groups based on presence or absence of preclinical macular edema defined CST of more than 220 microns. Group I without preclinical macular oedema, Group II with preclinical macular oedema. The OCT measurements – CST and TMV were correlated with HbA1c levels (average of at least 3 quarterly measurements. **Results** : The average CST of the entire study population was 237.305 ± 56.16 µ and macular volume was 9.432 ± 1.8 mm^3. By using Chi-square test a p-value > 0.05 was reached. Therefore, there is no significant association between HbA1c with CST values. However there was a poor positive correlation between macular volume and HbA1c levels.(p=0.048). **Conclusions:** Macular volume is a more specific indicator of progression of diabetes as compared to CST since diabetic changes are initially seen in paracentral regions rather than the foveal centre.

KEYWORDS : Blindness, Diabetic Retinopathy, Diabetes mellitus, Type 2 Macular Edema Tomography, Optical Coherence, Hemoglobin A, glycosylated

INTRODUCTION

Diabetic retinopathy(DR) is an important cause of visual impairment worldover. Different studies have shown different prevalences for diabetic retinopathy. In the Chennai urban rural eye disease study (CURES) the prevalence of retinopathy was found to be 17.6 % in urban population[1]. Loss of vision in DR is most commonly due to macular oedema.[2] Current guidelines for treatment require initiation of treatment only when oedema is clinically detectable and significant (ETDRS).[3]

The diagnosis of diabetic retinopathy is made on the basis of direct ophthalmoscopy and macular edema is diagnosed based on slit lamp biomicroscopy. The most widely used classification is the Early Treatment of Diabetic Retinopathy Study (ETDRS) classification based on which treatment is planned.

The diagnosis is confirmed by OCT (Ocular Coherence Tomography) and Fluorescein Angiography. OCT is used for detecting macular edema. Mode of treatment is based on these diagnostic tests.

Available treatment modalities include Macular grid and focal laser photocoagulation as established by the ETDRS group , intravitreal steroids[4] , intravitreal anti VEGF (RISE & RIDE studies).[4,5]However in a significant proportion the oedema continues unabated despite treatment.[6]

The Diabetes Control and Complications trial (DCCT) showed that poor systemic control in the initial stages is significantly associated with onset and progression of retinopathy.[7] Several studies using optical coherence tomography measurement have demonstrated increased macular thickness in diabetics with clinically normal macula.[8,9,10] OCT detected subclinical macular oedema could be a marker for inadequate metabolic control and early retinopathy.

There is only one small study on this subject which has used an older less accurate version of OCT.[11]

MATERIALS AND METHODS

Subject Selection : An prevalence study was carried out on the study population which comprised adult patients with Type 2 diabetes mellitus of any duration and Type 1 Diabetes mellitus of 5 years duration who underwent screening/yearly fundus examination for DR . The study was started after obtaining clearance from ethical committee of the institute. They underwent full ophthalmic evaluation including vision, slit lamp examination and fundus evaluation and blood tests (Hb, blood sugar, HB A1c, lipid profile and blood urea, creatinine) to assess state of metabolic control.

Sample Size Calculation:

Sample size was calculated using the formula

$N = 4*P*Q/L^2$

Where, P – Prevalence of disease
Q = 100 – P
L= Experimental error(10 % of P)

Using prevalence of macular edema of 70% from previous studies , sample size of 200 was arrived at.

400 eyes of 200 patients who have diabetes mellitus and did not have clinically detectable macular edema (CSME) on fundus examination (direct ophthalmoscope and slit lamp biomicroscopy using 90D lens) were selected. All consecutive patients were chosen provided they fulfilled the inclusion criteria. Grade of Diabetic Retinopathy and CSME were classified based on ETDRS classification. (Table – 1) Subjects without CSME and fitting the study criteria on clinical examination were subjected to OCT.

Exclusion Criteria:

Subjects having CSME and those with Severe Non Proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR) were excluded from the study. Those with any other co-existing retinopathy/ retinal vascular occlusion, macular disease , ocular surgery, laser, intravitreal injections, glaucoma were also excluded. Also those patients with refractive error were also excluded.

OCT evaluation:

OCT was done after taking written informed consent .The Spectral Domain Cirrus HD OCT machine was used for all measurements. Macular cube 512 x 128 protocol was used. The Central subfield thickness(CST) and Total macular volume (TMV) were noted. (Fig 1)

The subjects were segregated into two groups based on presence or absence of preclinical macular oedema defined as macular thickness within 500 microns of centre of fovea of more than 220 microns (>2 SD of the population mean for healthy individuals). Group I without preclinical macular oedema, Group II with preclinical macular oedema. The OCT measurements – CST and TMV were correlated with HbA1c levels (average of at least 3 quarterly measurements). HbA1c levels ≥7g% indicated poor glycemic control.

RESULTS

The study population included 200 subjects between ages 28 to 73 years out of which 28% of the subjects were in the 51 to 60 yrs age group and 27.5% in the 41 to 50 years age group . The mean age of the subjects in this study is 52.15 ± 22.02 years. Of the total of 200 subjects , there were 108 males and 92 female subjects the ratio being 1.17:1. Out of 400 eyes , 77.5% had No Diabetic Retinopathy , 20.5% had Mild NPDR and 2% had Moderate NPDR.(Table – 2)

The HbA1c level which shows the long term control of diabetes

mellitus was ≤7g% in 46% of the study population and > 7g% in 54% of the study population. Based on CST measurements the study population was divided into 2 groups , Group 1 with CST < 220µ and Group 2 with CST ≥ 220µ. Group 1 comprised 25.8% of the study population and 74.2% fell into Group 2. The average CST of the entire study population was 237.305 ± 56.16 µ and macular volume was 9.432 ± 1.8 mm^3.

The prevalence of pre-clinical macular edema(defined as CST ≥ 220µ) in the study population is 74.3%. The Mean CST value for Group 1 was 202.98 +/- 17.31µ and of Group 2 was 248.87+/- 21.34µ. The mean difference in the two groups was 45.89 µ. The mean TMV of Group 1 was 9.56 +/- 0.83 mm^3 and Group 2 was 9.07 +/- 0.97 mm^3.The mean difference in macular volume between the two groups was 0.49 mm^3.

On analysis of the results using chi-square test and Spearman's correlation coefficient no significant association was found between HbA1c with CST values(p > 0.05) among entire study population(Fig-2 and 3) as well as among different types of DR. Also it was found that there was no significant correlation between age and CST levels. There was no significant difference in CST levels seen in different types of Diabetic retinopathy.

However there was a weak positive correlation observed between HbA1c levels and TMV(p=0.048). (Fig 4)

DISCUSSION

Diabetic macular edema is seen as retinal thickening mainly due to exudation from incompetent macular retinal capillaries. Retinal thickening which occurs peripheral to the macula is not vision threatening. Clinically significant macular edema is a term coined by ETDRS to define treatment cutoffs. [12]

Macular edema is strongly positively associated with diabetic retinopathy severity.[13] Duration of diabetes is a risk factor and correlates with prevalence and incidence of macular edema, retinopathy progression, and other diabetic complications.

The Diabetes Control and Complications Trial (DCCT) was a landmark study which examined whether there was an association of Hb A1c values <8% against those of ≥8% in the progression of diabetic retinopathy. They found no concrete evidence to support the concept of a cut off for the HbA1c values in determining the progression of retinopathy, as seen in other studies.

In this study, we endeavoured to find a correlation between CST values with HbA1c values in the presence of a clinically normal macula prior to onset of macular edema (preclinical macular edema). The results showed that the average macular thickness among diabetics as seen on Spectral Domain OCT was similar to that in normal healthy population as shown in a study by Natung T et al. This shows that CST in diabetic eyes without CSME is comparable to healthy eyes in normal population.

Our study did not show a positive correlation between CST and HbA1c values. There has been a similar study by Yeung et al correlating chronic HbA1c levels with macular volume in diabetics without macular edema. The study included diabetics of more than 10 yrs duration. It showed a positive correlation between CST values and chronic HbA1c levels. However the study used time domain OCT.[13] No cut-off has been mentioned in this study for preclinical macular edema. There has been no comparison of CST in diabetics with the CST for normal population.

There is a study conducted by Parashar et al correlating HbA1c level and central foveal thickness measured by Optical coherence tomography (OCT) in patients with type 2 diabetes mellitus with CSME. Herein, DME diagnosed by OCT in diabetes was not statistically significant with age, sex , right or left eye , DM duration over 10 years or over. However,the HbA1C level (7 or over) showed a significant and positive association with macular thickness in OCT.[14]

This study again used time domain OCT and included patients with CSME. There have been no similar studies done using Spectral domain OCT.

On correlation of macular volume with HbA1c levels in the study population we found poor significant correlation between the two. This is in keeping with findings in earlier studies. In the study by Yeung et al which included both subjects without DR and with NPDR, it was concluded that there is a more stronger relationship between HbA1c levels and macular volume as compared to HbA1c and CST values.[15]

This proves the fact that long standing hyperglycemia in diabetics leads to excess amounts of fluid accumulation in the tissues as a result of the osmotic swelling of retinal tissue. Macular haemodynamics undergoes significant alteration due to microvascular damage and loss of autoregulation. Our study included subjects with clinically normal appearing macula. The haemodynamic changes at this stage probably represent a diffuse pathology rather than focal pathology at the centre of fovea. This may in fact explain why the macular volume is more sensitive to changes in glycemic status than CST.

Also, there was no correlation found between HbA1c and CST/macular volume in NPDR population and population with No DR when analysed separately. One of the drawbacks of this study is that the duration of diabetes was not taken into account. Earlier studies showing a positive correlation between HbA1c and CST values have taken subjects with longer duration of diabetes. Moreover these studies have used Time domain OCT. There are very few studies using spectral domain OCT.

CONCLUSION

On the basis of our study, it can be stated that Macular volume is a more specific indicator of progression of diabetes as compared to CST since diabetic changes are initially seen in paracentral regions rather than the foveal centre. Also, a higher cutoff value for CST i.e ≥ 220µ maybe required to quantify it as preclinical macular edema since the average CST in healthy population as determined by spectral domain OCT is more than this value. Larger studies maybe required on spectral domain OCT to determine the cutoff value for diagnosing macular edema.

Table 1 : Classification Of Diabetic Retinopathy As Per ETDRS(Early Treatment of Diabetic Retinopathy Study)

Nonproliferative Diabetic Retinopathy (NPDR) **A. Mild NPDR** At least a single microaneurysm **B. Moderate NPDR** Haemorrhages /Microaneurysms ,Soft exudates, Venous Beading(VB), and Intraretinal Microvascular Anomalies (IRMA) should be present. **C. Severe NPDR** 4-2-1 criteria Any one of Haemorrhages /Microaneurysms in all 4 quadrants, VB in 2 or more quadrants ,IRMA in a single quadrant **D. Very Severe NPDR** Any two or more of the criteria mentioned for severe NPDR.
Proliferative Diabetic Retinopathy (PDR) Presence of new vessel proliferation in the form of Neovascularisation of Disc(NVD) or Neovascularisation elsewehere(NVE), **E. Early PDR** New vessels at disc or elsewhere but not meeting criteria for high risk PDR. **F. High-risk PDR** NVD (1/3 – 1/2 disc area) *or* Any NVD and vitreous or preretinal or vitreous hemorrhage *or* Any NVE ≥ 1/2 disc area and vitreous or preretinal hemorrhage
Clinically Significant Macular Edema (CSME) 1. Thickening of the retina at or within 500µm from the centre of the macula *or* 2. Hard exudates with thickening of the retina close to it located at or within 500µm from the centre of the macula *or* 3. A zone of retinal thickening, 1 disc diameter area or larger in size located at or within 1 disc diameter from the centre of the macula

Table 2: Demographic Data Of Study Population

Study parameter	Distribution
Age	28 – 73 yrs (Mean 52.15 ± 22.02yrs)
Gender	Males 108(54%) Females 92(46%)

Type of Retinopathy(No of eyes)	No DR 310(77.5%) Mild NPDR 82 (20.5%) Moderate NPDR 8(2%)
HbA1c levels(g%)	<7 - 92(46%) ≥7 - 108(54%)
CST values(µm)	< 220 - 103 (25.8%) ≥ 220 - 297 (74.3%)

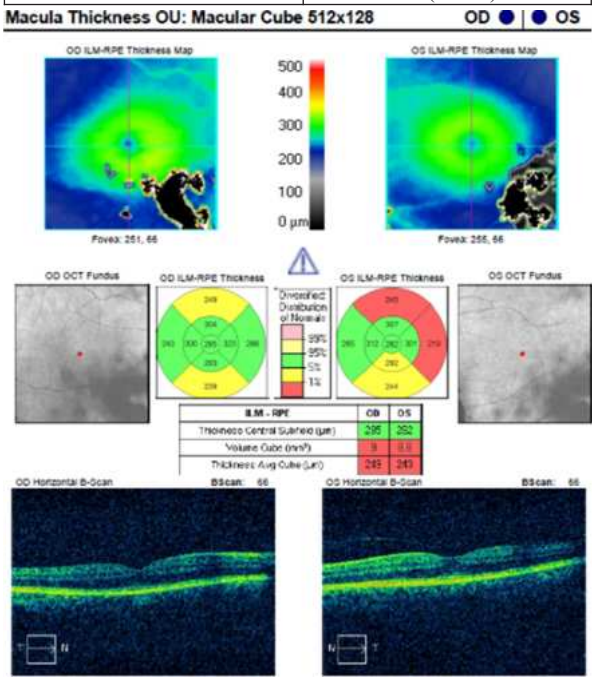

Fig 1: Image of OCT Macula

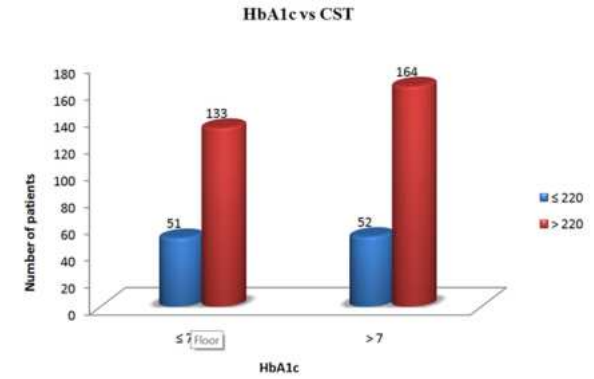

Fig 2: Bar Diagram showing correlation between HbA1c levels and Central Subfield Thickness {CST(µm)}

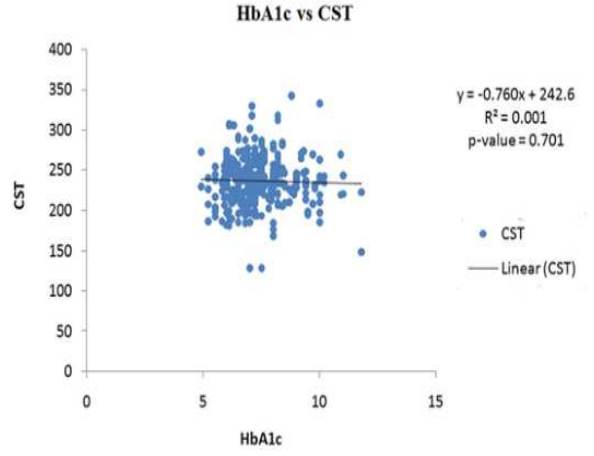

Fig 3: Scatter diagram showing correlation Between HbA1c With CST Among Entire Population

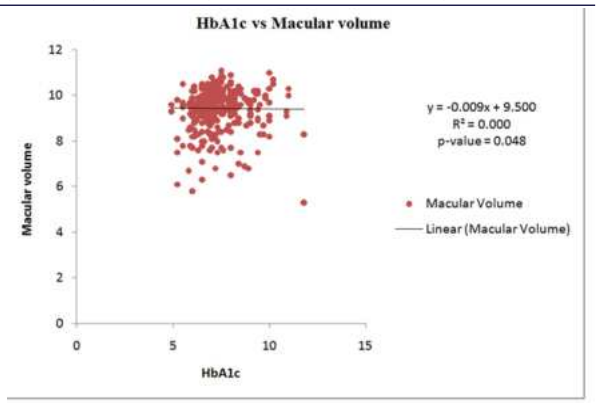

Fig 4: Scatter Diagram showing correlation Between HbA1c Levels And Macular Volume Among Entire Population

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