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J Kishore Kumar Jacob
Associate Professor, Sree Mookambika Institute of Medical Sciences Padanilam Kulasekharam, Kanniya Kumari District, Tamil Nadu, India

I. Anesha Isaac
Junior Resident, Sree Mookambika Institute of Medical Sciences Padanilam Kulasekharam, Kanniya Kumari District - 629161, Tamil Nadu, India

Janie Salor
Junior Resident, Sree Mookambika Institute of Medical Sciences Padanilam Kulasekharam, Kanniya Kumari District, Tamil Nadu, India

N Rajendran
Professor and Head of The Department, Sree Mookambika Institute of Medical Sciences Padanilam Kulasekharam, Kanniya Kumari District, Tamil Nadu, India

Corresponding Author:
N Rajendran
Professor and Head of the Department, Sree Mookambika Institute of Medical Sciences Padanilam Kulasekharam, Kanniya Kumari District, Tamil Nadu, India

Variation in central corneal thickness in diabetes: A comparative prospective study at a tertiary care hospital

J Kishore Kumar Jacob, I Anesha Isaac, Janie Salor and N Rajendran

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Abstract
Diabetes being the greatest challenge of the century and the fact that it affects almost all of the tissues and organs in the body warrants research into the effects of diabetes on every structure. This study was designed with the aim of finding out any association between diabetes and central corneal thickness and to evaluate the effect of diabetes treatment on central corneal thickness.

Objectives

a. To find out the differences between CCT values amongst diabetic and non-diabetic patients, if any.
b. To assess the presence of any significant change in these measurements after successful control of hyperglycaemia.

Methods: A comparative prospective study was conducted in the Dept. of Ophthalmology, Sree Mookambika Institute of Medical Sciences, Kulasekharam to evaluate the effect of diabetes on CCT. A total of 84 subjects were studied which included 42 diabetics. After thorough systemic and ocular CCT was measured using ultrasound pachymeter. The study was initiated after obtaining ethical clearance from the institution's ethical clearance committee. The collected data was analysed using SPSS software version 20.0.

Results: Majority of the study subjects were male in both diabetic group (52.4%) and non-diabetic group (54.8%). The mean CCT among non-diabetics were 529 and among diabetics were 554.5. Students 't' test was used to compare the corneal thickness between diabetic and non-diabetic patients. P value less than 0.05 is considered as significant. In this study it is found that there is significant difference in CCT OD 1 and CCT OS 1 in diabetic and non-diabetic patients. And the difference in CCT was found to be statistically significant. In this study we have also found out that there is strong positive correlation between CCT and diabetic control as per the pearson coefficient evaluation. In this study it is found that there is no significant difference in CCT following diabetic control in diabetic patients. Also, CCT was not correlated with the duration of diabetes. But the effect of control was not evaluated with serial HbA1c and a few patients didn't have good control of diabetes either.

Conclusion: Diabetes is a serious and extremely prevalent systemic illness in today's scenario which was previously considered a disease of the affluent, diabetes has become a problem of epidemic proportions, contributing to significant morbidity and mortality. And India is moving fast in this race to become a Diabetes Capital of the world. Such being the case, it warrants further research in the field by the medical fraternity, to aid in prevention, early diagnosis, delaying progression and management of the disease. The effects of diabetes on the eye have been studied but as the prevalence of diabetes increases with all the generation, it demands further detailed research activities into the effect's diagnosis and management of diabetes in the eye. In our study we tried to bring to light the effects of diabetes on corneal thickness, which in turn might affect even the management of glaucoma. We evaluated a group of diabetics and compared them with matched controls. After conducting this study we arrived at a conclusion that central corneal thickness is increased in diabetics and that control of diabetes doesn't have a significant effect on central corneal thickness.

Keywords: Central corneal thickness (CCT), diabetes, corneal hysteresis

Introduction

Diabetes mellitus is a syndrome characterized by inappropriate hyperglycemia and is chronically associated with microvascular and macro vascular complications [1]. It is a common disease which is associated with numerous secondary systemic complications. Diabetes is a very frequent disease worldwide, having a considerable impact on society, not only due to its high prevalence but also because of its chronic complications and high

mortality rate, affecting approximately 180 million people around the world [1]. According to W.H.O estimates by the year 2030, there will be approximately 370 million diabetics in the world [2]. In India alone, there will be around 80.9 million diabetics, thus by the year 2030, India will be approximately 21.8% of the global burden of the disease, achieving status of the diabetic capital of the world [2]. Diabetes is going to be a big burden on the health care facilities of the country due to the fact that hyperglycemia has toxic effect on almost all the cells in the body.

The so called "Asian Indian Phenotype" refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, greater abdominal adiposity i.e., higher waist circumference despite lower body mass index, lower adiponectin and higher highly sensitive C-reactive protein levels. This phenotype makes Asian Indians more prone to diabetes and premature coronary artery disease [3].

The most disturbing trend is the shift in age of onset of diabetes to a younger age in the recent years. This Introduction 2 could have long lasting adverse effects on nation's health and economy [3]. As the number of persons with diabetes increases, the development of micro vascular complications such as retinopathy, nephropathy and neuropathy also rise. Diabetes is known to be a leading cause for blindness throughout the world. It is the most frequent cause of blindness for working age individuals and the second cause of blindness for the whole population after age related macular degeneration.

Patients with diabetes mellitus often develop not only diabetic retinopathy but also corneal endothelial damage and keratoepitheliopathy such as superficial punctate keratitis, recurrent corneal erosion and persistent epithelial defects. The hemostasis of various structures of cornea can be altered by the diabetes in both the non-stressed and stressed cornea, causing myriad primary and postoperative manifestations. They have abnormalities like higher corneal autofluorescence, lower corneal sensitivity and lesser endothelial density [4].

Diabetic keratopathy is a frequent disease that entails several alterations, especially in the epithelium and endothelium in diabetics. Corneal epitheliopathy appears as punctate keratitis, decreased adherence to the basal membrane and corneal hypoesthesia [4, 5, 6]. At ocular level corneal endothelium plays a major role in maintaining the optical transparency of the cornea. These cells have limited mitotic capacity and a chronic metabolic change at the cellular level seems to affect the monolayer of corneal endothelial cells [5]. Diabetic keratopathy is a significant problem as it can affect corneal transparency and fluctuating vision. Also, the fact that keratopathy issues will be more in contact lens wearers also makes it an issue that can't be neglected. CCT influences the IOP values and hence in the management of glaucoma as it renders accurate IOP measurement challenging and prone for errors.

Moreover, diabetics are thought to be at higher risk of developing glaucoma. Although diabetes is associated with high IOP, the underlying mechanism is still unknown [5, 7]. Some previous studies showed increased central corneal thickness (CCT) in diabetic patients compared to non - diabetic control groups, but some others showed no difference in CCT between diabetic and control groups [8-14]. Also very few studies have been conducted in the Indian population.

The purpose of this study is to evaluate whether CCT has any variation in diabetics and if so whether there will be a significant change in these measurements after control of hyperglycaemia. In this dissertation, we are doing a hospital based prospective study to find the relationship between central corneal thickness and diabetes in patients attending SMIMS, Kulasekharam and to determine the relationship between central corneal thickness and glycaemic control.

Aims and Objectives

a. To find out the differences between CCT values amongst diabetic and non-diabetic patients, if any.
b. To assess the presence of any significant change in these measurements after successful control of hyperglycaemia.

Methodology

This study titled, 'Variation in central corneal thickness in diabetes: a comparative prospective study at a tertiary care hospital' was conducted in the Sree Mookambika Institute of Medical Sciences, Kulasekharam, Kanyakumari after obtaining ethical committee clearance.

a. Study design: Comparative prospective study
b. Study duration: Nov 2015 to Aug 2017.
c. Study setting: Department of Ophthalmology, Sree Mookambika Institute of Medical Sciences, Padanilam, Kulasekharam, Kanyakumari.
d. Source of data: A total of subjects 84 were selected during the study period, which included 42 diabetic patients who presented to our outpatient department and those referred from other departments. Each patient was subsequently evaluated as per the inclusion and exclusion criteria. The second group included age matched control group of 42 subjects.

Sampling

Sample size of each group: 30
Total sample size of the study: 60

Scientific basis of sample size used in the study

$$n=2S^2\frac{(z1+z2)^2}{(M1+M2)^2}$$

M1 = Mean of central corneal thickness in uncontrolled diabetic pt = 541
M2 = Mean of central corneal thickness in controlled diabetic pt = 518
S1 = Standard deviation of M1 = 22
S2 = Standard deviation of M1 = 34
S = Pooled Standard deviation = 28.63
Z1 = Z value associated with alpha = 1.64
Z2 = Z value associated with beta = 0.84
n = Minimum sample size = 19.16 ~ 20
But we are taking 30 sample size for each group
So total sample size = 30+30=60 (12)

Sampling technique: Systematic random sampling

Inclusion criteria

Group 1: Control group

a. Patients above 30 years of age (male or female)
b. No previous history of diabetes mellitus or treatment

for the same c) Recent (last 4 weeks) FBS/PPBS was within normal limits

Group 2: All self-reported diabetic cases (age greater than 30yrs) attending OPD giving consent for work up for the study. They may be established cases of diabetes mellitus or recently diagnosed.

Exclusion criteria

a. Patients who are not willing,
b. Any history of ocular diseases/any abnormalities of the conjunctiva or cornea
c. Any history of intraocular or corneal surgeries previously
d. History of using topical ocular medications
e. History of wearing contact lens
f. Any history of trauma to the eye
g. Any history of systemic collagen diseases

Whether placebo is used in the study: No
Whether drug used in the study: No
If research is a clinical trial: No
Parameters to be studied [If quantitative data mention the units of measurement]:

- CCT
- FBS/PPBS/RBS

Procedure

In every case, an informed written consent was obtained. A detailed ocular and medical examination were done preceded by a general physical examination. In all the cases, detailed general physical examination including vitals and systemic examination was done. Visual acuity for distance (Snellen's chart) and near, Best Corrected Visual Acuity (BCVA) and IOP (using Non-Contact Tonometer) was recorded in every case.

An elaborate slit lamp bio microscopy (Carl Zeiss Meditech) examination of the anterior segment was also performed. Lids, meibomian glands, conjunctival surface for dryness congestion, cornea for sheen surface and sensation were all checked in detail. Detailed fundus examination under mydriasis was done under direct and indirect ophthalmoscopic examination.

Central corneal thickness was measured using ultrasound pachymetry (NIDEK US 4000 Echoscan). Pachymetry readings were taken by aligning the probe perpendicular on the central cornea by the investigator. 10 values were taken and the highest and the lowest were excluded and the mean of the remaining was used for the study.

The ultrasonic pachymetry measurements depend on the reflection of ultrasonic waves from the anterior and posterior corneal surfaces. It is the measurement of the time difference (transit time) between echoes of ultrasonic signal pulses from the transducer of the probe and the reflected signal from the front and back surface of the cornea to the transducer. Ultrasound pachymeter Methodology 57 measures corneal thickness at 10-20 MHz with an estimated velocity of sound through cornea of 1630m/sec. if the probe is not positioned correctly or the reading shows great difference from each other, the series is rejected and done again.

Sample collection and storage

Assessment of fasting/post prandial/random blood sugar values: Blood sample of not less than 5 ml needs to be collected under asepsis from anterior cubital vein using a sterile disposable syringe. For assessment of fasting blood sugar values, glucose oxidase/peroxidase method is employed.

Laboratory investigations

Serum or plasma, free of haemolysis, may be used, mixed with Reagent (manufactured by Biosystems) that is ready to use, and analyzed using AU 480 automated analyzer. Glucose oxidase/peroxidase method (15) was employed.

Serum or plasma, free of haemolysis, was used, after mixing with Reagent (manufactured by Beckman Coulter) and analyzed using AU 480 automated analyzer.

Statistical analysis

The data was entered on office excel 2007. Data was analysed by using SPSS trial version 20.0. Continuous variables were expressed as mean and standard deviation; qualitative variable as percentage and frequency. Statistical test was done using correlation and student t test. A probability value (*p* value) of <0.05 was considered statistically significant.

Results

Students 't' test was used to compare the corneal thickness between diabetic and non-diabetic patients. P value less than 0.05 is considered as significant. In this study it is found that there is significant difference in CCT OD 1and CCT OS 1 in diabetic and non-diabetic patients.

Variable	Group	N	Mean	SD	t	p
BCVA OD	Diabetic	42	0.0857(20|20)	0.3	0.115	0.908
	Not diabetic	42	0.0796(20|24)	0.2		
BCVA OS	Diabetic	42	0.1190(20|26)	0.3	1.115	0.268
	Not diabetic	42	0.0571(20|22)	0.2		
IOP OD	Diabetic	42	15.5	3.1	1.07	0.286
	Not diabetic	42	14.8	2.8		
IOP OS	Diabetic	42	15.1	3.2	0.032	0.974
	Not diabetic	42	15.1	3.0		
CCT OD1	Diabetic	42	554.5	38.9	3.65	0.000
	Not diabetic	42	529.9	25.3		
CCT OS1	Diabetic	42	554.4	39.4	3.28	0.000
	Not diabetic	42	528.9	23.7		
CCT OD 2	Diabetic	42	554.6	37.3		
	Not diabetic	0[a]				
CCT OS 2	Diabetic	42	554.7	38.5		
	Not diabetic	0[a]				

The distribution of age in the diabetic group ranges from 34 to 76 years. The mean age of study participants were 56.76 years and a SD of 9.753 years. The distribution of age in non-diabetic group ranges from 40 to 83 years. The mean age of study participants were 62.21 years and a SD of 12.794 years.

Table 1: Distribution according to age of participants

Age characteristic	Diabetic	Non diabetic	Overall
Minimum	34	40	34
Maximum	76	83	83
Mean	56.76	62.21	59.49
Standard deviation	9.753	12.794	11.634

Comparison of CCT OD 1 and CCT OD 2 in diabetic group

Paired 't' test was used to compare CCT OD 1 and CCT OD 2 in diabetic patients. P value less than 0.05 is considered as significant. In this study it is found that there is no significant difference in CCT OD 1and CCT OD 2 in diabetic patients.

Group	CCT OD 1		CCT OD 2		t	p
	Mean	SD	Mean	SD		
Diabetic group	554.50	38.932	554.62	37.316	0.192	0.849

Comparison of CCT OS 1 and CCT OS 2 in diabetic group

Paired 't' test was used to compare CCT OS 1 and CCT OS 2 in diabetic patients. P value less than 0.05 is considered as significant. In this study it is found that there is no significant difference in CCT OS 1and CCT OS 2 in diabetic patients.

Group	CCT OS1		CCT OS2		t	p
	Mean	SD	Mean	SD		
Diabetic group	554.36	39.422	554.74	38.534	0.645	0.522

Discussion

Central corneal thickness is one of the most useful and direct measures of corneal health. It is one of the earliest indicators of the corneal health. Historically CCT has been used as an indicator of the endothelial pump function and the corneal barrier. Its importance has also been recognized in the management of glaucoma as it is an important factor that is necessary to adjust the IOP value to get a more accurate IOP. Diabetes being the greatest challenge of the century and the fact that it affects almost all the tissues and organs in the body warrants research into the effects of diabetes on every structure. Many recent studies have shown that diabetes mellitus does have an effect on the central corneal thickness. And few studies did show some contrasting results regarding the association between diabetes and central corneal thickness.

This study was designed with the aim of finding out any association between diabetes and central corneal thickness and to evaluate the effect of diabetes treatment on central corneal thickness. Our study was a one-and-a-half-year comparative prospective study conducted in the Dept. of Ophthalmology, Sree Mookambika Institute of Medical Sciences, Kulasekharam from November 2015. A total of 84 subjects were studied which included 42 diabetic patients and 42 healthy controls.

In our study majority of the study participants were 50-59 years of age. This was comparable to the study conducted by Jurangal *et al*., Dawood *et al.*, Huseynova *et al.*, Sahin *et al.* Majority of the study subjects were male in both diabetic group (52.4%) and non-diabetic group (54.8%). The same sex ratio was obtained in few of the studies like the study by Briggs *et al.*, Claramonte *et al.*, Jurangal *et al*. But this was not statistically significant. The mean CCT among non-diabetics were 529µm and among diabetics were 554.5µm. Students't' test was used to compare the corneal thickness between diabetic and non-diabetic patients. P value less than 0.05 is considered as significant. In this study it is found that there is significant difference in CCT OD 1 and CCT OS 1 in diabetic and non-diabetic patients. And the difference in CCT was found to be statistically significant. In this study we have also found out that there is strong positive correlation between CCT and diabetic control as per the Pearson coefficient evaluation. Storr-Paulsen *et al.* conducted a study 235 subjects which includes 107 diabetics and found similar results i.e. CCT is increased in diabetics.

The Singapore Malay Eye Study a population based cross section study having a very large sample size (3239) also had similar outcome i.e. diabetes and hyperglycaemia is associated with thicker central cornea. Discussion 74. The study done by Abdulghani *et al.* also had results correlating with our study finding. Claramonte PJ *et al.* also found out that diabetics had an increased central corneal thickness when compared to non-diabetics Scheler *et al.* arrived at the conclusion that CCT was higher in diabetes similar to the results we got in our study.

The Gutenburg Health Study also correlates with the results we obtained. Studies done by Sahin *et al.*, Sanchis-Gimeno *et al.*, Mathebula *et al.*, Jurangal *et al.* etc all had results that concluded that Central corneal thickness is increased in diabetes similar to the result we got. But the studies done by Yusekkaya *et al.*, Inou *et al.*, Dawood *et al.* etc had showed that there is no significant correlation between diabetes and central corneal thickness.

In this study it is found that there is no significant difference in CCT following diabetic control in diabetic patients. Also, CCT was not correlated with the duration of diabetes. But the effect of control was not evaluated with serial HbA1c and a few patients didn't have good control of diabetes either. But Studies done by Briggs *et al.*, Altay *et al.*, Dabas *et al.*, Kaur *et al.* had positive correlation between duration of diabetes, Control of diabetes.

A few studies like the study done by Emine Cinici etc had findings similar to our study where in there was no correlation between periods of diabetes, HbA1c on CCT. Now that the fact that diabetes affects the central corneal thickness has been established there needs to be more detailed research done on the effects of good control of diabetes and duration on corneal thickness.

Conclusion

Diabetes is a serious and extremely prevalent systemic illness in today's scenario which was previously considered a disease of the affluent, diabetes has become a problem of epidemic proportions, contributing to significant morbidity and mortality. And India is moving fast in this race to become the Diabetes capital of the world. Such being the case, it warrants further research in the field by the medical fraternity to aid in prevention, early diagnosis, delaying progression and management of the disease.

The effects of diabetes on the eye have been studied but as the prevalence of diabetes increases with all the generation, it demands further detailed research activity into the effects, diagnosis and management of diabetes in the eye.

In our study we tried to bring to light the effects of diabetes on corneal thickness, which in turn might affect even the management of glaucoma. We evaluated a group pf diabetic and compared them with matched controls. After conducting this study, we arrived at a conclusion the central corneal thickness is increased in diabetics and that control of diabetes doesn't have a significant effect on central corneal thickness.

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