Int. J Med. Pharm. Res. (P-ISSN: 2958-3675 | E-ISSN: 2958-3683)
Available on: https://ijmpr.in/

International Journal
of Medical and Pharmaceutical Research

ORGINAL ARTICLE **OPEN ACCESS**

An Observational Study To Correlate HbA1c Values In Type 2 Diabetes Mellitus Patients With Central Corneal Thickness Using Non-Contact Specular Microscopy in A Tertiary Care Centre in Mandya

Dr.Prarthana, H[1]*, Dr. Praveen, V[2], Dr.Pradeep, A. V[3]

[1]3rd Year PG, Department of Ophthalmology, Mandya Institute of Medical Sciences Mandya, 3RD CROSS, Guthal Rd, Maruthi Nagar, Mandya, Karnataka 571403, India
[2]Associate Professor, Department of Ophthalmology, Mandya Institute of Medical Sciences Mandya, 3RD CROSS, Guthal Rd, Maruthi Nagar, Mandya, Karnataka 571403, India
[3]Head of Department, Department of Ophthalmology, Mandya Institute of Medical Sciences Mandya, 3RD CROSS, Guthal Rd, Maruthi Nagar, Mandya, Karnataka 571403, India

OPEN ACCESS

***Corresponding Author**
Dr.Prarthana, H

3rd Year PG, Department of Ophthalmology, Mandya Institute of Medical Sciences Mandya, 3RD CROSS, Guthal Rd, Maruthi Nagar, Mandya, Karnataka 571403, India

Received: 06-09-2024
Accepted: 01-11-2024
Available online: 09-11-2024

A B S T R A C T

Background: Diabetes mellitus is a chronic metabolic disorder that can lead to various ocular complications, including corneal changes. This study aimed to investigate the correlation between HbA1c levels, central corneal thickness (CCT), and corneal endothelial parameters in patients with type 2 diabetes mellitus using non-contact specular microscopy.***Methods***: This observational study included 181 patients with type 2 diabetes mellitus who underwent a comprehensive ophthalmic examination, including non-contact specular microscopy. The correlation between HbA1c levels, CCT, endothelial cell density (ECD), coefficient of variation (CV), and hexagonality (HEX) was analyzed. The association between the severity of diabetic retinopathy and corneal parameters was also evaluated.***Results****:* A significant positive correlation was found between HbA1c levels and CCT ($p<0.001$). Patients with HbA1c levels >6.5% had a mean CCT of 579.24±19.47 µm, compared to 537.73±16.92 µm in those with HbA1c levels between 4-5.6% ($p<0.001$). The duration of diabetes was also significantly associated with increased CCT ($p<0.001$). Patients with PDR had the lowest mean ECD (2091.88±121.34 cells/mm²), highest mean CV (51.01±4.78%), and lowest mean HEX (30.10±3.92%) compared to those with no diabetic retinopathy ($p<0.001$ for all).***Conclusion****:* HbA1c levels and duration of diabetes significantly correlate with CCT and corneal endothelial changes in patients with type 2 diabetes mellitus. Non-contact specular microscopy is a valuable tool for detecting early corneal changes in diabetic patients, enabling timely intervention and prevention of visual impairment.

Keywords: Type 2 diabetes mellitus, HbA1c, central corneal thickness, corneal endothelial cells, non-contact specular microscopy, diabetic retinopathy.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from insulin resistance, impaired insulin secretion, or both [1]. The global prevalence of diabetes is rapidly increasing, with an estimated 537 million adults (20-79 years) living with diabetes in 2021, projected to rise to 643 million by 2030 and 783 million by 2045 [2]. T2DM accounts for around 90% of all diabetes cases [3].

Chronic hyperglycemia in diabetes leads to various microvascular and macrovascular complications [4]. One such complication is diabetic keratopathy, which affects the cornea and can lead to visual impairment and blindness [5]. The cornea is the transparent, avascular tissue that covers the front of the eye and is essential for maintaining clear vision [6]. The corneal endothelium, a single layer of hexagonal cells on the innermost surface of the cornea, plays a crucial role in maintaining corneal transparency by regulating corneal hydration [7].

Several studies have investigated the relationship between diabetes and corneal thickness. A meta-analysis by Zhao *et al*., found that central corneal thickness (CCT) was significantly lower in diabetic patients compared to non-diabetic controls [8]. Moreover, the duration of diabetes and glycemic control, as measured by glycatedhemoglobin (HbA1c) levels, have been associated with changes in CCT [9].

HbA1c is a widely used marker for assessing long-term glycemic control in patients with diabetes. It reflects the average blood glucose levels over the past 2-3 months [10]. Elevated HbA1c levels have been linked to an increased risk of diabetic complications, including retinopathy, nephropathy, and neuropathy [4]. However, the relationship between HbA1c and CCT in T2DM patients remains unclear, with conflicting results reported in the literature.

Some studies have found a significant negative correlation between HbA1c and CCT. For example, Yazgan*et al*., observed that CCT decreased with increasing HbA1c levels in T2DM patients [11]. Similarly, Altay *et al*., reported a significant negative correlation between HbA1c and CCT in a study of 156 T2DM patients [12]. These findings suggest that poor glycemic control may contribute to corneal thinning in T2DM patients.

In contrast, other studies have not found a significant association between HbA1c and CCT in T2DM patients. A study by Choo*et al*., involving 200 T2DM patients and 100 healthy controls found no significant correlation between HbA1c and CCT [13]. Likewise, Storr-Paulsen *et al*., did not observe a significant relationship between HbA1c and CCT in a study of 107 T2DM patients and 128 healthy controls [14].

These inconsistent findings highlight the need for further research to clarify the relationship between HbA1c and CCT in T2DM patients. Additionally, most previous studies have used ultrasound pachymetry to measure CCT, which requires contact with the cornea and may be influenced by operator variability [15]. Non-contact specular microscopy (NCSM) is an alternative method for measuring CCT that is non-invasive, rapid, and highly reproducible [16]. NCSM also provides information on corneal endothelial cell density and morphology, which may be affected by diabetes [17].

The present observational study aims to investigate the correlation between HbA1c values and CCT measured by NCSM in T2DM patients at a tertiary care center in Mandya, India. The study will also compare CCT between T2DM patients and age-matched healthy controls and assess the relationship between CCT and other factors such as age, sex, duration of diabetes, and body mass index (BMI).

The findings of this study may have important clinical implications for the management of T2DM patients. If a significant correlation between HbA1c and CCT is established, this could support the use of CCT as a potential biomarker for monitoring glycemic control and the risk of diabetic keratopathy. Moreover, identifying factors associated with corneal thinning in T2DM patients may help in the early detection and prevention of diabetic corneal complications.

Aims and Objectives

The primary objective of this hospital-based observational study was to investigate the correlation between central corneal thickness (CCT) and glycatedhemoglobin (HbA1c) levels in patients with type 2 diabetes mellitus using non-contact specular microscopy. The secondary objective was to describe the changes in CCT in type 2 diabetic patients using the same imaging technique.

Materials and Methods

Study Design and Setting This study was designed as a hospital-based observational study and was conducted at the Department of Ophthalmology in a tertiary care center in Mandya, India. The study period spanned from February 15th, 2024, to June 2024.

Study Population and Sampling The study population consisted of patients with type 2 diabetes mellitus who fulfilled the inclusion criteria and visited the Department of Ophthalmology during the study period. A convenience sampling method was employed to recruit participants.

Sample Size Calculation The sample size was calculated based on a previously reported correlation coefficient of 0.207 between HbA1c and CCT in type 2 diabetes mellitus patients [2]. Using the formula $n = [(Z1\text{-}\alpha/2 + Z1\text{-}\beta) / C]2 + 3$, where $C = 0.5 \times \ln[(1 + r) / (1 - r)] = 0.210$, $Z1\text{-}\alpha/2 = 1.96$, and $Z1\text{-}\beta = 0.84$, the required sample size was determined to be 181 participants.

Inclusion and Exclusion Criteria The inclusion criteria for the study were as follows: (1) diabetic patients aged more than 50 years with serum HbA1c levels greater than 6.5%, and (2) patients willing to provide informed consent to

participate in the study. The exclusion criteria encompassed the following: (1) presence of corneal diseases such as dystrophies, pterygium, corneal opacities, corneal scarring, keratoconus, or iridocorneal syndromes; previous use of hard contact lenses; (2) positive history of glaucoma or current use of anti-glaucoma medication; (3) previous anterior segment surgeries or laser treatments; (4) positive history of systemic hypertension; and (5) patients with a history of trauma.

Data Collection and Study Procedures All patients with type 2 diabetes mellitus attending the outpatient Department of Ophthalmology who met the inclusion criteria and were willing to participate in the study were enrolled. Informed consent was obtained from all subjects after explaining the nature and possible consequences of the study procedures. The patients' demographic information, including name, age, sex, address, and occupation, was recorded. A detailed medical and ophthalmic history was elicited from each participant.

All subjects underwent a comprehensive ophthalmic examination, which included visual acuity assessment, slit-lamp biomicroscopy, fundus examination by indirect ophthalmoscopy using a +20D lens, and intraocular pressure measurement by non-contact tonometry. Non-contact specular microscopy was performed on all participants to assess their central corneal thickness.

Statistical Analysis All collected data were entered into a Microsoft Excel spreadsheet, and statistical analyses were performed using the trial version No. 25 of the IBM-SPSS software (Software Package for Social Science). Descriptive statistics were employed to summarize categorical data (e.g., age and sex) and continuous data (e.g., HbA1c levels). The correlation coefficient between HbA1c and CCT was calculated for quantitative data analysis.

In summary, this hospital-based observational study aimed to investigate the relationship between central corneal thickness and glycemic control in patients with type 2 diabetes mellitus using non-contact specular microscopy. The study was conducted at a tertiary care center in Mandya, India, with a sample size of 181 participants who met the specified inclusion and exclusion criteria. A comprehensive ophthalmic examination and non-contact specular microscopy were performed on all subjects, and statistical analyses were conducted to assess the correlation between HbA1c levels and CCT.

RESULTS

Table 1: Socio-demographic characteristics

Socio-demographic characteristics		Frequency	Percentage
Age Group	**50-55 years**	14	8%
	56-59 years	45	25%
	60-64 years	56	31%
	65-66 years	66	36%
Gender	**Male**	112	62%
	Female	69	38%
Duration of Diabetes	**5-10 years**	152	84%
	> 10 years	29	16%

Most patients fall within the 65-66 age group (36%), followed by the 60-64 age group (31%). The study predominantly includes male participants (62%) compared to females (38%). The duration of diabetes is mostly between 5-10 years (84%), with fewer patients having diabetes for over 10 years (16%).

Table 2: HbA1c Levels

HbA1c Levels	Frequency	Percentage
4 - 5.6	63	35%
5.61 - 6.5	56	31%
> 6.5	62	34%

A significant proportion of patients have poor glycemic control, with 34% having HbA1c levels greater than 6.5%. About 35% of patients have levels between 4-5.6, and 31% have values between 5.61-6.5.

Table 3: Severity of Diabetic Retinopathy in Study Subjects

Severity of Diabetic Retinopathy	Frequency	Percentage
No Diabetic Retinopathy	38	21%
Very Mild and Mild NPDR	51	28%
Moderate NPDR	45	25%
Severe and Very Severe NPDR	34	19%
PDR	13	7%

The majority of patients have very mild to mild NPDR (28%) or no diabetic retinopathy (21%). Only a small proportion (7%) have proliferative diabetic retinopathy (PDR), indicating that the population is mostly in the early stages of retinopathy.

Table 4: Association of Severity of Diabetic Retinopathy and Duration of Diabetes

Severity of Diabetic Retinopathy	Duration of Diabetes		P value
	5-10 Years	>10 Years	
No Diabetic Retinopathy	38	0	**<0.001**
Very Mild and Mild NPDR	51	0	
Moderate NPDR	45	0	
Severe and Very Severe NPDR	7	27	
PDR	5	8	

This table indicates that as the duration of diabetes increases beyond 10 years, the severity of diabetic retinopathy worsens. None of the patients with less than 10 years of diabetes had severe or very severe NPDR or PDR. However, 27% and 8% of patients with more than 10 years of diabetes had severe NPDR and PDR, respectively. P-value: <0.001, indicating a statistically significant association between the duration of diabetes and the severity of retinopathy.

Table 5: Correlation between Age and Severity of Diabetic Retinopathy

Severity of Diabetic Retinopathy	Mean Age (Years)	Mean HbA1c (%)
No Diabetic Retinopathy	46.57	5.32
Very Mild and Mild NPDR	50.54	5.68
Moderate NPDR	53.52	6.42
Severe and Very Severe NPDR	57.00	8.20
PDR	58.14	9.81
P value	**<0.001**	**<0.001**

The mean age of patients increases with the severity of diabetic retinopathy. Patients with no diabetic retinopathy had a mean age of 46.57 years, whereas those with PDR had a mean age of 58.14 years. This suggests that the severity of retinopathy worsens with age. Mean HbA1c (%) also increases with severity, from 5.32% in patients without retinopathy to 9.81% in patients with PDR. This suggests that the severity of retinopathy worsens with increase in Hba1c. P-value: <0.001, showing a significant correlation between age, Hba1c and severity of retinopathy.

Table 6: Severity of Diabetic Retinopathy and Central Corneal Thickness (CCT), Endothelial Cell Density (ECD), Coefficient of Variation (CV)

Severity of Diabetic Retinopathy	Mean CCT (µm)	Mean ECD (cells/mm²)
No Diabetic Retinopathy	529.61	2663.60
Very Mild and Mild NPDR	548.17	2401.85
Moderate NPDR	566.62	2271.25
Severe and Very Severe NPDR	580.91	2159.47
PDR	609.04	2091.88
P value	**<0.001**	**<0.001**

This table demonstrates that as the severity of diabetic retinopathy increases, central corneal thickness (CCT) increases, while endothelial cell density (ECD) decreases. Patients with PDR have the highest CCT (609.04 µm) and the lowest ECD (2091.88 cells/mm²). The coefficient of variation (CV) also increases with severity, indicating more variation in endothelial cell size as retinopathy worsens. P-value: <0.001 for both CCT and ECD, showing a strong correlation between retinopathy severity and these corneal parameters.

Table 7: Severity of Diabetic Retinopathy and Coefficient of Variation (CV), Hexagonality of Cells (HEX)

Severity of Diabetic Retinopathy	Mean CV (%)	Mean HEX (%)
No Diabetic Retinopathy	32.91	44.16
Very Mild and Mild NPDR	38.92	40.09
Moderate NPDR	42.98	36.22
Severe and Very Severe NPDR	49.12	32.07
PDR	51.01	30.10
P value	**<0.001**	**<0.001**

As retinopathy severity increases, the CV of endothelial cells increases, and the hexagonality (percentage of hexagonal cells) decreases. Patients with no retinopathy had a mean CV of 32.91% and hexagonality of 44.16%. Patients with PDR had a CV of 51.01% and hexagonality of 30.10%. P-value: <0.001 for both CV and HEX, indicating significant differences between groups.

Table 8: Correlation between HbA1c and CCT

HbA1c Level	Mean CCT (µm)	P value
4 - 5.6	**537.73**	**<0.001**
5.61 - 6.5	**549.82**	
> 6.5	579.24	

This table shows a clear correlation between higher HbA1c levels and increased CCT. Patients with HbA1c levels between 4-5.6 had a mean CCT of 537.73 µm, while those with HbA1c levels greater than 6.5 had a mean CCT of 579.24 µm. P-value: <0.001, showing a significant correlation between HbA1c and CCT.

Table 9: Correlation between ECD and Duration of Diabetes

Duration of Diabetes (Years)	Mean ECD (cells/mm²)	P value
5-10	2362.32	**<0.001**
>10	2140.00	

The ECD decreases with the duration of diabetes. Patients with 5-10 years of diabetes had a mean ECD of 2362.32 cells/mm², while those with more than 10 years of diabetes had a mean ECD of 2140.00 cells/mm². P-value: <0.001, indicating a significant correlation between the duration of diabetes and ECD.

Table 10: Correlation between CCT and Duration of Diabetes

Duration of Diabetes (Years)	Mean CCT (µm)	P value
5-10	549.51	**<0.001**
>10	587.91	

This table shows that patients with more than 10 years of diabetes have a higher mean CCT (587.91 µm) compared to those with 5-10 years of diabetes (549.51 µm). P-value: <0.001, indicating a statistically significant correlation between the duration of diabetes and CCT.

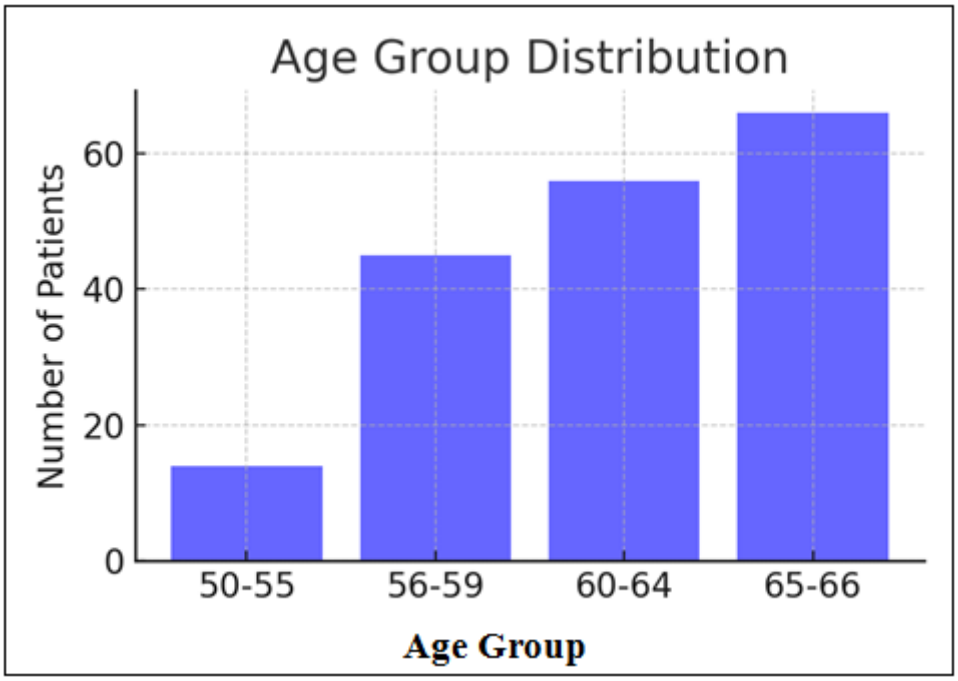

Figure 1: Age Group Distribution

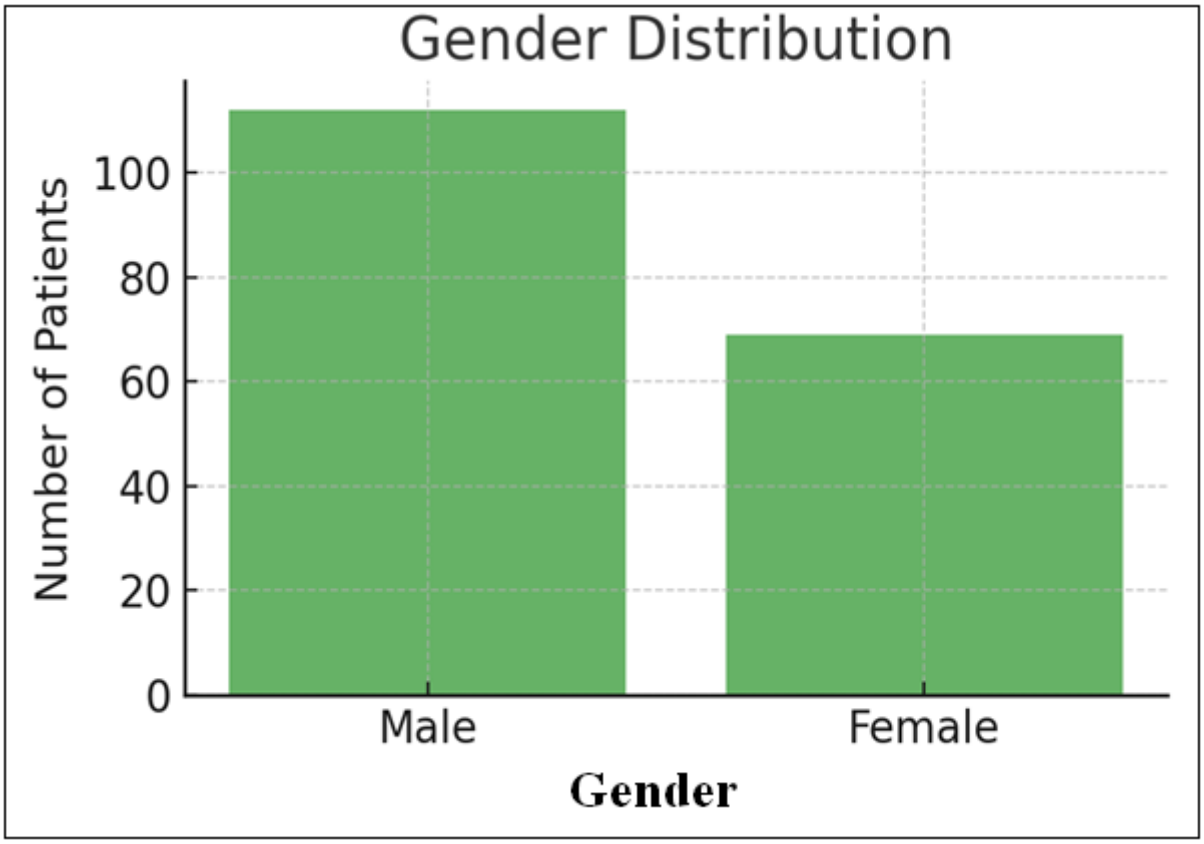

Figure 2: Gender Distribution

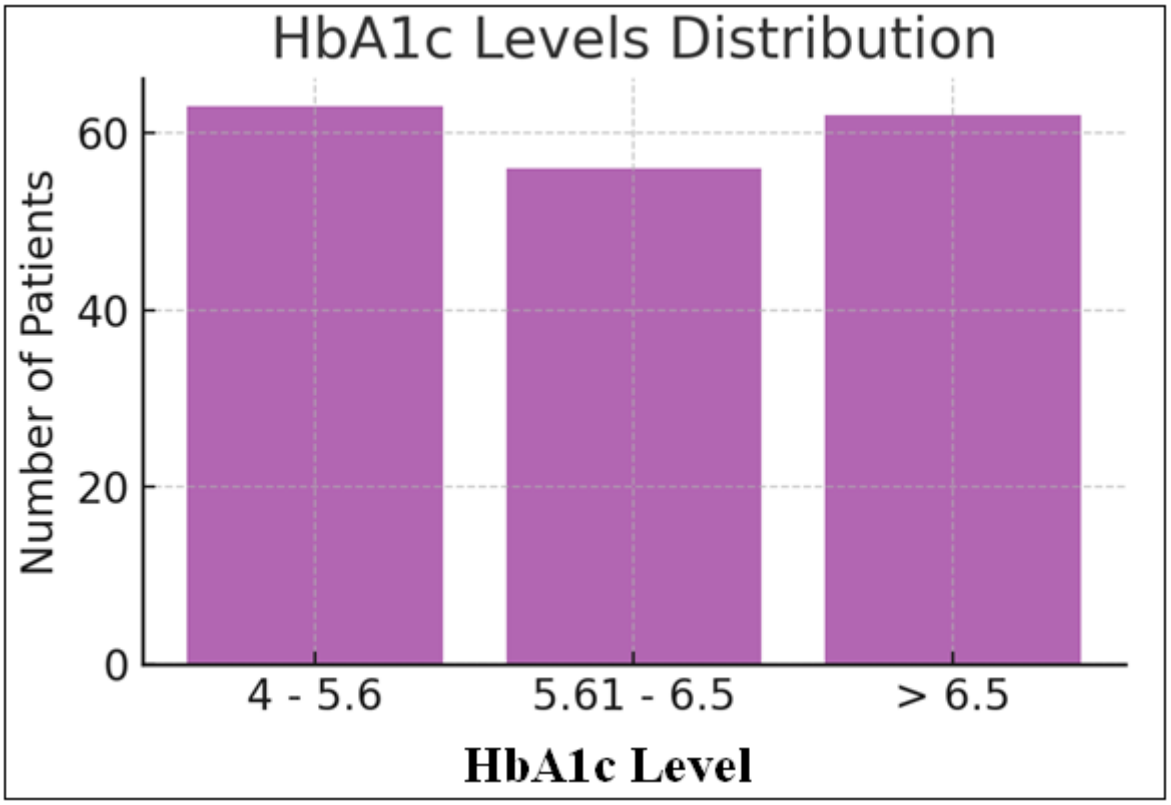

Figure 3: HbA1c Levels Distribution

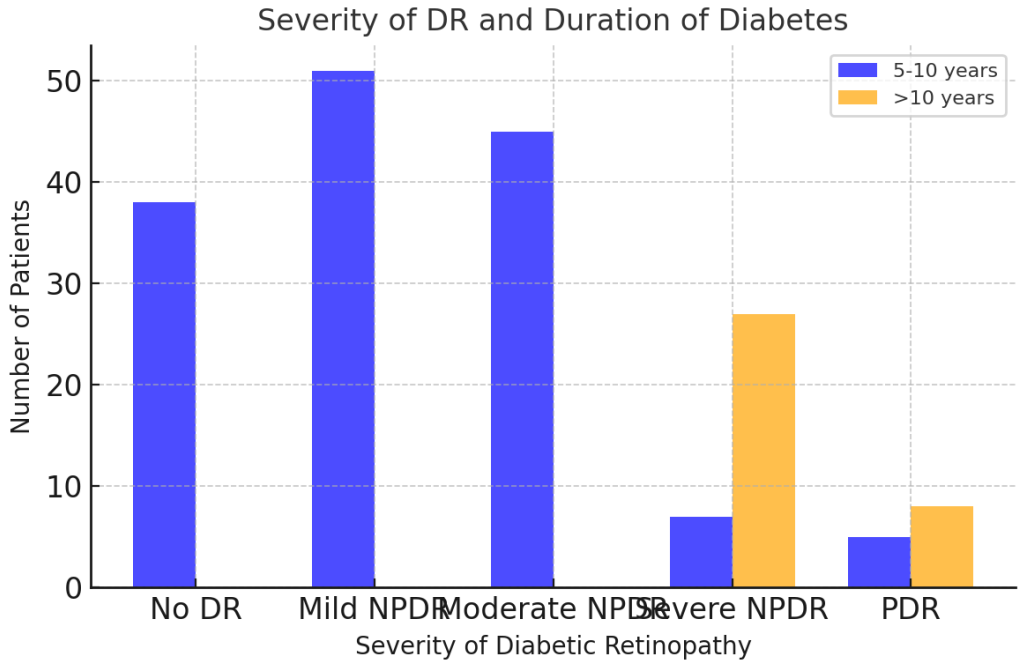

Figure 4: Severity of DR and Duration of Diabetes

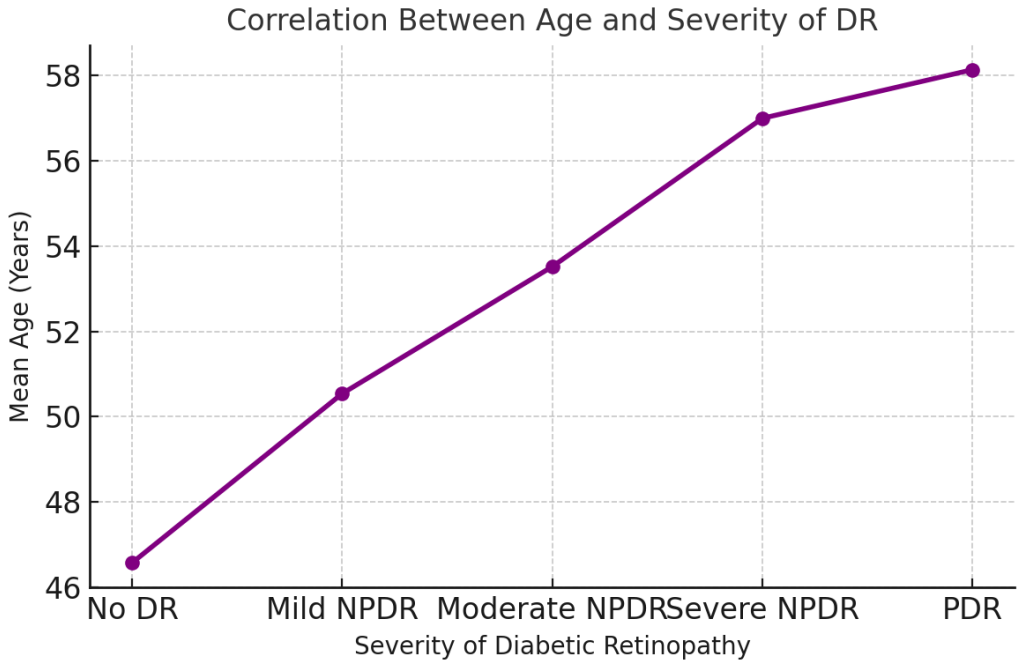

Figure 5: Correlation between Age and Severity of DR

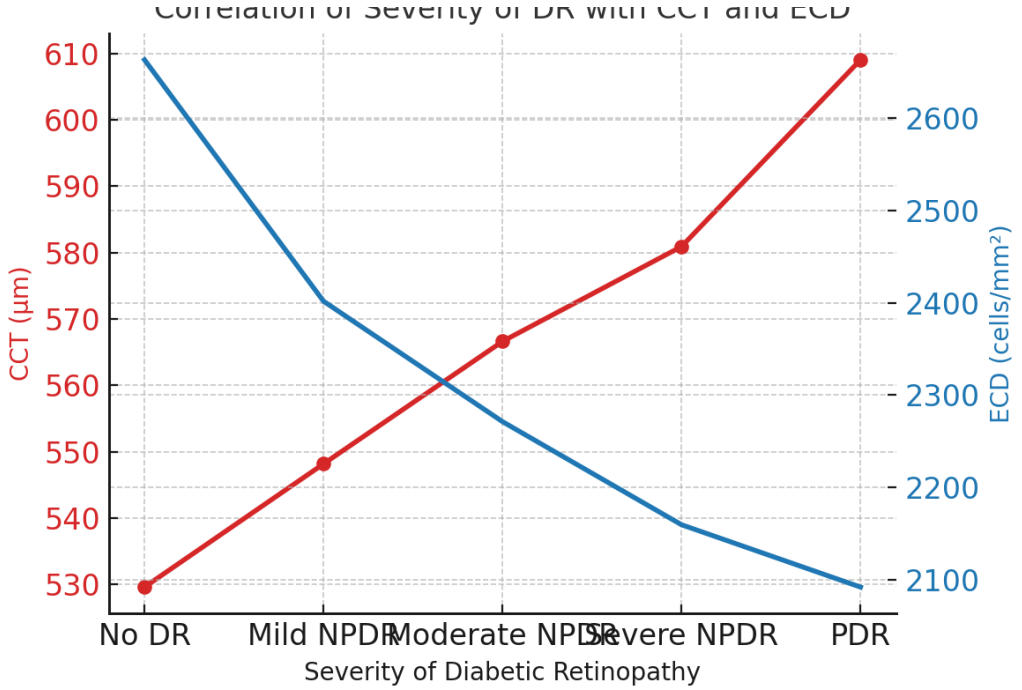

Figure 6: Correlation of Severity of DR with CCT and ECD

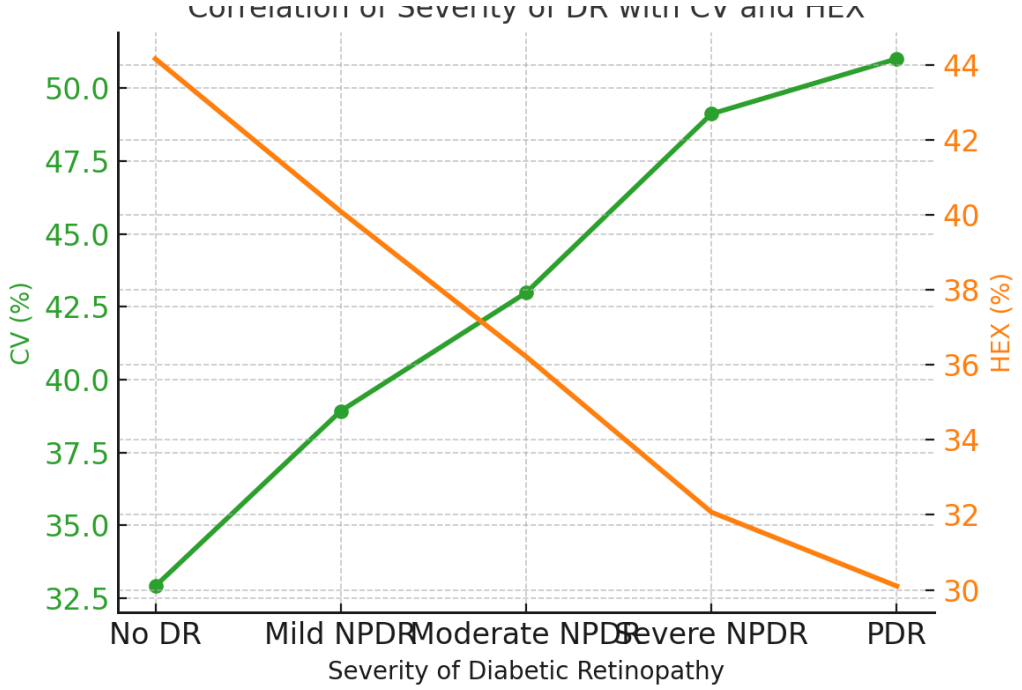

Figure 7: Correlation of Severity of DR with CV and HEX

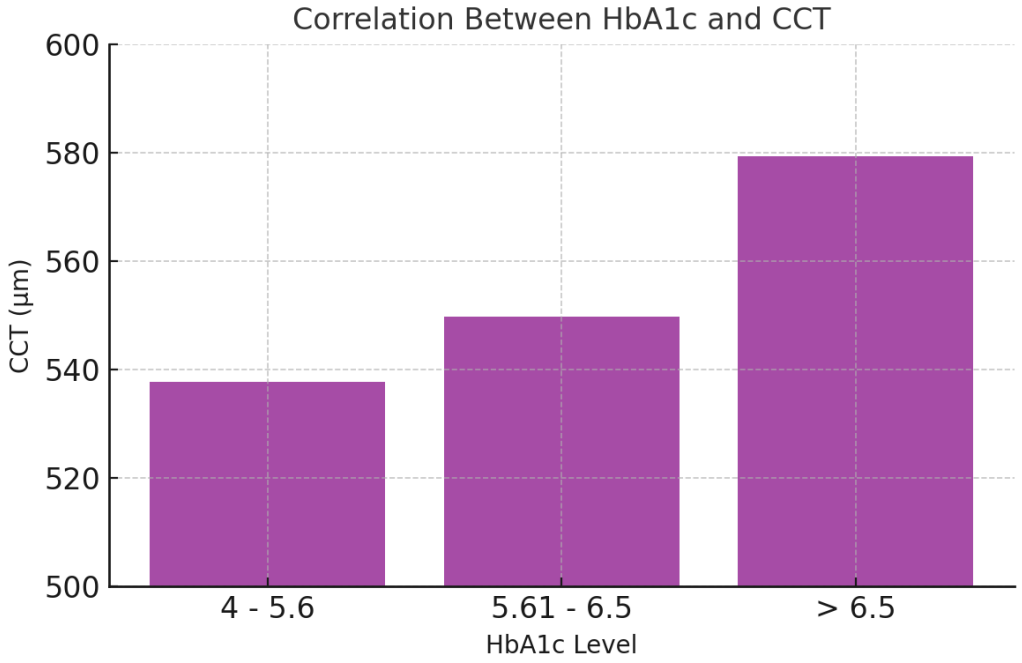

Figure 8: Correlation between HbA1c and CCT

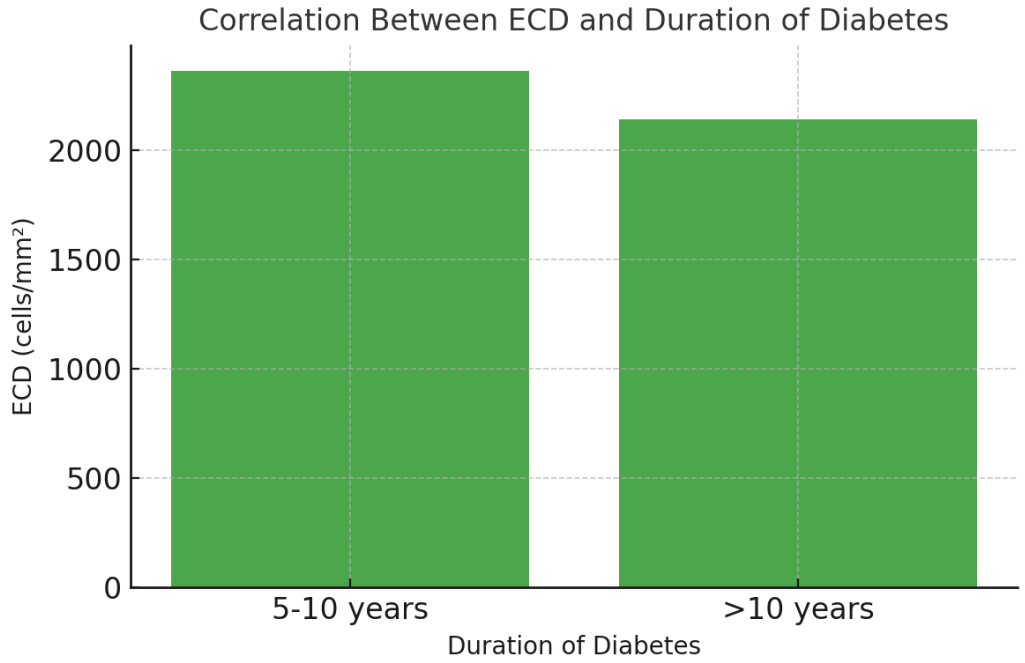

Figure 9: Correlation between ECD and Duration of Diabetes

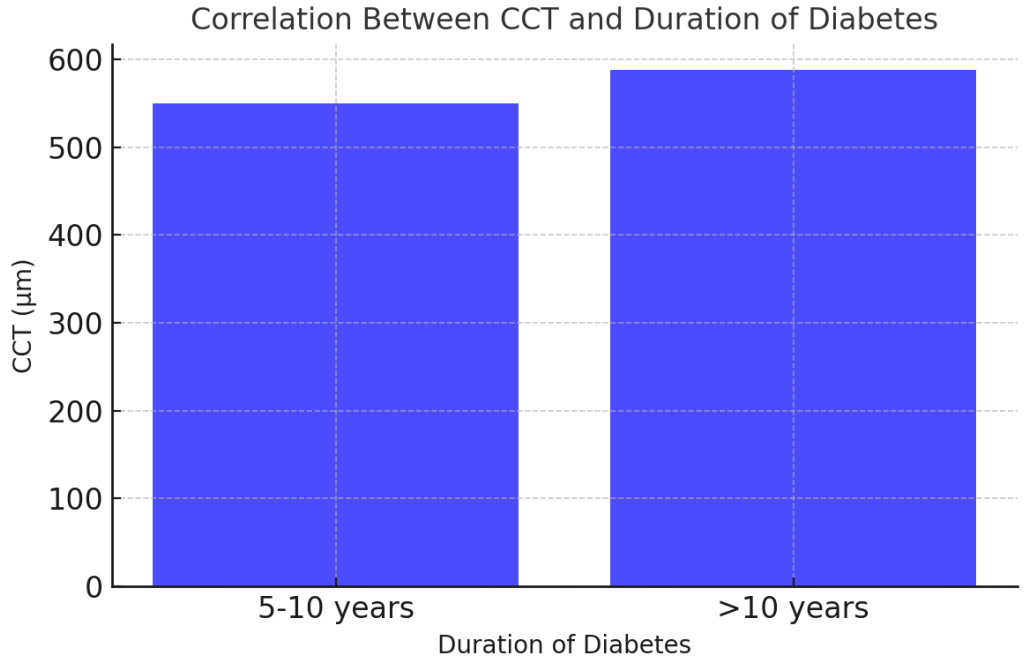

Figure 10: Correlation between CCT and Duration of Diabetes

DISCUSSION

The present study investigated the correlation between HbA1c levels and central corneal thickness (CCT) in patients with type 2 diabetes mellitus using non-contact specular microscopy. Additionally, it evaluated the changes in CCT, endothelial cell density (ECD), coefficient of variation (CV), and hexagonality (HEX) in relation to the severity of diabetic retinopathy (DR).

Our study found a significant correlation between higher HbA1c levels and increased CCT ($p<0.001$). Patients with HbA1c levels greater than 6.5% had a mean CCT of 579.24 µm, compared to 537.73 µm in those with HbA1c levels between 4-5.6%. This finding is consistent with a study by Yazgan*et al.*, which reported a significant negative correlation

between HbA1c and CCT in type 2 diabetic patients (r=-0.398, p<0.001) [11]. Similarly, Kotecha*et al*., found that CCT was significantly higher in diabetic patients with HbA1c levels >7% compared to those with HbA1c <7% (p=0.032) [18].

However, some studies have reported contrasting results. Choo*et al*., found no significant correlation between HbA1c and CCT in a study of 200 type 2 diabetic patients (p=0.869) [13]. Briggs *et al*., also did not find a significant association between HbA1c and CCT in a study of 100 diabetic patients (p=0.54) [19]. These discrepancies may be attributed to differences in studies populations, sample sizes, and measurement techniques.

Our study demonstrated a significant correlation between the duration of diabetes and CCT (p<0.001). Patients with more than 10 years of diabetes had a higher mean CCT (587.91 µm) compared to those with 5-10 years of diabetes (549.51 µm). This finding is in agreement with a study by Suraida*et al*., which reported a significant positive correlation between diabetes duration and CCT (r=0.373, p<0.001) [9]. Storr-Paulsen *et al*., also found that diabetes duration was significantly associated with increased CCT (p=0.01) [14].

We observed a significant decrease in ECD with increasing severity of DR (p<0.001). Patients with proliferative diabetic retinopathy (PDR) had the lowest mean ECD (2091.88 cells/mm²) compared to those with no DR (2663.60 cells/mm²). This finding is consistent with a meta-analysis by He *et al*., which reported a significant reduction in ECD in diabetic patients compared to non-diabetic controls (weighted mean difference: -58.18 cells/mm², p<0.001) [20]. Sudhir*et al*., also found a significant decrease in ECD with increasing severity of DR (p<0.001) [21].

Our study found a significant increase in CV and a decrease in HEX with increasing severity of DR (p<0.001 for both). Patients with PDR had the highest mean CV (51.01%) and the lowest mean HEX (30.10%) compared to those with no DR (CV: 32.91%, HEX: 44.16%). These findings are in line with a study by Módis*et al*., which reported a significant increase in CV and a decrease in HEX in diabetic patients compared to non-diabetic controls (p<0.001 for both) [22]. Similarly, El-Agamy and Alsubaie found a significant increase in CV and a decrease in HEX with increasing severity of DR (p<0.001 for both) [23].

CONCLUSION

In conclusion, this observational study provides valuable insights into the relationship between glycemiccontrol, duration of diabetes, severity of diabetic retinopathy, and corneal parameters in patients with type 2 diabetes mellitus. The study demonstrates a significant correlation between higher HbA1c levels and increased central corneal thickness (CCT) (p<0.001). Patients with HbA1c levels greater than 6.5% had a mean CCT of 579.24 µm, compared to 537.73 µm in those with HbA1c levels between 4-5.6%. Additionally, the duration of diabetes was found to be significantly associated with increased CCT (p<0.001), with patients having more than 10 years of diabetes showing a higher mean CCT (587.91 µm) compared to those with 5-10 years of diabetes (549.51 µm).

Moreover, the study highlights the significant impact of diabetic retinopathy on corneal endothelial health. As the severity of diabetic retinopathy increased, a significant decrease in endothelial cell density (ECD) (p<0.001), increase in coefficient of variation (CV) (p<0.001), and decrease in hexagonality (HEX) (p<0.001) were observed. Patients with proliferative diabetic retinopathy (PDR) had the lowest mean ECD (2091.88 cells/mm²), highest mean CV (51.01%), and lowest mean HEX (30.10%) compared to those with no diabetic retinopathy.

These findings emphasize the importance of maintaining good glycemic control and regular monitoring of corneal health in patients with type 2 diabetes mellitus. The study suggests that non-contact specular microscopy can be a valuable tool for early detection of corneal changes in diabetic patients, enabling timely intervention and prevention of visual impairment. Furthermore, the results underscore the need for increased awareness among healthcare professionals regarding the potential impact of diabetes on corneal health and the necessity for comprehensive eye examinations in diabetic patients.

Future research should focus on longitudinal studies to better understand the progression of corneal changes in diabetic patients over time and to identify potential preventive measures. Additionally, investigating the molecular mechanisms underlying diabetes-induced corneal changes may lead to the development of targeted therapies to preserve corneal health in patients with diabetes.

REFERENCES

1. American Diabetes Association. 2. (2021). Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. *Diabetes Care, 44*(Suppl 1), S15-S33. doi: 10.2337/dc21-S002.
2. International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: International Diabetes Federation, 2021. https://www.diabetesatlas.org.

3. Zheng, Y., Ley, S. H., & Hu, F. B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature reviews endocrinology*, *14*(2), 88-98.doi: 10.1038/nrendo.2017.151.
4. Fowler, M. J. (2008). Microvascular and macrovascular complications of diabetes. *Clinical diabetes*, *26*(2), 77-82.doi: 10.2337/diaclin.26.2.77.
5. Bikbova, G., Oshitari, T., Tawada, A., & Yamamoto, S. (2012). Corneal changes in diabetes mellitus. *Current diabetes reviews*, *8*(4), 294-302.doi: 10.2174/157339912800840479.
6. DelMonte, D. W., & Kim, T. (2011). Anatomy and physiology of the cornea. *Journal of Cataract & Refractive Surgery*, *37*(3), 588-598.doi: 10.1016/j.jcrs.2010.12.037.
7. Joyce, N. C. (2003). Proliferative capacity of the corneal endothelium. *Progress in retinal and eye research*, *22*(3), 359-389.doi: 10.1016/s1350-9462(02)00065-4.
8. Zhao, D., Xin, H., Wei, X., & Liu, X. (2020). Comparison of central corneal thickness in diabetic and non-diabetic patients: a meta-analysis. *Cornea*, *39*(10), 1247-1253. doi: 10.1097/ICO.0000000000002378.
9. Suraida, A. R., Ibrahim, M., &Zunaina, E. (2018). Correlation of the anterior ocular segment biometry with HbA1c level in type 2 diabetes mellitus patients. *PloS one*, *13*(1), e0191134.doi: 10.1371/journal.pone.0191134.
10. Sherwani, S. I., Khan, H. A., Ekhzaimy, A., Masood, A., &Sakharkar, M. K. (2016). Significance of HbA1c test in diagnosis and prognosis of diabetic patients. *Biomarker insights*, *11*, BMI-S38440.doi: 10.4137/BMI.S38440.
11. Yazgan, S., Celik, U., Kaldırım, H., Ayar, O., Elbay, A., Aykut, V., ...&Taş, M. (2014). Evaluation of the relationship between corneal biomechanic and HbA1C levels in type 2 diabetes patients. *Clinical Ophthalmology*, 8, 1549-1553.doi: 10.2147/OPTH.S67984.
12. Choo, M. M., Prakash, K., Samsudin, A., Soong, T., Ramli, N., &Kadir, A. J. (2010). Corneal changes in type II diabetes mellitus in Malaysia. *International journal of ophthalmology*, *3*(3), 234-236. doi: 10.3980/j.issn.2222-3959.2010.03.12.
13. Storr-Paulsen, A., Singh, A., Jeppesen, H., Norregaard, J. C., &Thulesen, J. (2014). Corneal endothelial morphology and central thickness in patients with type II diabetes mellitus. *ActaOphthalmologica*, *92*(2), 158-160.doi: 10.1111/aos.12064.
14. Kotecha, A., Oddone, F., Sinapis, C., Elsheikh, A., Sinapis, D., Sinapis, A., &Garway-Heath, D. F. (2010). Corneal biomechanical characteristics in patients with diabetes mellitus. *Journal of Cataract & Refractive Surgery*, *36*(11), 1822-1828.doi: 10.1016/j.jcrs.2010.08.027.
15. Briggs, S., Osuagwu, U. L., &AlHarthi, E. M. (2016). Manifestations of type 2 diabetes in corneal endothelial cell density, corneal thickness and intraocular pressure. *Journal of Biomedical Research*, *30*(1), 46-51. doi: 10.7555/JBR.29.20140075.
16. He, X., Diakonis, V. F., Alavi, Y., Yesilirmak, N., Waren, D., & Donaldson, K. (2017). Endothelial cell loss in diabetic and nondiabetic eyes after cataract surgery. *Cornea*, *36*(8), 948-951.doi: 10.1097/ICO.0000000000001245.
17. Sudhir, R. R., Raman, R., & Sharma, T. (2012). Changes in the corneal endothelial cell density and morphology in patients with type 2 diabetes mellitus: a population-based study, SankaraNethralaya Diabetic Retinopathy and Molecular Genetics Study (SN-DREAMS, Report 23). *Cornea*, *31*(10), 1119-1122.doi: 10.1097/ICO.0b013e31823f8e00.
18. MódisJr, L., Szalai, E., Kertész, K., Kemény-Beke, Á.,Kettesy, B., & Berta, A. (2010). Evaluation of the corneal endothelium in patients with diabetes mellitus type I and II. *Histology and histopathology*, 25(12), 1531-1537. doi: 10.14670/HH-25.1531.
19. El-Agamy, A., &Alsubaie, S. (2017). Corneal endothelium and central corneal thickness changes in type 2 diabetes mellitus. *Clinical Ophthalmology*, 11, 481-486.doi: 10.2147/OPTH.S126217.
20. He, X., Diakonis, V. F., Alavi, Y., Yesilirmak, N., Waren, D., & Donaldson, K. (2017). Endothelial cell loss in diabetic and nondiabetic eyes after cataract surgery. *Cornea*, *36*(8), 948-951.doi: 10.1097/ICO.0000000000001245.
21. Sudhir, R. R., Raman, R., & Sharma, T. (2012). Changes in the corneal endothelial cell density and morphology in patients with type 2 diabetes mellitus: a population-based study, SankaraNethralaya Diabetic Retinopathy and Molecular Genetics Study (SN-DREAMS, Report 23). *Cornea*, *31*(10), 1119-1122. doi: 10.1097/ICO.0b013e31823f8e00.
22. MódisJr, L., Szalai, E., Kertész, K., Kemény-Beke, Á.,Kettesy, B., & Berta, A. (2010). Evaluation of the corneal endothelium in patients with diabetes mellitus type I and II. *Histology and histopathology*, 25(12), 1531-1537. doi: 10.14670/HH-25.1531.
23. El-Agamy, A., &Alsubaie, S. (2017). Corneal endothelium and central corneal thickness changes in type 2 diabetes mellitus. *ClinOphthalmol*, 11, 481-486. doi: 10.2147/OPTH.S126217.