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Original Research Article

Clinical assessment of corneal alterations in endocrine disorders

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ABSTRACT

Background: Corneal alterations are frequent in many endocrine disorders like Grave's ophthalmopathy and diabetes mellitus. Since early diagnosis of such a change can prevent visual impairment, it presents a challenge to an ophthalmologist.
Aim of the Study: Clinical assessment & significance of corneal alterations in endocrine disorders.
Objective of the Study: 1. To conduct comprehensive assessment of corneal alterations in endocrine disorders. 2. To Identify specific corneal abnormalities in patients with endocrine disorders. 3. To delineate the clinical significance of corneal alterations in endocrine disorders by determining their impact on visual function and guiding therapeutic strategies.
Materials and Methods: This study was a prospective, observational, hospital-based study conducted over a period of two years including 150 patients of different endocrine disorders. Ocular examination included physical examination to check for any pain on ocular movements, ophthalmoplegia, diplopia, or proptosis. Visual acuity was examined by Snellen's chart, anterior segment by slit-lamp, intra-ocular pressure by non-contact tonometer, qualitative measurement of corneal sensation by a cotton-wisp and central corneal thickness was measured by pachymetry. Corneal endothelial cell parameters like endothelial cell density (ECD), coefficient of variation of cell area (CV), percentage of hexagonal cell (HEX) were measured by clinical specular microscope.
Result: The age range was 14 to 82 years with mean age being 48.43±14.2 years. The male to female ratio was 1.34:1. Type-2 diabetes mellitus was the most frequently encountered endocrine disorder (64.7%), followed by hypothyroidism (13.3%). Addison's disease was the least encountered (0.7%). The most severe changes to the cornea, such as chronic epithelial abnormalities, superficial punctate keratopathy, altered corneal sensations, and dry eyes, were observed in patients with type 2 diabetes, followed by Graves's ophthalmopathy and hypothyroidism. Patients with T2DM and T1DM had elevated CCT values, reduced endothelial cell density, abnormally high coefficient of variance and low hexagonal cells.
Conclusion: The present study showed that different corneal alterations can be possible in endocrine disorders. So all endocrine disorders should undergo comprehensive ophthalmological examination to prevent visual impairment.

1. Introduction

Disorders of the endocrine system manifest in the eye through a variety of distinct pathophysiological factors, owing to the hyper or hypo secretion of the endocrine glands. Ocular manifestations are common in various endocrine disorders notably Diabetes mellitus and Graves' disease.[1] Other lesser-known endocrine disorders cause considerable ocular damage; the first step in diagnosing and treating which, is understanding their

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symptoms. Corneal changes are often the most prominent findings that alert eye care practitioners to significant endocrine diseases.[2]

In order to prevent, diagnose, treat, and monitor these manifestations in a timely manner and to significantly lower the morbidity associated with these disorders, including permanent visual impairment, it is imperative to understand the significance of corneal changes and the potential relationship between the changes and the endocrine disease process. This study attempted to investigate the corneal changes in diverse endocrine illnesses in light of the consequences of endocrine disorders on the eye. Early detection of corneal alterations in endocrine disorders like Grave's ophthalmopathy and diabetes mellitus is crucial to prevent visual impairment, necessitating comprehensive ophthalmological examinations for timely intervention and preservation of vision.

2. Materials and Methods

The current study was a hospital-based cross-sectional, observational study conducted over a period of two years from December 2020 to November 2022 at the post-graduate Department of Ophthalmology, Veer Surendra Sai institute of medical sciences and research (VIMSAR), Burla, Odisha. The study aimed at assessing the spectrum of corneal changes associated with different endocrine disorders. The primary objective was to determine the prevalence of various corneal pathologies encountered in the different endocrine disorders and the secondary objective was to assess the possible interventions to preserve vision and prevent complications. Ethical clearance was obtained from the Institutional Ethics Committee of VIMSAR (VIREC), Burla prior to the start of the study. Written informed consent was taken from all the participants before enrolling them into the study. Strict confidentiality and anonymity were maintained over relevant patient information throughout the study. The study was executed in accordance with the principles of ICH-GCP and Declaration of Helsinki.

Patients diagnosed with endocrine disorders visiting the outpatient department of Ophthalmology comprised the study population. Patients of all ages and genders presenting with corneal alternations were included in the study. Patients with systemic problems other than endocrine disorders or those with local pathologies such as keratitis brought on by infection, inflammation, or trauma were excluded from the study. A total of 150 patients who met the inclusion and exclusion criteria were included in the study. A standard clinical proforma was maintained in all cases. Patients of known endocrine disorders were subjected to a detailed history taking, systemic and ocular examination. Ocular examination included physical examination to check for any pain on ocular movements, ophthalmoplegia, diplopia, or proptosis. Visual acuity was examined by Snellen's chart, anterior segment by slit-lamp, intra-ocular pressure by non-contact tonometer, qualitative measurement of corneal sensation by a cotton-wisp and central corneal thickness was measured by pachymetry. Corneal endothelial cell parameters like endothelial cell density (ECD), coefficient of variation of cell area (CV), percentage of hexagonal cell (HEX) were measured by clinical specular microscope. We received assistance with clinical specular microscopy from the Kar Clinic, Bhubaneswar.

Corneal surface integrity was determined by staining the ocular surface with 2% fluorescein sodium and examining under cobalt blue light. Appearance of bright-green staining suggested presence of an epithelial defect. Dry eye evaluation was done by tear break-up time (TBUT) and Schirmer′s test. TBUT of less than 10 seconds was indicative of dry eye i.e. dry eye positive, and equal to or greater than 10 seconds was considered dry eye negative. Similarly, a measurement of less than 10 mm in Schirmer′s test was indicative of dry eye.

The data were entered into Microsoft Excel and analyzed using SPSS v2.1 software. Quantitative variables are expressed as mean±standard deviations (SD) and qualitative variables were expressed as frequency and percentages.

3. Observations and Results

A total of 150 patients were studied. Table 1 displays the baseline characteristics of the study participants. Male patients outnumbered female patients. The minimum age encountered was 14 years and the maximum age was 82. Most of the patients (29.2%) belonged to the age range of 50 to 59 years. The mean age was 48.43±14.27 years. Type-2 diabetes mellitus was the most frequently encountered endocrine disorder (64.7%), followed by hypothyroidism (13.3%). Addison's disease was the least encountered (0.7%). The most common corneal alteration was dry eye (32.6%), followed by corneal sensations (21.3%) and superficial punctate keratopathy (17.3%). The least common corneal alteration was superior limbic keratoconjuctivitis (1.3%).

The diverse corneopathies observed in the numerous endocrine illnesses we met during our study are graphically represented in Figure 1. The most severe changes to the cornea, such as chronic epithelial abnormalities, superficial punctate keratopathy, altered corneal sensations, and dry eyes, were observed in patients with type 2 diabetes, followed by Graves's ophthalmopathy and hypothyroidism. There were no corneopathies associated with hyperparathyroidism, Cushing's syndrome and Addison's disease (Table 2).

The central corneal thickness (in microns) and endothelial cell parameters (endothelial cell density [ECD], coefficient of variance [CV], and hexagonal cells [HEX]) of the study participants in the different endocrine disorders are shown in Table 3. Patients with T2DM and

Table 1: Baseline characteristics of the study participants (N=150)

Variables	Frequency (%)
Age distribution (years)	
10-19	6 (4)
20-29	11 (7.3)
30-39	22 (14.6)
40-49	33 (21.9)
50-59	44 (29.2)
60-69	26 (17.3)
70-79	5 (3.3)
80-90	3 (2)
Gender distribution	
Male	86 (57.3)
Female	64 (42.7)
Prevalence of endocrine diseases	
Type-1 diabetes mellitus	7 (4.7)
Type-2 diabetes mellitus	97 (64.7)
Graves's ophthalmopathy	18 (12)
Hypothyroidism	20 (13.3)
Hyperparathyroidism	3 (2)
Cushing's syndrome	4 (2.7)
Addison's disease	1 (0.7)
Incidence of corneopathies	
Dry eye (DE)	49 (32.6)
Corneal sensations (CS)	32 (21.3)
Superficial punctate keratopathy (SPK)	26 (17.3)
Persistent epithelial defects (PED)	9 (6)
Recurrent corneal erosion (RCE)	7 (4.7)
Corneal ulcers (CU)	6 (4)
Exposure keratopathy (EK)	8 (5.3)
Superior limbic keratoconjuctivitis (SLKC)	2 (1.3)

Table 2: The frequency of different corneopathies in the various endocrine illnesses (N=150)

	DE	CS	SPK	PED	RCE	CU	EK	SLKC
Type-1 DM	1	2	2	1	1	0	0	0
Type-2 DM	31	26	19	8	6	4	0	0
Grave's ophthalmopathy	10	4	0	0	0	2	8	2
Hypothyroidism	7	0	5	0	0	0	0	0
Hyperparathyroidism	0	0	0	0	0	0	0	0
Cushing's syndrome	0	0	0	0	0	0	0	0
Addison's disease	0	0	0	0	0	0	0	0

T1DM had elevated CCT values. Individuals with T2DM and T1DM had reduced endothelial cell density. The patients with T2DM and T1DM had an abnormally high coefficient of variance—more than 40%. Likewise, the proportion of hexagonal cells was also aberrant i.e. less than 60% in patients with T2DM and T1DM.

4. Discussion

This was a cross-sectional study conducted on 150 patients to assess the corneal changes seen in endocrine disorders. The average age of our study population was 48.43±14.27 years. This was similar to average ages found in other studies like Cankurtara et al.[5] (54.9±6.6), Calvo-Maroto et al.[13] (52.2±6.18), Larson et al.[11] (36±12), Zhou M et al.[14] (44.90±12.49) and Ozturk et al.[15] (40.58±1.32). Males outnumbered females in this study, similar to Choo et al. study.[4] T2DM, Grave's disease and hypothyroidism were the most common endocrine disorders encountered in our study. The gender trend observed in these disorders was consistent with findings from earlier investigations. Of the 97 T2DM patients, 67 were male and 30 were female in our study. This was consistent with studies by Calvo-Maroto et al.[13] (T2DM:40, males: 17, females: 23), Cankurtara et al.[5] (T2DM:153, males:76, females:77), Choo et al.[4] (T2DM:100, males:70, females:30). There were 18 patients with Grave's ophthalmopathy, out of which 6 and 12 were

Table 3: Comparison of our study with the previous studies

Study	Endothelial cell density	Coefficient of variance	Hexagonal cells	CCT
Dawood Y.F. et al.[3] DM2	2584.87±259.15 p = 0.017, statistically significant	49.8 ± 4.17, p = 0.019, statistically significant	44.36 ± 9.87 p < 0.001, statistically significant)	581.1 ± 32.4 p < 0.001, statistically significant
Choo M.M et al.[4] DM2	2541.6± 516.4	67.2± 47.2% Higher in diabetics	41.1±19.6	Higher in diabetics but not significant
Cankurtara et al.[5] 2019 DM2	2483 ± 326		54 ± 10	534 ± 34
Durukan et al.[6] 2020 DM2	2295 ± 311		49 ± 10	544 ± 38
Galgauskas et al.[7] 2016 DM2	2722 ± 264		52 ± 11	570 ± 36
Sudhir et al.[8] 2012 DM2	2550 ± 96		49 ± 7	525 ± 35
Anbar et al.[9] 2016 DM1	3142 ±416		50 ± 7	539 ± 30
Fernandes et al. ,[10] 2019 DM1	3040 ± 293	45.2±5.54	NS	525 ± 33
Larsson et al.[11] 1996 DM1	2422 ± 313		59 ± 8	580 ± 50
Keoleian et al. ,[12] 1992 DM1	2383 ± 280		68 ± 8	560 ± 20
Our study, 2022 DM2	2313.13±227.46	48.77±6.59	51.36±6.65	572.8±21.54

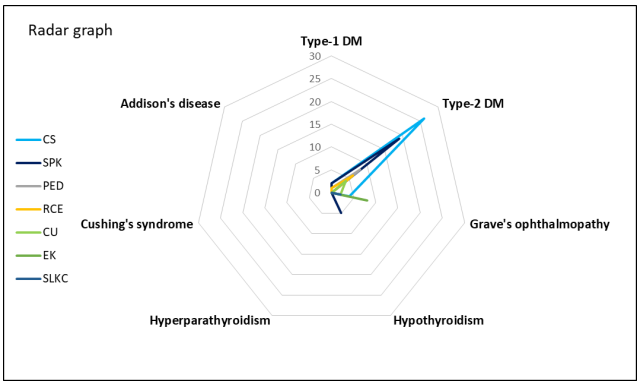

Figure 1: Prevalence of various corneopathies in the different endocrine disorders (N=150)

males and females, respectively. This was comparable to studies by Zhou M et al.[14] (GO: 39, males:18, females: 21) and Edoardo Villani et al.[16] (GO:26, males:8, females:18). In all of the aforementioned investigations, there were more female patients with GO than males. There were 20 hypothyroid individuals in our study, 17 of whom were female and 3 of whom was male. This was consistent with another study by Ozturk et al.,[15] in which 33 individuals with hypothyroidism were found, 32 of them female and 1 male.

According to our research, the prevalence of corneal ulcers was 4.1%, recurrent corneal erosion was 6.2%, and punctate keratopathy was determined to be 19.59% in T2DM. This was comparable to another study by Didenko et al.[17] where the prevalence of corneal ulcer in T2DM was 6.6%, recurrent corneal erosion was 8.2% and punctate keratopathy was 21.3%. In our investigation, we found that 26.9% of T2DM patients had reduced corneal sensations, which was higher than the 12% prevalence found in the study by Naik K et al.[18] In our investigation, we discovered that the prevalence of dry eye was 14.3% in T1DM, 32% in T2DM, 35% in hypothyroidism and highest (55.6%) in GO. Naik k et al.[18] carried out a similar investigation with T1DM and T2DM, wherein dry eye was shown to be more common in T2DM (66 out of 160 cases) than in T1DM (15 out of 160 cases). The prevalence of dry eye in individuals with GO was determined to be 57.6% (15 out of 26) by Achtsidis V et al.[19] In research on individuals with hypothyroidism, Kan et al.[20] discovered that the patients' mean Schirmer and mean TBUT scores were considerably lower than those of the control group.

Our investigation revealed that the mean CCT in T2DM patients was 572.8±21.5μm, which was significantly higher than the normal CCT (540-550 μm). Our findings were comparable with the other studies, by Dawood Y.F. et al.[3] (581±32.4μm) and Galgauskas et al.[7] (570±36μm) which also displayed a significantly high CCT in T2DM. Furthermore, we discovered that the mean CCT was high in T1DM, measuring 571.2± 7.41μm, comparable to a similar research by Larsson et al.[11] wherein the mean CCT was 580±50μm. In our study, the average CCT was 544.9±6.15μm and 537±5.45μm in GO and hypothyroidism, respectively. These were within the normal limits, as found in similar studies by Zhou M et al.[14] and Ozturk et al.[15]

This study revealed a statistically significant decrease in the mean corneal endothelial cell density in patients with T2DM (2313.13±227.46 cells/mm^2). This was comparable to what Durukan et al.[6] (2295±311 cell/mm^2) and Cankurtara et al.[5] (2483±326 cell/mm^2) discovered in their studies with T2DM. In our finding, diabetics had a noticeably higher corneal endothelial cell coefficient of variation (CV). The rise in CV is suggestive of polymegathism, a condition where endothelial cells proliferate to bridge the spaces between neighbouring cells. This was comparable to findings by Choo M.M. et al.[4]

(67.2±47.2%) and Dawood Y.F. et al.[3] (49.8±4.17%). Additionally, our investigation revealed that diabetics had a much lower percentage of hexagonal cells (51.36±6.65%), suggesting the existence of pleomorphism. These outcomes were comparable to those of Sudhir et al.[8] (49±7%) and Galgauskas et al.[7] (52±11%). According to our research, the mean ECD and CV of patients with Graves ophthalmopathy were 2719.2 cells/mm^2 and 34.06%, respectively. Zhou M et al. analogously reported a similar outcome (CV-33.9%, ECD-2696.1)[14] However, our study's hexagonal cell percentage was 66.3 (>60%), which differed from Zhou M et al.'s finding that was 54% (<60%).[14] There's still no apparent explanation for the morphologic alterations in the corneal endothelium occurring in GO. It is plausible to hypothesise that the aqueous humour of the cornea may harbour autoantibodies that target the thyrotropin or insulin-like growth factor receptors expressed by the corneal endothelium, leading to changes in the endothelium as a result of immunoreactivity.

4.1. Clinical significance

Corneal alterations, often observed in endocrine disorders like Grave's ophthalmopathy and diabetes mellitus, represent a significant clinical concern. These alterations can manifest as various abnormalities, including chronic epithelial changes, superficial punctate keratopathy, altered corneal sensations, and dry eyes. Detecting these alterations early is paramount, as they can lead to visual impairment if left untreated. Due to the potential severity of these changes and their impact on vision, ophthalmologists face a challenge in diagnosing and managing corneal alterations associated with endocrine disorders. Therefore, comprehensive ophthalmological examinations are essential for individuals with endocrine disorders to identify and address any corneal abnormalities promptly. By conducting thorough ocular assessments, including visual acuity testing, anterior segment evaluation, and measurement of corneal parameters such as central corneal thickness and endothelial cell density, ophthalmologists can detect corneal alterations early in the course of endocrine disorders. This early detection allows for timely intervention and management strategies aimed at preserving visual function and quality of life for affected individuals.

In summary, recognizing the clinical significance of corneal alterations in endocrine disorders underscores the importance of regular ophthalmological screenings for individuals with these conditions. Early detection and management of corneal abnormalities can help prevent vision loss and improve overall patient outcomes.

5. Conclusion

Many ophthalmic conditions are secondary to endocrine and hormonal imbalances. Long-term poorly controlled hyperglycemia has a notable impact on corneal endothelium (counts, morphology and structure) as well as corneal thickness, necessitating the need to carry out specular microscopy routinely for every diabetic patient. A team-based approach and early initiation of therapy is an important factor in stopping the development of the disease and the increasing risk of persistent ocular changes, including vision impairment.

6. Source of Funding

Nil.

7. Conflict of Interest

None.

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