Original Article

Evaluation of changes in corneal endothelium in chronic kidney disease

Surbhi Kanawa, Kalpna Jain, Vinod Sagar, Dinesh K Yadav

Purpose: Chronic kidney disease (CKD) is an emerging health problem worldwide. In CKD corneal endothelial changes also occur probably due to accumulation of inflammatory cytokines and increased multiple toxic products. The aim of this study was to analyze the effect of CKD on corneal endothelium and correlate the findings with severity of disease with help of noninvasive technique. **Methods:** The study comprised 75 eyes of 75 cases divided into three groups with group A comprising of CKD cases on dialysis, group B of nondialysis CKD cases, and group C of controls. Each group had 25 cases each of either sex and between 15–80 age groups. All patients were investigated for blood urea, serum creatinine, and blood sugar and underwent complete ophthalmic examination of both eyes along with wide-field specular microscopy examination. **Results:** The majority of patients (33.3%) belonged to age range of 61–70 years with male predominance and the most common cause of CKD was found to be diabetes with 17 (34%) cases. We found normal corneal endothelial cell density (ECD) with the mean ECD of 2364.52 ± 397.72 mm^2 in the dialysis group, 2467.8 ± 352.88 mm^2 in nondialysis group, and 2521.68 ± 250.26 mm^2 in the control group of patients. However, we found significant increase in coefficient of variation (CV) with 36 ± 5.8% in dialysis group, 37 ± 4.5% in nondialysis group and 32 ± 0.8% in controls (P = 0.001) and decreased hexagonality (Hx) with 47 ± 7.3% in dialysis group, 46 ± 4.7% in nondialysis group and 51 ± 6.7% in the controls (P = 0.031). This showed increased tendency of pleomorphism and polymegathism in corneal endothelial cells in CKD cases. No correlation was found between blood urea or serum creatinine levels with endothelial parameters in any group. **Conclusion:** CKD causes morphological changes like polymegathism and pleomorphism in corneal endothelium and hence these cases are more vulnerable and special care should be taken before any intraocular surgical procedure.

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Chronic kidney disease (CKD) is an emerging health problem worldwide affecting about 10% of the world`s population.[1] Diabetes and hypertension contribute to about two-third cases of CKD in the world.[2] CKD is irreversible and progressive process that results in end-stage renal disease (ESRD) where patient has to be dependent on renal replacement therapy for survival. Approximately 1,30,000 patients are receiving dialysis and the number might rise to about 232 per million population.[3]

The kidney and retina both develop at the same embryonic stage about fourth to sixth week of gestation; hence, strong correlation is present between kidney and eye diseases.[4] Studies suggest higher prevalence of eye diseases and vision impairment among people with CKD.[5,6] Starting from the anterior segment to posterior segment numerous ocular findings are present in the patients with CKD including refractive changes, dry eye, corneal, and conjunctival epithelial erosions, perilimbal calcium deposits, band keratopathy, intraocular pressure (IOP) fluctuations, posterior subcapsular cataract, ischemic optic neuropathy, choroidal perfusion delay, corneal endothelium alterations, and thickness changes in the central cornea, retinal nerve fiber layer, and choroid.[5] Major mechanisms contributing to CKD and eye diseases are vascular remodeling, inflammation, oxidative stress, endothelial dysfunction, and atherosclerosis. With the help of early ocular screening in these cases, early changes can be detected. The aim of this study was to analyze the effect of CKD on corneal endothelium and correlate the findings with severity of disease with help of noninvasive technique of specular microscopy. We also aimed to estimate difference in corneal changes between Diabetic CKD and CKD due to other factors.

Methods

This was a cross-sectional study conducted from May 2017 to December 2019 at a tertiary care hospital. Prior approval of the institutional ethical committee had been taken. The study comprised three groups of cases and each group had 25 cases of either sex and between 15 and 80 years of age. Group A comprised stage 5 CKD cases who were on dialysis, group B comprised the nondialyzed group of stage 3 and 4 CKD cases, whereas group C comprised the age-matched control. Hemodialysis patients were patients on dialysis therapy with bicarbonate dialysate for at least 3 months, three times a week, for 3–5 hours per session. Cases with a history of ocular surgery or laser therapy, any corneal disorder, trauma history, on any topical medication, and any active or old ocular disease history were excluded from the study. CKD is classified in five stages according to GFR with G3 and G4 are nondialyzed stages (GFR 59–15 mL/min per 1.73 m^2) and G5 is the dialyzed stage (GFR <15 mL/min per 1.73 m^2).[7]

Department of Ophthalmology, S.P. Medical College, PBM Hospital, Bikaner, Rajasthan, India

Correspondence to: Dr. Kalpna Jain, Department of Ophthalmology, S.P. Medical College, PBM Hospital, Bikaner, Rajasthan - 334 001, India. E-mail: kalpnadaga@gmail.com

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Informed consent was obtained from each participant. Complete medical history with dialysis history was obtained. They were also investigated for complete blood profile, blood urea, serum creatinine, and blood sugar levels. In dialysis cases, the blood investigations were retrieved before dialysis. After enrolment a complete ophthalmic examination of both eyes was carried out and were examined for corneal Endothelial cell density, coefficient of variation (CV%), percentage of hexagonality (Hx%), central corneal thickness (CCT), average size of cells (Avg), with a noncontact type (TOPCON SP 300P) Specular microscope which uses Topcon Cell Count Software to compute cell counts. In the dialysis group, the ophthalmic examination was done 30 minutes prior to dialysis. Average reading from 3 images was taken for all the parameters and the eye with the worst readings was selected.

Statistical analysis

Data analysis was done by using SPSS (Statistical Package for Social Sciences) version 21.0. According to the power analysis, at least 25 participants were required in each group. Analysis of variance (ANOVA) test was used to compare the CCT, CV, ECD, and % Hx in control, dialyzed, and nondialyzed groups. Pearson correlation coefficient and R^2 were calculated with respect to serum urea and serum creatinine to assess the influence on endothelial parameters. A value of $P < 0.05$ was considered statistically significant.

Results

The mean age of patients in the dialyzed, nondialyzed, and control groups was 52.36 ± 17.1 years (range, 15–80 years), 55.2 ± 11.6 years (range, 35–80 years), and 56.68 ± 12.53 years (range, 18–81 years), respectively. A total of 25 (33.3%) patients belonged to age range of 61–70 years which is the age group prone to systemic disease [Table 1]. We also observed male predominance in CKD patients with 18 (72%) males in dialysis group and 13 (52%) in nondialysis group.

Most common etiological cause of CKD in our observation was diabetes with 17 (34%) cases and followed by hypertension with 13 (26%) of all the patients. Other etiological causes found were Autosomal Dominant Polycystic Kidney Disease (ADPKD), chronic glomerulo-nephritis, and other unidentified causes.

When we compared all corneal endothelial parameters we found no significant difference in ECD in all three groups ($P = 0.25$) using ANOVA test; however, CV which is sign of pleomorphism showed significant difference in between the three groups ($P = 0.001$). Hexagonality which is a measure of polymegathism was found to be decreased in the patients with CKD ($P = 0.031$). Average cell size in various groups was found to be significantly raised ($P = 0.0001$) [Fig. 1] in CKD cases. However, central corneal thickness was found not to be significantly affected ($P = 0.521$) [Table 2 and Fig. 2]. The duration of dialysis also influenced on corneal endothelial cell parameters and we found significant difference ($P = 0.015$) in the central corneal thickness with the duration of dialysis [Table 3].

Table 1: Age-wise distribution of study population

AGE (years)	Group A		Group B		Group C		Total	
	No.	%	No.	%	No.	%	No.	%
<20	2	8.0	0	-	1	4.0	3	4.0
21-30	1	4.0	0	-	0	-	1	1.3
31-40	4	16.0	6	24.0	1	4.0	11	14.6
41-50	5	20.0	3	12.0	5	20.0	13	17.3
51-60	4	16.0	7	28.0	7	28.0	18	24.0
61-70	7	28.0	8	32.0	10	40.0	25	33.3
>70	2	8.0	1	4.0	1	4.0	4	5.3
Total	25	100.0	25	100.0	25	100.0	75	100.0

The mean blood urea in dialysis group was found to be 137 mg/dL and in nondialysis group 75 mg/dL. We however could not find any strong correlation between Blood Urea and any corneal endothelial parameter [Table 4]. We also observed similar results of poor correlation between serum creatinine and corneal endothelial parameters.

Many studies have already proven anatomical changes in corneal endothelium in diabetic cases. Here we have attempted to understand if any superlative effect of kidney disease on corneal endothelial cell parameters in both diabetic CKD and nondiabetic CKD cases occurs. The Diabetic CKD showed marked decrease in endothelial cell density compared to other nondiabetic CKD cases. Similarly hexagonality and CCT are also noted to be lower in Diabetic cases, whereas CV was higher in Diabetic CKD showing more pleomorphic tendency in Diabetes [Table 5].

Discussion

CKD, also known as chronic renal disease, is a progressive loss of renal function over a period of months or years. Correlation between eye and kidney started in mid nineteenth century when embryogenic correlation between both was started and many similarities were found. Many studies have already shown its association with major eye diseases such as age related macular degeneration, diabetic retinopathy, glaucoma and cataract which cause high chances of visual impairment along with marked corneal and conjunctival calcification deposition.[6,8-10]

In our study we assessed the corneal endothelial cell changes in CKD. We found that the ECD ranged between 1533 and 3191 mm^2 in dialysis group, 1502 and 3035 mm^2 in nondialysis group and between 2108 and 3188 mm^2 control groups. These parameters even though were found to be nonsignificant showed that cell density varied markedly in kidney disease cases compared to controls. However in studies by Sati *et al*.[11] and Diaz *et al*.[12] they found lower cell density in the patients undergoing dialysis, than those not undergoing dialysis.

We found significant difference in the CV, hexagonality and average cell size between the 3 groups in our observation signifying polymegathism and pleopmoprhism in these cells. The results were similar with observation of Ohguro *et al*. who also noticed marked polymegathism and pleomorphism in corneal endothelium of CKD cases after negating age factor.[13] These results showed that despite normal endothelial cell density, there is a chronic insult on the corneal endothelium leading to cellular alternations causing polymegathism and pleomorphism. Probably increased toxin levels which get accumulated in aqueous humor may have a toxic effect on the corneal endothelial cells, causing morphological changes in them to combat this insult. These morphological changes can be attributed to increased aqueous urea levels and markedly increased oxidized glutathione levels in the aqueous humor in patients with CKD that may cause stress to the cells. Kim *et al*. reported that due to continuous osmotic stress like in diabetes and age, endothelial cells undergo alteration with irregular F-actin fibers and hence subsequently lead to polymegathism to maintain cell volume regulation.[14] A similar mechanism can be hypothesized for CKD as also there is deranged equilibrium leading to these changes.

Table 2: Comparison of endothelial parameters among various groups

Parameter	Dialysis (Group A)			Nondialysis (Group B)			Control (Group C)			*P*
	Median	SD	Range	Median	SD	Range	Median	SD	Range	
ECD, cells/mm^2	2289	397.72	1533-3191	2479	352.88	1502-3035	2488	250.63	2108-3188	0.25
CV, %	35	5.8	25-56	36	4.5	31-48	31	0.8	25-42	0.001**
Hx, %	48	7.3	29-59	46	4.7	37-56	50	6.7	40-63	0.031*
Avg, um2	419	75.46	318-652	400	77.01	329-666	357	20.89	341-421	0.0001**
CCT, um	502	34.37	438-559	506	44.57	442-612	512	24.77	460-556	0.521

Table 3: Influence of duration of dialysis on endothelial parameters

Parameter	<1 year (*n*=15)		1-3 years (*n*=5)		>3 years (*n*=5)		*P*
	Mean	SD	Mean	SD	Mean	SD	
ECD, cells/mm^2	2373.2	419.76	2205.6	280.50	2497.4	447.01	0.388
CV, %	37%	0.06	36%	0.055	35%	0.065	0.866
Hx, %	47%	0.078	47%	0.067	48%	0.079	0.671
Avg, µm^2	421.4	89.21	447.2	72.70	423	19.45	0.441
CCT, µm	514	34.90	486	39.57	490.2	15.59	0.015*

Table 4: Linear correlation between mean blood urea and endothelial parameters in both dialysis and nondialysis group

Various parameters	Blood urea	
	Group A	Group B
ECD (cells/mm^2)		
Pearson correlation coefficient (*r*)	0.15	0.14
CV (%)		
Pearson correlation coefficient (*r*)	0.076	-0.15
Hx (%)		
Pearson correlation coefficient (*r*)	0.24	-0.159
Avg (um^2)		
Pearson correlation coefficient (*r*)	-0.16	-0.08
CCT (um)		
Pearson correlation coefficient (*r*)	-0.04	0.28

Table 5: Endothelial parameters in diabetic cases and other CKD cases in dialysis and nondialysis group

Parameter	DM II		Other causes	
	Group A	Group B	Group A	Group B
ECD, cells/mm^2	2244.83	2302	2402.32	2598
CV, %	39%	39%	36%	35%
Hx, %	43%	46%	49%	46%
Avg, µm^2	425.33	436.72	427.37	372.43
CCT, µm	488.17	510.18	508.53	518.35

We observed increased central corneal thickness in patients who have recently been diagnosed and started on dialysis than those who have been on dialysis since long time. However, patients with prolonged disease showed thinner cornea, suggesting they have undergone adaptation changes. Another study by Elbay *et al*. and Chen *et al*. also did not find any significant difference in CCT after hemodialysis.[15,16] We observed the mean CCT in CKD cases to be 509.2 ± 39.47 um and in controls to be 511.8 ± 24.77 µm, which was similar to a study conducted in Chennai on 6574 healthy subjects, which reported mean CCT for the population to be 511.4 ± 33.5 µm.[17] This observation shows the propensity towards thinner corneas in Indian population.

In terms of endothelial parameters, we failed to find any strong relationship between blood urea and endothelial parameters. This observation of ours is in contrary to the observation by Sati *et al*. who noted the positive correlation between blood urea and corneal endothelial parameters.[11] But even though we did not find any correlation between blood urea or serum creatinine we are not neglecting the thought of its toxic effect on the corneal endothelium. In CKD there is a rise in inflammatory markers along with hyperuricemia which is known to induce oxidative stress and inflammatory response, thus reducing nitric oxide release and hence it can lead to endothelial dysfunction.[18]

We also observed high prevalence of diabetes with 17 out of 50 (34%) being responsible for causing CKD, whereas Dahal *et al*.[19] found commonest cause of CKD to be HTN in 123 (41%) and diabetes in 98 (32.6%) out of 300 cases. We also found reduced ECD and Hexagonality in diabetic CKD cases as compared to nondiabetics, whereas CV was increased in comparison to nondiabetic patients with CKD. These data show that Diabetes which is a known major risk factor for causing endothelial cell damage with renal failure causes a superadded toxic effect on the corneal endothelial cells. However, studies by Parekh *et al*.[20] and Inoue *et al*.[21] also could not establish relationship between these changes and the systemic factors.

We conclude that in CKD cases the corneal endothelium is under continuous stress, causing morphological changes like polymegathism, pleomorphism to occur to combat this toxic external insult. These cases are vulnerable and special care should be taken before any intraocular surgical procedure. We also observed patients undergoing dialysis have more significant endothelial alterations when compared with nondialyzed group. Even more consideration should be given to CKD cases secondary to diabetes. An appropriate ocular examination protocol should also be established for patients

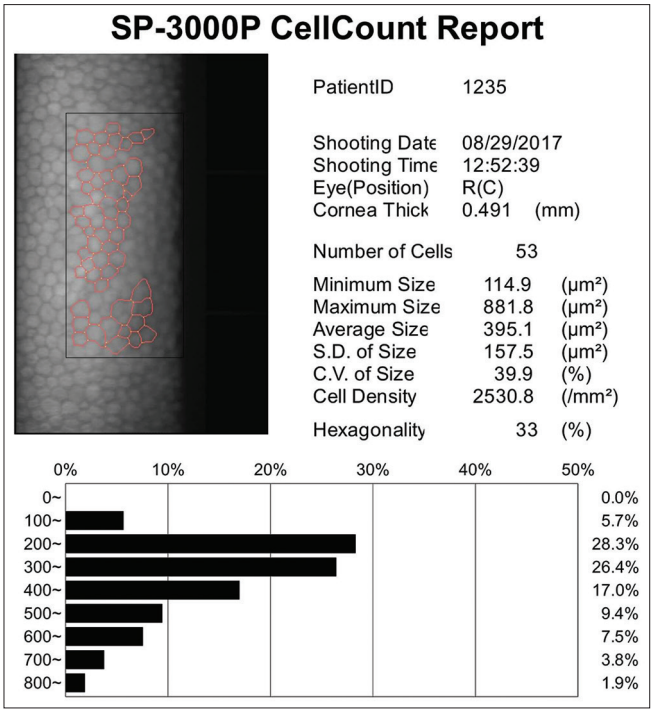

Figure 1: Specular microscopy image of CKD case

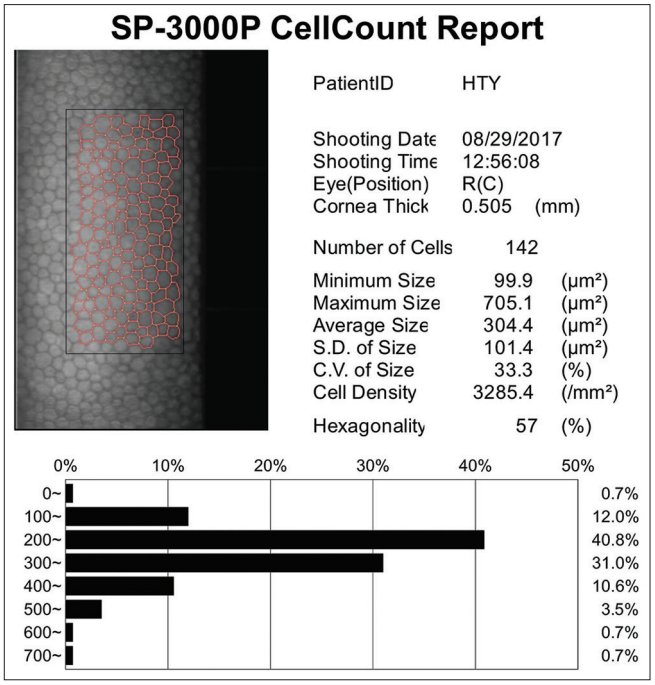

Figure 2: Specular microscopy image of control case

with CKD as they too suffer from many ocular morbidities. We however need more research in understanding which toxins play a major role in causing these changes. Our study is a cross-sectional study and hence further research in larger patient series and follow-ups is needed for better evaluation.

Conclusion

CKD causes morphological changes in corneal endothelium such as polymegathism and pleomorphism, and hence such patients may be relatively more vulnerable to endothelial decompensation. This warrants special care in patients with CKD when they undergo an intraocular surgical procedure.

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Conflicts of interest

There are no conflicts of interest.

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