



Ocular Status with Chronic Kidney Disease- a Hospital Based Two Year Study on 150 Cases

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Abstract

Background: Chronic Kidney Disease (CKD) is a growing public health problem affecting millions of people worldwide. Along with its well-known systemic effects, CKD has been associated with various ocular abnormalities, including uveitis, macular edema, and retinal vascular changes. Early detection and management of these ocular complications can prevent significant visual loss and improve the quality of life of patients with CKD. This highlights the importance of regular ophthalmic examinations as part of the comprehensive management of CKD. The aim of this study was to evaluate the ocular status of chronic kidney disease. **Material & Methods:** This was an observational study. The present study was conducted on 150 Patients attending the Department of Ophthalmology at Dr. Sirajul Islam Medical College and Hospital Ltd, Dhaka, Bangladesh. The duration of the study was 2 years. All collected data was entered in MS Excel and Statistical analysis was done using the SPSS-24 version. **Results:** The study analyzed a population between the ages of 40-59 years, with a slight majority of women (52.67%) and moderate CKD (64.00%). The most common cause of CKD in the population was hypertension and diabetes (52.00%). 66.67% of 300 eyes had good vision (6/18 or better), while the remainder had impaired or legally blind vision (increasing as the severity of CKD increases). Ocular anterior segment findings showed that lid oedema and conjunctival pallor were present in 3.5% and 56.9% of the eyes, respectively. Dry eyes and cataract were present in 5.6% and 11.1% of the eyes, respectively. Hypertensive retinopathy was present in 48.00% of eyes in the moderate CKD group, and diabetic retinopathy was present in 32.00% of eyes in the severe and end-stage CKD groups. Maculopathy and vitreous hemorrhage were present in 12.67% and 6.33% of eyes in the end-stage CKD group. Of the 100 eyes with poor or blind visual acuity, 24 (24%) were affected by Maculopathy and 21 (21%) by Cystoid Macular Edema. The causes of visual impairment were also listed with their corresponding percentage. **Conclusion:** In CRF patients, eye exams can detect ocular problems. Early treatment prevents negative outcomes and those with a history of abnormal renal function need close monitoring due to increased risk of vision loss. Awareness of ocular complications is important, as well as thorough eye exams and control of diabetes and hypertension for maintaining eye health.

Keywords:- Chronic kidney disease (CKD); Ocular pathology; Renal function.



INTRODUCTION

The eye and kidney share substantial structure developmental, physiological and pathogenic pathways, suggesting that many kidney and ocular diseases may be interlinked. The extensive vascular network found in the glomerulus and choroid are structurally very similar. Chronic Kidney Disease (CKD) is becoming a global public health issue, impacting 10-16% of the adult population in Asia, Australia, Europe, and the United States.^[1] It has been linked to various chronic conditions, including cardiovascular disorders, cancers, and cognitive characteristics. Recent studies have revealed various ocular fundus pathologies related to CKD, such as retinal microvascular abnormalities, age-related macular degeneration, and increased intraocular pressure.^[2] A recent study of 1904 CKD patients in the United States found that the prevalence of ocular fundus pathology among CKD patients was as high as 45%, highlighting the need for regular eye examinations in these patients. The occurrence of eye pathology varies among races, reflecting the effects of genetic and socioeconomic differences.^[3,4] Chronic Renal Failure (CRF) is an irreversible and progressive condition that leads to End-Stage Renal Disease (ESRD), where the patient must be put on renal replacement therapy to survive. Richard Bright was the first to link renal disease and blindness in 1836.^[5] It was later discovered that uremic retinitis was a manifestation of hypertension (HTN). The deterioration of eyesight can be attributed to worsening hypertensive or diabetic retinopathy, ischemic optic neuropathy, central retinal vein occlusion, and cortical blindness. By the time the patient reaches ESRD, 80.0% of patients will have

developed secondary HTN.^[6] Ocular morbidity can also be directly due to HTN, uremia, and anemia, or related to the causes of renal failure. Some effects are due to hemodialysis. Important ocular findings associated with renal insufficiency include lid edema, conjunctival pallor, and xanthelasma, which is linked to elevated serum lipids.^[7] Corneal and conjunctival calcification may also occur due to secondary hyperparathyroidism. Inflammatory reactions of the conjunctiva and episclera can be triggered by a sudden rise in serum calcium. Conjunctival degenerative changes, such as pinguecula, are commonly seen in CRF. Goblet cell density is reduced.^[8] Recurrent subconjunctival hemorrhage can occur due to sclerosed conjunctival vessels secondary to HTN. Rubeosis iridis and neovascular glaucoma are manifestations of posterior segment pathology. Rising intracellular calcium concentrations may contribute to early cataract formation and calcium deposition in the lens.

MATERIAL AND METHODS

This study was an observational study conducted on 150 patients, both male and female, at the Department of Ophthalmology in Dr. Sirajul Islam Medical College & Hospital, Dhaka, Bangladesh. The study took place from January 2021 to December 2022, and the primary decision-makers were the medical ophthalmologist and physician. Patients made their own treatment choices after a full discussion with the multidisciplinary team, which included the medical ophthalmologist and physician. The ocular examination was performed in the ophthalmology department and involved recording the patient's history and best-corrected visual acuity, measuring

intraocular pressure, and conducting a detailed examination of the anterior and posterior segments. Pupils were dilated for indirect ophthalmoscopy with a 20-diopter lens and the anterior segment was examined using a slit lamp with 90 diopter lenses. Hypertensive retinopathy was graded using the Keith and Wagner classification and diabetic and macular edema were classified based on the Early Treatment Diabetic Retinopathy Study (ETDRS). Additional investigations, such as color fundus photography, optical coherence tomography, OCT angiography, Goldmann perimetry, and Schirmer test, were performed as needed. Data were collected from patient's medical records and radiographs and were analyzed using Statistical Packages for Social Sciences (SPSS-24) through a window-based computer software program.

RESULTS

The majority of the population is between 50-59 years old, accounting for 35.33% of the sample. The second largest age group is those between 40-49 years old, representing 21.33% of the population. In terms of gender, the population is slightly more female (52.67%) than male (47.33%). When it comes to CKD grading, the majority of the population (64.00%) has

moderate CKD, followed by those with severe CKD (24.00%), while the smallest group has end-stage renal disease (12.00%).

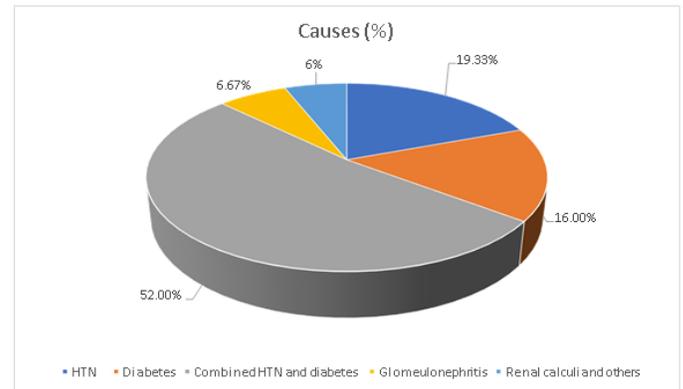


Figure 1: Distribution of participants by cause of CKD

[Figure 1] demonstrated the Causes of CKD of the study population. The results indicate that the most common cause of chronic kidney disease in this population is combined hypertension and diabetes, accounting for 52.00% (78 individuals) of the cases. This is followed by hypertension alone, which represents 19.33% (29 individuals) of the cases. Diabetes alone was found to be the cause in 16.00% (24 individuals) of the cases. The least common causes of chronic kidney disease in this population were glomerulonephritis (6.67% or 10 individuals) and renal calculi and other factors (6.00% or 9 individuals).

Table 1: Distribution of participants by baseline characteristics (n=150).

Variables	n	%
Age Group		
20-29	15	10.00%
30-39	23	15.33%
40-49	32	21.33%
50-59	53	35.33%
≥60	27	18.00%
Gender		



Male	71	47.33%
Female	79	52.67%
	CKD Grading	
Moderate	96	64.00%
Severe	36	24.00%
End Stage Renal Disease	18	12.00%

Table 2: Best corrected visual acuity in the eyes among different stages of chronic kidney disease.

Stages of CKD Visual acuity	Moderate	Severe	End-Stage Renal Disease	total eyes n=300 n, (%)
Good vision \geq 6/18	94.00%	6.00%	-	200, (66.67%)
Impaired vision 6/60 – 6/24	6.90%	93.10%		58, (19.33%)
Legally blind <6/60	-	14.29%	85.71%	42, (14.00%)

[Table 2] demonstrated the Best corrected visual acuity in the eyes among different stages of chronic kidney disease. The table shows that the majority (66.67%) of the total 300 eyes had good vision, with a visual acuity of 6/18 or better. 19.33% of the participants had impaired vision, with a visual acuity between 6/60 and 6/24. The smallest group (14.00%) of participants had legally blind vision, with a visual acuity less than 6/60. The table also shows that as the severity of the CKD increases, the proportion of participants with impaired or legally blind vision also increases.

Table 3: Ocular anterior segment findings in the eyes among different stages of chronic kidney disease.

Stages of CKD ocular anterior segment findings	Moderate	Severe	End-Stage Renal Disease	% of total eyes	P value
Lid oedema	20.0%	40%	40%	3.5%	0.0001
Conjunctival pallor	63.30%	24.40%	7.30%	56.9%	0.023
Pinguecula	31.40%	42.90%	25.70%	12.2%	0.015
Corneal calcification	-	50.0%	50.0%	1.4%	0.001
Dry eyes	25.0%	37.50%	37.50%	5.6%	0.003
Cataract	12.5%	46.90%	40.60%	11.1%	0.0001
Glaucoma	25.0%	35.0%	35.0%	5.7%	0.0001
Normal	55%	-	-	19.1%	0.0001

[Table 3] demonstrated the Ocular anterior segment findings in the eyes among different stages of chronic kidney disease. The findings show that lid oedema was present in 3.5% of the eyes and was more frequent in the severe and end-stage CKD groups, with a P value of 0.0001. Conjunctival pallor was present in 56.9% of the eyes, with a higher frequency in the moderate CKD group and a lower frequency in the end-stage CKD group. This finding had a P value of 0.023. Pinguecula was present in 12.2% of the eyes, with a higher frequency in the moderate and severe CKD groups and a P value of 0.015. Corneal calcification was present in 1.4% of the eyes and was more frequent in the end-stage

CKD group. This finding had a P value of 0.001. Dry eyes were present in 5.6% of the eyes, with a similar frequency in the moderate, severe, and end-stage CKD groups. This finding had a P value of 0.003. Cataract was present in 11.1% of the eyes, with a higher frequency in the severe and end-stage CKD groups. This finding had a P value of 0.0001. Glaucoma was present in 5.7% of the eyes, with a similar frequency in the moderate, severe, and end-stage CKD groups. This finding had a P value of 0.0001. Normal findings were present in 19.1% of the eyes and were only present in the moderate CKD group. This finding had a P value of 0.0001.

Table 4: Ocular posterior segment findings in the eyes among different stages of chronic kidney disease.

Stages of CKD	Moderate	Severe	End-Stage Renal Disease	% of total eyes	P value
Ocular posterior segment findings					
HR	45.14%	31.25%	23.61%	48.00%	0.0001
DR	25.00%	39.58%	35.42%	32.00%	0.0001
Maculopathy		71.05%	28.95%	12.67%	0.0001
VH		52.63%	47.37%	6.33%	0.0001
Tractional retinal detachment		50.00%	50.00%	0.67%	0.0046
branch retinal vein occlusions		100.00%		0.33%	0.372

[Table 4] demonstrated the Ocular posterior segment findings in the eyes among different stages of chronic kidney disease. The findings show that Hypertensive retinopathy (HR) was present in 48.00% of the eyes and was more frequent in the moderate CKD group and less frequent in the end-stage CKD group. This finding had a P value of 0.0001. Diabetic retinopathy (DR) was present in 32.00% of the eyes, with a higher frequency in the severe and end-stage CKD groups and a P value of 0.0001. Maculopathy was present in 12.67% of the eyes and was more frequent in the end-stage CKD group. This finding had a P value of 0.0001. Vitreous hemorrhage (VH) was present in 6.33% of the eyes and was more frequent in the end-stage CKD group. This finding had a P value of 0.0001. Tractional retinal detachment was present in 0.67% of the eyes and was only present in the end-stage CKD group. This finding had a P value of 0.0046. Branch retinal vein occlusions were present in 0.33% of the eyes and were only present in the severe CKD group. This finding had a P value of 0.372.

Table 5: Causes of visual impairment in chronic kidney disease patients (n=100)

Causes of visual impairment	Number of eyes		% of the total eyes
	n	%	
Maculopathy	24	24.00%	8.00%
Cystoid Macular Edema (CME)	21	21.00%	7.00%
Non-exudative (Dry) age-related Macular degeneration (ARMD)	17	17.00%	5.67%
Exudative ARMD	11	11.00%	3.67%
Central retinal vein occlusion (CRVO)	9	9.00%	3.00%
Epiretinal membrane (ERM)	7	7.00%	2.33%



PDR	6	6.00%	2.00%
Glaucoma	4	4.00%	1.33%
Cataract	1	1.00%	0.33%

[Table 5] demonstrated the Causes of visual impairment among the 100 eyes with poor or blind visual acuity in chronic kidney disease patients. The findings of the table show that 24 eyes (24%) were affected by Maculopathy, 21 eyes (21%) by Cystoid Macular Edema (CME), 17 eyes (17%) by Non-exudative (Dry) age-related Macular degeneration (ARMD), 11 eyes (11%) by Exudative ARMD, 9 eyes (9%) by Central retinal vein occlusion (CRVO), 7 eyes (7%) by Epiretinal membrane (ERM), 6 eyes (6%) by PDR, 4 eyes (4%) by Glaucoma, and 1 eye (1%) by Cataract. The percentage of the total eyes affected by each cause is also provided.

Table 6: Comparison of grades of HR with stages of chronic kidney disease.

Stages of CKD	Moderate	Severe	End-stage renal disease	Total
Grades of HR	(192 eyes)	(72 eyes)	(36 eyes)	(300 eyes)
Grade I	53.13%	27.78%	-	32.67%
Grade II	46.88%)	54.17%	52.78%	50.67%
Grade III	-	18.06%	47.22%	16.67%
Grade IV	-	-	-	-

In this table, the percentage of eyes with Hypertensive Retinopathy (HR) at different stages of Chronic Kidney Disease (CKD) are presented. For the Moderate stage of CKD, 53.13% of the 192 eyes had grade I HR, while 46.88% of them had grade II HR. None of the eyes had grades III or IV HR. For the Severe stage of CKD, 27.78% of the 72 eyes had grade I HR, 54.17% of them had grade II HR, and 18.06% of them had grade III HR. None of the eyes had grade IV HR. For the End-stage Renal Disease stage, 52.78% of the 36 eyes had grade II HR, and 47.22% of them had grade III HR. None of the eyes had grades I or IV HR. Overall, 32.67% of the 300 eyes had grade I HR, 50.67% of them had grade II HR, and 16.67% of them had grade III HR. None of the eyes had grade IV HR.

Table 7: Comparison of grades of DR with stages of chronic kidney disease.

Stages of CKD	Moderate	Severe	End-stage renal disease	Total
Grades of DR	(192 eyes)	(72 eyes)	(36 eyes)	(300 eyes)
Mild NPDR	9.90%	11.11%	11.11%	10.33%
Moderate NPDR	3.13%	6.94%	16.67%	6.00%
Severe NPDR	-	12.50%	22.22%	6.00%
Very severe NPDR	-	4.17%	16.67%	3.00%
High risk PDR	-	18.06%	30.56%	8.00%

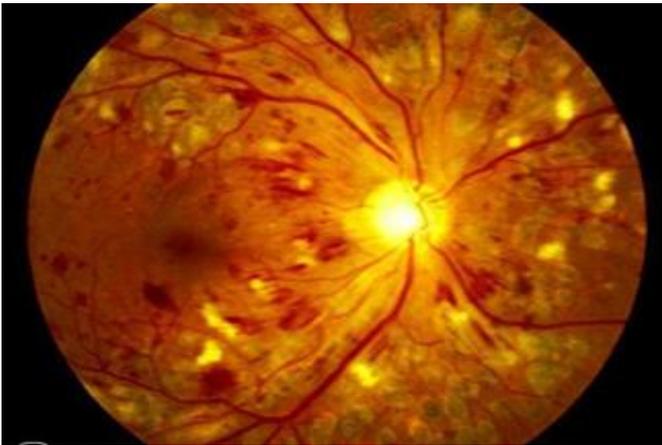


Figure 2: Example of a diabetic hypertensive patient with retinopathy



Figure 3: Example of a Central Retinal Vein Occlusion

In the moderate stage of CKD, 9.90% of eyes have Mild Non-Proliferative Diabetic Retinopathy (NPDR), 3.13% have Moderate NPDR, and no eyes have Severe or Very severe NPDR or High-risk Proliferative Diabetic Retinopathy (PDR). In the severe stage of CKD, 11.11% of eyes have Mild NPDR, 6.94% have Moderate NPDR, 12.50% have Severe NPDR, 4.17% have Very Severe NPDR, and 18.06% have High-risk PDR. In the end-stage renal disease stage of CKD, 11.11% of eyes have Mild

NPDR, 16.67% have Moderate NPDR, 22.22% have Severe NPDR, 16.67% have Very Severe NPDR, and 30.56% have High-risk PDR. The total distribution across all stages of CKD shows that 10.33% of eyes have Mild NPDR, 6.00% have Moderate NPDR, 6.00% have Severe NPDR, 3.00% have Very Severe NPDR, and 8.00% have High-risk PDR.

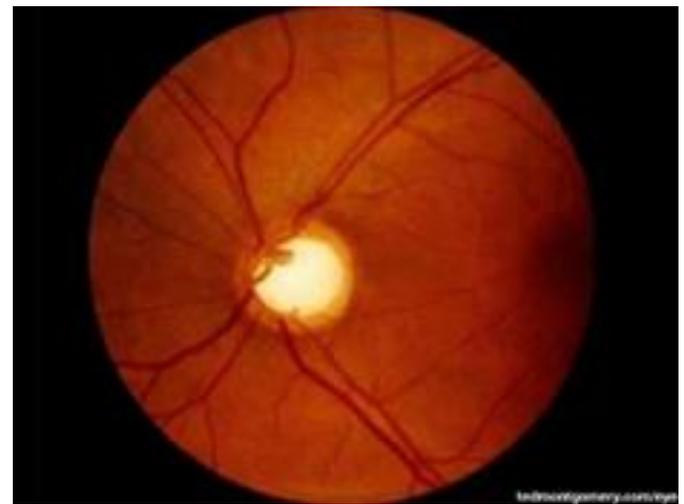


Figure 4: Example of a Glaucomatous Optic Atrophy

DISCUSSION

Several types of ocular fundus pathology have been associated with Chronic Kidney Disease (CKD). One of the most extensively studied is the relationship between retinal microvascular abnormalities and CKD. In a cross-sectional study from Singapore,^[9] retinal arteriolar diameters and retinopathy were found to be independently related to the presence of CKD. The Atherosclerosis Risk in Communities Study,^[10] and the Cardiovascular Health Study both found that retinal microvascular abnormalities are related to declining renal function. Possible explanations for the retinopathy-kidney connection might include



the following: retinal microvascular abnormalities caused by diabetes, hypertension, cigarette smoking, inflammation, and other factors that could provide a common pathophysiological link for the development and progression of CKD. In our study, the incidence of retinopathy was significantly higher among individuals with CKD compared to those without, which is consistent with previous reports.^[11] Among the two markers of kidney damage, proteinuria was found to be independently related to retinopathy, supporting the notion that both retinopathy and proteinuria are markers of systemic microvascular abnormalities. Additionally, the relationship between proteinuria and retinopathy was present among individuals without hypertension or diabetes, suggesting that susceptibility to microvascular disease might be triggered by mechanisms other than those directly stemming from hypertension or diabetes.^[12] In terms of age distribution in our study, 10% of the participants were between 20-29 years of age, 16 (15.33%) were between 30-39 years of age, 23 (21.33%) were between 40-49 years age group, 35 (35.33%) were between 50-59 years of age group, and 18 (18.0%) were from ≥ 60 age group. In terms of gender, 71 (47.33%) were male and 79 (52.66%) were female.

The relationship between age-related macular degeneration (AMD) and CKD has produced various results. In an Austrian cohort study,^[13] individuals with an estimated Glomerular Filtration Rate (eGFR) of less than 60 mL/min/1.73m² were found to be three times more likely to develop early AMD. Another population-based cohort study found that the level of serum cystatin C was related to the incidence of early AMD, while the results for

eGFR were not conclusive.^[14] A recent cross-sectional study suggested that proteinuria is related to AMD in men but not in women. In addition to AMD, intraocular pressure was also found to be related to CKD in a population-based cross-sectional study from Singapore.^[15] However, no significant association between glaucoma suspects and CKD was observed, possibly due to the small number of participants with glaucoma suspects (4.5%). In our study, the incidence of both AMD and glaucoma suspects was significantly higher among participants with CKD compared to those without, as reported.^[16]

The gradual decline in kidney function in Chronic Kidney Disease (CKD) can occur in individuals of any age, but it progresses faster in males with specific types of glomerulonephritis and polycystic kidney disease.^[17,18] Our study consisted of 150 patients, with a mean age of 55.9 years and a standard deviation of 7.5, which is in line with the study conducted by Dr. Manjula MS et al.^[19] Our research aimed to examine the anterior segment ocular findings in individuals with varying stages of CKD. The results showed that lid edema was present in 20.0% of moderate CKD patients, 40% of severe CKD patients, 40% of end-stage renal disease patients, and 3.5% of total eyes, with a P value of 0.0001. Conjunctival pallor was present in 63.30% of moderate CKD patients, 24.40% of severe CKD patients, 7.30% of end-stage renal disease patients, and 56.9% of total eyes, with a P value of 0.023. Pinguecula was found in 31.40% of moderate CKD patients, 42.90% of severe CKD patients, 25.70% of end-stage renal disease patients, and 12.2% of total eyes, with a P value of 0.015%. Dry eyes were present in 25.0% of moderate CKD patients,

37.50% of severe CKD patients, 37.50% of end-stage renal disease patients, and 5.6% of total eyes, with a P value of 0.0001. Cataracts were observed in 12.4% of moderate CKD patients, 46.90% of severe CKD patients, 40.60% of end-stage renal disease patients, and 11.1% of total eyes, with a P value of 0.0001. Finally, glaucoma was present in 25.0% of moderate CKD patients, 35.0% of severe CKD patients, 35.0% of end-stage renal disease patients, and 5.7% of total eyes, with a P value of 0.0001.

Research conducted by Bajracharya L, et al. and Dahal P, et al. revealed that hypertension was the main cause of CKD. 73% of patients reported CRF for less than 1 year.^[20] 57% of patients had never undergone an eye exam before, and only 43% had a prior record of ocular examination, indicating a lack of awareness about the associated ocular complications. A higher percentage of patients with end-stage renal disease (64.7% compared to 38% in the average group) had undergone an eye exam in the past, which suggests that ocular issues become more prevalent with advancing renal disease. 33% of the total eyes had a visual acuity of less than 6/18.^[21] In our study, among the 100 eyes with poor or blind visual acuity in chronic kidney disease patients, the causes of poor visual acuity was observed, which showed that 24 eyes (24%) were affected by Maculopathy, 21 eyes (21%) by Cystoid Macular Edema (CME), 17 eyes (17%) by Non-exudative (Dry) age-related Macular degeneration (ARMD), 11 eyes (11%) by Exudative ARMD, 9 eyes (9%) by Central retinal vein occlusion (CRVO), 7 eyes (7%) by Epiretinal membrane (ERM), 6 eyes (6%) by PDR, 4 eyes (4%) by Glaucoma, and 1 eye (1%) by Cataract. The

percentage of the total eyes affected by each cause is also provided.

This was similar to the study by Bajracharya L., et al., where impaired vision was found in 23% of eyes, with maculopathy as the main cause of vision loss, followed by cataracts and diabetic retinopathy. Conjunctival pallor was present in 56.9% of total eyes, which is a consistent finding in CKD and was found to be statistically significant.^[22] This could be due to low hemoglobin levels.

Lid edema occurs in only 3.5% of cases, primarily in the extreme and end-stage renal disease categories, which differs from the study conducted by L. Bajracharya et al. which found a much higher proportion of 63%. The altered renal function hinders the effective excretion of salt and water from the body, causing retention.^[23] This fluid retention leads to generalized swelling, including pedal edema, facial puffiness, and lid edema. Corneal calcification was present in 1.4% of patients in the extreme and end-stage renal disease groups. The calcification was near the temporal and nasal limbus and did not affect vision. Other studies reported calcification rates ranging from 60.0 to 80.0%. The calcification in the cornea and conjunctiva may occur due to secondary hyperparathyroidism.^[24] Degenerative conditions of the conjunctiva, such as pinguecula, were observed in 12.2% of all eyes, which is a common finding in chronic renal failure according to a study by Pahor D, et al. Inflammatory reactions of the conjunctiva and episclera may also be associated with an increase in calcium.^[25] 5.6% of all eyes were diagnosed with dry eye, which was more common in the extreme and end-stage renal

disease groups (37.5%) compared to the moderate group (25%).

Our study shows the comparison of hypertensive retinopathy grades with stages of chronic kidney disease. For the Moderate stage of CKD, 53.13% of the 192 eyes had grade I HR, while 46.88% of them had grade II HR. None of the eyes had grades III or IV HR. For the Severe stage of CKD, 27.78% of the 72 eyes had grade I HR, 54.17% of them had grade II HR, and 18.06% of them had grade III HR. None of the eyes had grade IV HR. For the End-stage Renal Disease stage, 52.78% of the 36 eyes had grade II HR, and 47.22% of them had grade III HR. None of the eyes had grades I or IV HR. Overall, 32.67% of the 300 eyes had grade I HR, 50.67% of them had grade II HR, and 16.67% of them had grade III HR. None of the eyes had grade IV HR.

This is likely due to differences in lacrimal secretion in patients with chronic renal failure undergoing hemodialysis. Cataract was present in 11.1% of all eyes and may be related to increased intracellular calcium and calcium deposition in the lens.^[26] The study by Liu et al. highlighted the increased occurrence of cataracts in chronic kidney disease and suggested that cataracts become more common as renal failure worsens, but did not conclude whether chronic kidney disease was necessary for cataract initiation or progression.^[27] The diagnosis of cataracts was most common in the extreme (46.9%) and end-stage renal disease (40.6%) groups compared to the moderate group, indicating its association with the progression of renal disease.^[28] Ocular posterior findings are the most important in patients with chronic kidney disease and are responsible for visual impairment. Hypertensive retinopathy

was the most frequent finding in our study, occurring in 49.3% of eyes. Of the 105 cases diagnosed with hypertension, 71 (67.6%) had retinopathy changes.

Limitations of The Study

The present study was conducted in a very short period due to time constraints and funding limitations. The small sample size was also a limitation of the present study.

CONCLUSIONS

In patients with Chronic Renal Failure (CRF), ocular problems can be identified through detailed eye exams. Early detection and treatment can prevent adverse outcomes. Patients with a history of abnormal renal function should receive close monitoring, as they are at an increased risk of visual loss. Awareness of the potential ocular complications associated with CRF is crucial. Proper measures, such as thorough ophthalmic examinations, and strict control of diabetes and hypertension, are important for maintaining overall eye health.

Recommendation

This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

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