ANALYSIS OF OCULAR MANIFESTATIONS IN RENAL TRANSPLANT RECIPIENTS

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ABSTRACT: AIM: To determine the proportion of ocular abnormalities in renal transplant patients and to correlate them with the: Underlying cause of renal insufficiency. Post-transplant duration. Immune suppressive regimens. **MATERIALS AND METHODS:** This cross sectional study was performed on 100 patients in M S Ramaiah Hospital between Nov 2010 to May 2012 who had received a renal transplant of at least 3 months duration with serum creatinine levels <3 mg/dl. All patients underwent a complete ophthalmologic examination. Clinical variables related to the transplant included cause of renal failure, duration of renal transplantation and immunosuppressive regimen. **RESULTS:** Overall, 83 male and 17 female patients with mean age of 43.22 ± 9.34 years were included. Ocular abnormality could be detected in 65%. The most common primary etiology of renal failure in patients was DM Nephropathy found in 37 (37%). Visual acuity < 6/9 seen in 48%, Conjunctival degenerative changes is seen in 24%, Cataractous changes mainly PSC seen in 34%, Clinically Significant Macular Edema (CSME) was seen in 4%, Central Serous Retinopathy changes seen in 3%, Hypertensive Retinopathy changes seen in 15%, Branch Retinal Vein Occlusion (BRVO) was seen in 4%, Mild NPDR changes was seen in 6%, Moderate NPDR changes was seen in 11%. Severe NPDR changes were seen in 15%, Proliferative Diabetic Retinopathy (PDR) changes was seen in 11%, Ocular HTN seen in 2%. Abnormal ocular findings were not correlated with the renal disorder or use of post-transplant immunosuppressive regimen but correlated with post-transplant duration. **CONCLUSION:** All patients undergoing renal transplant at should undergo complete ocular examination post renal transplantation for early detection, better management of ophthalmic complications for good visual outcome and improved quality of life.

KEYWORDS: Renal Transplant, Ocular Manifestations, Immunosuppressive Regimens.

INTRODUCTION: Organ transplantation has evolved over the years. Renal transplantation has become a very successful and routine procedure in the present scenario. Nowadays patients with end stage renal disease (ESRD) have better survival rates and enjoy improved quality of life after renal transplantation.¹

Renal replacement therapy by hemodialysis, peritoneal dialysis, and renal transplantation became available in the 1960; thereafter, a growing number of patients have undergone treatment of end-stage renal disease.²

Due to improvements in surgical techniques and immunology of transplantation, renal allografts provide remarkable rehabilitation and survival of chronic renal failure patients. Thereon, due to the immunosuppressive regimen and the incomplete correction of the physiologic state of the recipient, a variety of complications have been observed among renal transplant patients, including ocular complications, which are a significant cause of morbidity.^{3,4}

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With better control of adverse immunological events during early post-renal transplantation period, graft loss caused by rejection has significantly been reduced and successful transplantation is common.

The majority of complications are attributed to immunosuppressive therapy. However, medical complications directly related to renal transplantation such as cardiovascular diseases, hypertension, thromboembolism, and hyperparathyroidism can also result in significant ocular morbidity.⁵

Renal transplant recipients may develop a spectrum of complications related to the transplantation, the immunosuppression, their underlying disease or the previous uremia state.

Ocular manifestations following renal trans-plantation are mainly secondary to³:

- The cause of the underlying renal disease.
- Accumulation of noxious materials.
- Opportunistic infections.
- Immunosuppressive therapy.

These factors can result in significant ocular morbidity secondary to conditions such as cataracts, glaucoma, hypertensive retinopathy, conjunctival deposits, and drug-induced retinitis.³

Thus, it is important to assess ocular manifestations at an early stage in renal transplant recipients to:

1. Decrease ocular morbidity and improve their quality of life.
2. Assess and modify risk factors that may lead to complications.
3. Prevent and manage ocular complications.

AIMS AND OBJECTIVES: To determine the proportion of ocular abnormalities in renal transplant patients and to correlate them with the:

- Underlying cause of renal insufficiency.
- Post-transplant duration.
- Immunosuppressive regimens.

MATERIALS AND METHODS: Patients attending ophthalmology OPD in M.S. Ramaiah Hospital between Nov 2010 and May 2012. It is Cross-sectional Hospital based Observational Study. Hundred patients were recruited in our study according to the inclusion and exclusion criteria.

Inclusion Criteria:

- At least 3 months post renal transplant.
- Serum creatinine levels < 6mg/dL.

Exclusion Criteria:

- Known Case of Glaucoma pre renal transplantation.
- Age related macular degenerative changes.
- Known case of uveitis.

METHODOLOGY:

1. Informed consent taken from the patient.
2. Patients were chosen according to the inclusion and exclusion criteria.
3. Detailed history was taken and recorded.
 - History of any ocular complaints was noted in detail.
 - NEUROLOGIC HISTORY including
 - History of underlying disease causing end stage renal failure.
 - Post-transplant duration.
 - Immunosuppressive regimens including drugs, doses and duration of therapy.
4. General physical examination: including consciousness, orientation, pallor, icterus, cyanosis, clubbing, lymphadenopathy, and edema. PR, BP, RR measurement.
5. Systemic examination including CVS, RS, CNS, P/A.

OCULAR EXAMINATION:

- BCVA measured on a Snellen chart.
- Slit lamp evaluation.
- Lens Opacities Classification System III used for grading cataract.
- Application tonometry.
- Bio microscopy: 90D/78D ophthalmoscopy.
- Indirect ophthalmoscopy.
- ETDRS classification for grading Diabetic retinopathy.
- Visual fields - whenever possible.
- Fundus photograph — whenever possible.
- FFA resolution - whenever possible.
- OCT resolution — whenever possible.

RESULTS:

STUDY DESIGN: Cross - sectional hospital based observational study consisting of 100 patients undertaken to analyse ocular manifestations in renal transplant recipients.

METHOD OF STATISTICAL ANALYSIS:

- Data will be tabulated & analyzed, quantitative parameters like post-transplant duration, immunosuppressive regimens and serum creatinine will be summarized by Mean & Median.
- Variation present in data will be estimated by standard deviation. Proportion of patient with ocular abnormalities among renal transplant recipients will be estimated along with 95% confidence interval.
- Analysis of ocular manifestations will be carried out for various factors such as age, serum creatinine, use of immunosuppressant underlying cause of renal insufficiency, post-transplant duration.
- The differences in proportion will be tested by employing Chi - square test of significance.

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Age	Frequency	Percentage
20-29 yrs.	8	8.0
30-39 yrs.	21	21.0
40-49 yrs.	41	41.0
50-59 yrs.	30	30.0
Total	100	100.0

Table 1: Mean age of the patients studied

The mean age group was 43.22 ± 9.34 yrs. for the study population.

Graph 1: Depicting the distribution of patients based on age.

Graph 1

Gender	Frequency	Percentage
Male	83	83.0
Female	17	17.0
Total	100	100.0
Out of 100 patients 83	(83%) were males and 17	(17%) were females

Table 2: Gender distribution of the patients studied

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Graph 2: Depicting the percentage of distribution of patients based on gender.

Graph 2

	Frequency	Percentage
Glomerulonephritis	25	25.0
DM Nephropathy	37	37.0
Hypertensive Nephropathy	15	15.0
IgA Nephropathy	4	4.0
Polycystic Kidney	5	5.0
Reflux Nephropathy	4	4.0
Unknown Causes	10	10.0
Total	100	100.0

Table 3: Primary etiology of renal failure in patients

The most common primary etiology of renal failure in patients was DM Nephropathy found in 37(37%). Then followed by Glomerulonephritis in 25 (25%).

Graph 3: Depicting the percentage of patients with primary etiology of renal failure.

Graph 3

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Primary Etiology	Number (% of total) of Primary etiology		Number (%) of ocular finding in each Etiologic group.	
	n	%	N	%
Glomerulonephritis	25	25.0%	14	56.0%
DM Nephropathy	37	37.0%	30	81%
Hypertensive Nephropathy	15	15%	13	86.66%
IgA Nephropathy	4	4.0%	3	75.0%
Polycystic Kidney	5	5.0%	5	100.0%
Reflux Nephropathy	4	4.0%	4	100.0%
Unknown Causes	10	10.0%	7	70.0%

Table 4: Primary etiology of renal failure patients ocular complications in patients renal transplant

The most common primary etiology of renal failure in patients was DM Nephropathy found in 37(37%) among them abnormal ocular finding present in 30 (81%).

Primary Etiology	Best Corrected Visual Acuity				Total
	VA >or 6/9 N (%)	6/12 - 6/24 N (%)	6/36 — 6/60 N (%)	< 6/60 N (%)	
Glomerulonephritis	31 (29.80)	18 (26.86)	1 (5.27)	0 (0.0)	50 (25)
DM Nephropathy	14 (13.46)	32 (47.76)	18 (94.73)	10 (100.0)	74 (37)
Hypertensive Nephropathy	16 (15.38)	14 (20.89)	0 (0.0)	0 (0.0)	30 (15)
IgA Nephropathy	6 (5.76)	2 (2.98)	0 (0.0)	0 (0.0)	8 (4)
Polycystic Kidney	10 (9.61)	0 (0.0)	0 (0.0)	0 (0.0)	10 (5)
Reflux Nephropathy	8 (7.69)	0 (0.0)	0 (0.0)	0 (0.0)	8 (4)
Unknown Causes	19 (18.26)	1 (1.49)	0 (0.0)	0 (0.0)	20 (10)
Total	104(100.0)	67 (100.0)	19 (100.0)	10(100.0)	200 (100.0)

Table 5: Correlation of visual outcome in terms of visual acuity in patients with respect to primary etiology of renal failure. Results of both eyes were recorded.

- Visual acuity greater than or equal to 6/9 seen in 52%.
- Visual acuity between 6/12 to 6/24 was seen in 33.5%.
- Visual acuity between 6/36 and 6/60 was seen in 9.5%.
- Visual acuity less than 6/60 was found to be 5%.
- The majority of patients with DM nephropathy had visual acuity <6/36.

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The Conjunctival degenerative changes are seen in 24 (24%) patients in study population. Among them 5 (20.8%), 13 (54.2%), 6 (25%) patients had <1 yr., 1-5 yr., >5yr post-transplant duration respectively. This shows that the incidence was not statistically significant. (p value 0.30)

The Cataractous changes were seen in 34 (34%) patients in study population. Among them 5 (14.7%), 20(58.8%), 9 (26.5%) patients had <1 yr., 1-5 yr., >5yr post-transplant duration respectively. This shows that the incidence was not statistically significant. (P value 0.12)

The clinically Significant Macular Edema (CSME) was seen in 4 (4%) patients in study population. Among them 1 (25%), 2 (50%), 1 (25%) patients had <1 yr., 1-5 yr., >5yr post-transplant duration respectively. This shows that the incidence was not statistically significant. (P value 0.78)

Central Serous Retinopathy changes are seen in 3 (3%) patients in study population. Among them 0 (0%), 2 (66.7%), 1 (33.3%) patients had <1 yr., 1-5 yr., >5yr post-transplant duration respectively. This shows that the incidence was not statistically significant. (P value 0.56)

The Hypertensive Retinopathy change is seen in 15 (15%) patients in study population. Among them 3 (20. %), 9 (60%), 3 (20%) patients had <1 yr., 1-5 yr., >5yr post-transplant duration respectively. This shows that the incidence was not statistically significant. (P value 0.85)

Branch Retinal Vein Occlusion (BRVO) was seen in 4 (4%) patients in study population. Among them 1 (25%), 2 (50%), 1 (25%) patients had <1 yr., 1-5 yr., >5yr post-transplant duration respectively. This shows that the incidence was not statistically significant. (P value 0.78)

The Mild NPDR changes were seen in 6 (6%) patients in study population. Among them 0 (0%), 5 (83.3%), 1 (16.7%) patients had <1 yr., 1-5 yr., >5yr post-transplant duration respectively. This shows that the incidence was not statistically significant. (P value 0.48)

The MODERATE NPDR changes were seen in 11 (11%) patients in study population. Among them 2 (18.2%), 8 (72.7%), 1 (9.1%) patients had <1 yr., 1-5 yr., >5yr post-transplant duration respectively. This shows that the incidence was not significant. (P value 0.79)

The Proliferative Diabetic Retinopathy (PDR) changes were seen in 11 (11%) patients in study population. Among them 0 (0%), 7 (63.6%), 4 (36.4%) patients had <1 yr., 1-5 yr., >5yr post-transplant duration respectively. This shows that the incidence was not statistically significant. (P value 0.066)

SEVERE NPDR	Duration of Transplant			Total N (%)
	<1 yr.	1-5 yr.	>5 yr.	
	N (%)	N (%)	N (%)	
Present	1 (6.7)	8 (53.3)	6 (40.0)	15 (100)
Absent	17 (20.0)	58 (68.2)	10 (11.8)	85 (100)
Total	18 (18.0)	66 (66.0)	16 (16.0)	100 (100.0)

Table 6: correlation of Severe NPDR with duration of renal transplantation

The Severe NPDR changes were seen in 15 (15%) patients in study population. Among them 1 (6.7%), 8 (53.3%), 6 (40%) patients had <1 yr., 1-5 yr., >5yr post-transplant duration respectively. This shows that the incidence is statistically significant. (P value 0.018).

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Graph 6: Depicting the percentage of patients with severe NPDR correlating with duration of renal transplantation.

Graph 6

Ocular Complications	Number (% of related ocular finding) Of patients based on duration of transplant (years)			Total	P Value
	<1 yr.	1-5 yr.	>5yr		
BRVO	1 (25.0)	2 (50.0)	1 (25.0)	4 (100)	0.78
Cataract	4 (13.3)	18 (60.0)	8 (26.7)	30 (100)	0.12
Conjunctival degeneration	5 (20.8)	14 (58.3)	5 (20.8)	24 (100)	0.30
CSME	2 (50.0)	1 (25.0)	1 (25)	4 (100)	0.78
CSR	0 (0)	2 (75)	1 (25)	3 (100)	0.56
HTN Retinopathy	3 (20)	9 (60)	3 (20)	15 (100)	0.85
Mild NPDR	0 (0)	5 (83.3)	1 (16.7)	6 (100)	0.48
Moderate NDPR	2 (18.2)	8 (72.7)	1 (9.1)	11 (100)	0.79
Severe NDPR	1 (6.7)	8 (53.3)	6 (40.0)	15 (100)	0.01
Ocular HTN	0 (0)	2 (100)	0 (0)	2 (100)	0.53
PDR	0 (0)	7 (63.6)	4 (36.4)	11 (100)	0.06

Table 7: Distribution of ocular complications based on post-transplant duration

This table summarizes the frequency of ocular complications based on post-transplant duration and shows that only the incidence of severe NPDR was statistically significant correlated with the duration of renal transplant. The mean duration of renal transplant was 3.03 ± 2.67 years.

Ocular Manifestations	Duration of Transplant			Total N (%)
	<1 yr.	1-5 yr.	>5 yr.	
	N (%)	N (%)	N (%)	
Present	9 (13.8)	41 (63.1)	15 (23.1)	65 (100.0)
Absent	9 (25.7)	25 (71.4)	1 (2.9)	35 (100.0)
Total	18 (18.0)	66 (66.0)	16 (16.0)	100 (100.0)

Table 8: Correlation of Ocular manifestations with duration of renal transplantation

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The ocular manifestations were seen in 65 (65%) patients in study population. Among them 9 (13.8%), 41 (63.1%), 15 (23.1%) patients had <1 yr., 1-5 yr., >5yr post-transplant duration respectively. This shows that the incidence was statistically significant. (P value 0.020)

Graph 7: Depicting the percentage of patients with ocular manifestations correlating with duration of renal transplantation.

Graph 7

DISCUSSION: Ocular complications after renal transplantation are associated with notable morbidity.⁸ Renal transplant recipients may develop a spectrum of complications related to the transplantation, the immunosuppression, their underlying disease or the previous uremia state.

Ocular manifestations following renal transplantation are mainly secondary to³:

- The cause of the underlying renal disease.
- Accumulation of noxious materials.
- Opportunistic infections.
- Immunosuppressive therapy.

Cross-sectional hospital based observational study consisting of 100 patients undertaken to analyze ocular manifestations in renal transplant recipients.

The mean age group was 43.22 ± 9.34 yrs. for the study population.

In the present study only patients with good transplant function (serum creatinine <3 mg/dl) were selected to avoid interference by ocular complications associated with renal failure.

The mean duration of renal transplant was 3.03 ± 2.67 years.

The post-transplant immunosuppressive regimen consisted of triple therapy in all patients. The current standard immunosuppression protocol followed in our hospital: calcineurin inhibitor (CNI; cyclosporine or tacrolimus) + mycophenolate (mycophenolate mofetil [MMF] or enteric-coated mycophenolate sodium [EC-MPS]) + corticosteroid (prednisolone or methylprednisolone).

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Diabetes mellitus was the most prevalent underlying etiology of chronic renal failure in our study. Based on previous studies, the most common cause of renal failure is HTN followed by Diabetes mellitus.⁶

Our study shows that 65% of patients had ocular manifestations post renal transplant. A study by T. Das, Amod Gupta et al concluded that 52.5% developed ocular complications post renal transplant.⁴

Visual outcome in terms of visual Acuity in patients following renal transplant was correlated with respect to etiology of chronic renal failure. Based on study Farzan Kian-Ersi et al visual Acuity less than 6/9 was seen in 47%.⁶ Other study by Jayamanne DG et al Visual acuity greater than or equal to 6/9 seen in 75% and visual acuity less than 6/24 was seen in 10% of patients.³

In our study Visual acuity greater than or equal to 6/9 seen in 52%, between 6/12 to 6/24 was seen in 33.5%, between 6/36 and 6/60 was seen in 9.5% and less than 6/60 was found to be 5%.

The majority of patients with DM nephropathy had visual acuity <6/36.

In our study the most common ocular manifestation seen was cataract. The incidence of this complication varies from 5% to 62.5% in different studies.^{3,7,9} In our study incidence of cataract mainly Posterior Sub capsular Cataract (PSC) was found in 34 (34%) patients.

Various studies have documented dose dependent relationship between oral corticosteroids and cataract formation.⁸ In our study due to lack of various patient groups with different steroid doses it was not possible to evaluate the correlation between total steroid dose and cataract formation- However we have correlated cataract formation with duration of renal transplant, among them 5 (14.7%), 20 (58.8%) patients had <1yr, 1-5 yr., >5yr post-transplant duration respectively.

The second most frequent anatomical disorders in the study were conjunctival degenerations and depositions found in 24 (24%) patients. A study by Farzan Kian-Ersi et al conjunctival degenerations and depositions was found to be (36.7%).⁶ Conjunctival degenerative lesions often result from ultraviolet radiation,¹⁰ but in renal transplant patients they seem to be mainly correlated with hemodialysis.

In a study on patients who were on hemodialysis treatment, the most frequently observed anterior segment abnormality was also conjunctival deposits (66.6%). These conjunctival lesions may result from accumulation of toxic materials in the body.¹¹ we have correlated conjunctival degenerations with duration of renal transplant, among them 5 (20.8%), 13 (54.2%), 6 (25%) patients had <1 yr., 1-5 yr., >5yr post-transplant duration respectively.

Raised intraocular pressure is potentially hazardous but fortunately rare complication of prolonged oral steroid therapy. Although IOP rise is a common side effect of topical steroids, systemic corticosteroid treatment rarely causes glaucoma.^{12,13} In a study by Jayamanne et al incidence was found to be 1.7%.³ In our study Ocular hypertension was observed in 2 (2%) patients. When correlated with duration of renal transplant was found in 2 (100%) patients 1-5 yr. post-transplant duration.

Renal transplant recipients may be predisposed to the development of CSC, perhaps by virtue of their underlying renal disease, the vascular effects of prior hemodialysis, the effect of rejection and resumption of hemodialysis after transplantation.¹⁴ Corticosteroids, both exogenous and endogenous, have been implicated in the development of CSC, and they have been associated with the initiation, exacerbation, and prolongation of CSC.¹⁵

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In a similar study by Farzan Kian-Ersi et al incidence of CSC was found to be 3.3%.⁶ In present study incidence of CSC was seen in 3 (3%) patients. Correlation of CSC with duration of renal transplant was found to be 0 (0%), 2 (66.7%), 1 (33.3%) patients had <1 yr., 1-5 yr., >5yr post-transplant duration respectively.

Vascular Events such as Hypertensive Retinopathy, Diabetic Retinopathy, BRVO were related to primary etiology of renal failure such as diabetes and hypertension.

The Ocular findings were classified as diabetes related complications including clinically significant macular edema, non-proliferative diabetic retinopathy and proliferative diabetic retinopathy; and non-diabetes related complications.

In present study incidence of Hypertensive Retinopathy changes was observed in 15 (15%) patients. The incidence of BRVO was seen in 4 (4%) patients. In a study by H. R. Jahadi - hosseini Hypertensive retinopathy was observed in (54%) prior to transplantation. In our study patient was not examined pre transplant, no correlation was done between grade of Hypertensive Retinopathy and change in grades of Hypertensive retinopathy post-transplant examination.

However we have correlated severity of Hypertensive Retinopathy with duration of renal transplant was found to be 3 (20%), 9 (60%), 3 (20%) patients had <1 yr., 1-5 yr., >5yr post-transplant duration respectively.

The diabetes related ocular complications include clinically significant macular edema, non-proliferative diabetic retinopathy and proliferative diabetic retinopathy. In a similar study by Farzan Kian - Ersi et al incidence of Diabetes-related ocular complications were seen in 40% of diabetic subjects.⁶

In present study incidence of CSME was observed in 4 (4%) patients, Mild NPDR in 6 (6%) patients, Moderate NPDR in 11 (11%) patients, Severe NPDR in 15 (15%) patients, PDR in 11 (11%). In our study patient was not examined pre-transplant, no correlation was done between grade of diabetic retinopathy and change in grades of diabetic retinopathy post-transplant examination.

However we have correlated severity diabetic retinopathy with duration of renal transplant, only Severe NPDR it found to be statically significant.

Acute cytomegalic retinitis as a major complication following renal transplant has been reported previously.¹⁶ It was unusual that none of the patients in this series had suffered from this complication. Abnormal ocular findings were not correlated with the underlying renal disorder or use of post-transplant immunosuppressive regimen but correlated with post-transplant duration.

CONCLUSION: There can be sight threatening complications in long term survivors of renal transplantation, if ocular examinations are not carried out at regular intervals.

The Ocular complications are attributed to immunosuppressive therapy, medical complications directly related to renal transplantation such as Diabetes mellitus, hypertension & post transplantation complications.

Our Study concludes that:

- The long term prognosis for normal vision in patients who have undergone renal transplantation is good.
- The incidence of ocular complication in renal transplant patients is high.
- The most common ocular manifestation seen was cataract.

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- All patients undergoing renal transplant should undergo complete ocular examinations pre and post renal transplantation for good visual outcome and management of ophthalmic complications.
- Although most complications are not sight-threatening, regular ophthalmologic examinations can result in early detection, better management and improved quality of life.
- Hence it is necessary for all renal transplant patients to have periodical ophthalmological examinations.

SUMMARY: This is Cross-sectional Hospital based Observational Study for in renal analysis of ocular manifestations transplant recipients.

Patients attending Ophthalmology OPD and inpatients of MSR Hospitals, who had undergone renal transplant, were recruited in the study.

Detailed ocular examination was done by slit lamp biomicroscopy, Goldmann applanation tonometer, Fundus photograph, visual fields analysis, Optical coherence tomography, Fundus fluorescein angiography were done wherever required.

After analyzing the data and applying appropriate statistical analysis we conclude that all patients should undergo ophthalmological examination pre and post renal transplantation.

The incidence ocular manifestations in renal transplant patients are high. Early diagnosis of ophthalmic complications can be managed well and patient can have good visual outcome.

The long term prognosis for normal vision in patient who has undergone renal transplantation is good.

The major drawbacks of the study was, it was a cross sectional study, so that the progression of ocular complications could not be assessed.

In our study due to lack of various patient groups with different steroid doses it was not possible to evaluate the correlation between total steroid dose and steroids related complications.

Thus to conclude that all renal transplant patients to have periodical ophthalmological examinations especially to detect early ocular complications to improve quality of life.

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