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Ocular Manifestations in Chronic Renal Failure Patients

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ABSTRACT

The study was done during a period of two years from november 2011 to September 2013 on 200 consecutive patients who were admitted to the nephrology ward, Kurnool medical college, Kurnool and met the inclusion and exclusion criteria. Inclusion criteria: All cases diagnosed as chronic renal failure. Exclusion criteria: Cases of reversible renal failure, Patients on peritonial dialysis.

Chronic kidney disease (CKD) is a worldwide public health problem, both for the number of patients and cost of treatment involved. Globally, CKD is the 12th cause of death and the 17th cause of disability, respectively. The chronic diseases account for 60% of all deaths worldwide. 80% of chronic disease deaths worldwide occur in low and middle socio economic countries¹. In India the projected number of deaths due to chronic disease was around 5.21 million in 2008 and is expected to raise to 7.63 million in 2020 (66.7% of all deaths)².

As a part of multi organ involvement, eye is not an exception. The common Ocular manifestations include some anterior segment manifestations like lid puffiness, conjuctival pallor, conjuctival & corneal calcification, posterior segment manifestations like hypertensive retinopathy, diabetic retinopathy, CSME, maculopathy, retinal detachment.

Chronic renal failure is irreversible and progressive process that results in end stage renal disease where patient has to be dependent on renal replacement therapy for survival⁵.

The most common cause of CRF is diabetic nephropathy followed by hypertensive nephro angiosclerosis and various primary and secondary glomerulo nephropathies.

This study is an attempt to access the ocular status/complications associated with CRF.

To analyse the ocular status/complications in the patients with chronic renal failure. To screen patients for any potential visual threat so that necessary treatment and or advice can be given before they become irreversibly visually impaired.

Admissions due to CRF (Chronic renal failure) the patients were 1308 (69.5%) the common age affected being 40 to 80 years (65%) male dominant 143 patients (71.5%), CRF with DM 55 patients (27.5%), CRF

2015

with HTN 45 patients (22.5%), patients with diminished vision 124 patients(62%) patients with DM, Maculopathy 39 patients (9.75%), patients with PDR 24 patients (5.8%), Conjunctival Pallor 152 patients (75.60%), Lid Oedema 126 patients(63%) Diabatic retinopathy 64 patients (88.8%), Hypertensive retinopathy 31 patients (47%).

These above results are observed by us in our study.

we aimed to prospectively analyze the ocular manifestations among CRF patients.

A detailed history, detailed ophthalmic examination was done for all the cases and recorded.

When CRF patients were evaluated the patients in the age group of 40-80 years were commonly affected. There was a definite male preponderance among the cases. The most common aetiological factor leading to CRF in these patients is diabetes mellitus followed by hypertension and some are due to glomerulonephritis and Autosomal dominant polycystic kidney disease.

Diminished vision was the most common symptom seen with CRF patients and it was commonly attributed to maculopathy followed by cataract and PDR.lid puffiness and conjuctival pallor were the most common signs observed in CRF patients. These findings are statistically significant and can be regarded as consistent finding in CRF.

Among the posterior segment signs hypertensive retinopathy findings are most common followed by diabetic retinopathy.

Ocular manifestations are common in CRF patients. The most frequently encountered manifestations in CRF is conjuctival pallor and lid edema. The most common cause of CRF in our study is diabetes mellitus. Regular screening for diabetic retinopathy in cases of CRF can help patients with early intervention with laser photocoagulation and alert physician for more aggressive management of diabetes. Ocular condition is an indicator of the metabolic control of the disease process.

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem, both for the number of patients and cost of treatment involved. Globally, CKD is the 12th cause of death and the 17th cause of disability, respectively. The chronic diseases account for 60% of all deaths worldwide. 80% of chronic disease deaths worldwide occur in low and middle socio economic countries ¹. In India the projected number of deaths due to chronic disease was around 5.21 million in 2008 and is expected to raise to 7.63 million in 2020 (66.7% of all deaths)^{2.}

As a part of multi organ involvement, eye is not an exception. The common Ocular manifestations include some anterior segment manifestations like lid puffiness, conjuctival pallor, conjuctival & corneal calcification, posterior segment manifestations like hypertensive retinopathy, diabetic retinopathy, CSME, maculopathy, retinal detachment.

Unlike other organs, all the consequences can be directly related in the eye-as renal cortex is mirror of retina.

As per the Diabetes Atlas 2006, the number of patients with DM in India (currently around 40.9 million) is expected to rise to 69.9 million by 2025 unless urgent preventive measures are taken³. With increasing prevalence of CKD, CKD related excess CVD, ESRD and the consequent financial burden of renal replacement therapy (RRT), the importance of CKD and its risk factors has to be realized. The prevalence of ESRD and patients on RRT has increased over last two decades⁴.

2015

Chronic renal failure is irreversible and progressive process that results in end stage renal disease where patient has to be dependent on renal replacement therapy for survival ⁵. It is characterised by a numerous disorders that involve many organs : bone, heart and blood vessels, peripheral nerves. In dialysis patients some disorders could be consequence of dialysis treatment perse.

The most common cause of CRF is diabetic nephropathy followed by hypertensive nephro angiosclerosis and various primary and secondary glomerulo nephropathies. by the ESRD, 80% of

MATERIALS & METHODS

A. Source of data:

The study was done during a period of two years from november 2011 to September 2013 on 200 consecutive patients who were admitted to the nephrology ward, Kurnool medical college, Kurnool and met the inclusion and exclusion criteria.

Inclusion criteria:

All cases diagnosed as chronic renal failure.

Exclusion criteria:

- 1. Cases of reversible renal failure.
- 2. Patients on peritonial dialysis.

B. Method of collection of data:

- The study was prospective in nature in which 200 cases of CRF from November 2011 to september 2013 were selected.
- 2. A prepared proforma was used for collection of data.

patients will have developed secondary hypertension ⁶. Ocular morbidity may be directly due to hypertension, uremia and anaemia , some are related to the causes leading to chronic renal failure. Some effects are due to haemodialysis.

This study is an attempt to access the ocular status/complications associated with CRF. It is intended to highlight the importance of ocular examination, to screen patients for any potential visual threat so that necessary treatment and or advice can be given before they become irreversibly visually impaired.

- This study included all chronic renal failure disease patients visited nephrology ward, G.
 G. H, Kurnool between november 2011 to september 2013.
- 4. Ophthalmic examination included:
 - a. History taken.
 - b. Best corrected visual acuity by snellen's chart.
 - c. Detailed examination of anterior& posterior segments .
 - d. Pupils were dilated with tropicamide for
 - indirect ophthalmoscope
 - direct ophthalmoscope.
 - evaluation in slit lamp by +90D lens.
- 5. Hypertensive retinopathy was graded on basis of keith Wagener classification.
- Diabetic retinopathy and macular edema were classified on basis of early treatment diabetic retinopathy study.
- Other investigations done according to need were

2015

-fundus fluorescein angiography. -visual fields.

-fundus photography.

-schirmer's test.

8. Other Investigations required in this study:-Hb%,TC,DC,ESR.

- Blood urea, serum creatinine.

- serum calcium, phosphorous.

- serum sodium,potassium.

- urine routine.

- lipid profile.

- RBS,FBS,PPBS.

- ultrasound abdomen.

- GFR calculation by Cockcroft -gault equation.

9. Statistical methods used:

First measures of central tendency and dispersion like mean and standard deviation were used to anlayse the data.Frequency of anterior &posterior segment findings in the population studied is calculated.

Then each of variables studied ie., stage of CRF,blood sugar,hypertension,visual impairement.

RESULTS

TABLE 1: Incidence of CRF in our hospital

S.No	AdmissionsFromNov2011To2013Sep	No.Of Cases.	Percentage (%)
1.	Total number of admissions in nephrology department.	1880	100
2.	Admissions due to CRF.	1308	69.5%

ADMISSION RATE: In the present study CRF contributed to 69.5% our nephrology department admissions during our study period.

TABLE2: Distribution Of Patients In NephrologyDepartment & Their Ages: (Age Wise Distribution)

Age Group	No.Of Cases	Mean	Standard Deviation
0-20	7 (3.5%)	12.666666667	7.571877794
20-40	63 (31.5%)	31.13793103	5.507943212
40-80	130 (65%)	54.10294118	7.58462645

AGE INCIDENCE: 200 patients who were admitted to the nephrology department, GGH, kurnool and met the inclusion&exclusion criteria were included in our study of which males are more commoner than females.Their ages ranged from 40 to 80 with a mean age of 54.1 years and a standard deviation of 7.58 years.

This is similar to the study done by L. Bajracharya et al who observed that maximum incidence was in the age groups of 48.3 ± 14.9 years.

TABLE 3: Incidence of Crf According to The Sex:

Sex	No.Of Cases	Percentage (%)
Males	143	71.5
Females	57	28.5

In the present study male patient constituted 143 ,female patients constituted of the study group 57 &M:F ratio is 2.5:1 .it is in consistent with the study of L.Bajracharya et al who observed the male: female ratio was 2.3:1.The reason for this could be

2015

due to faster rate of deterioration of kidney function in male with some forms of glomerulonephritis and polycystic kidney disease.

Diagnosis	No.Of Patients	Percentage(%)
CRF with diabetes	55	27.5
CRF with	45	22.5
hypertension		
CRF with DM,HTN	30	15
CRF due to	20	10
pyelonephritis		
CRF with ADPCKD	5	2.5
CRF with BOO	10	5
CRF with nephritic	10	5
syndrome		
CRF with	20	10
glomerulonephritis		
CRF (drug induced)	5	2.5

TABLE4: Etiology Of Crf At Admission:

Etiology of CRF at admission:

In our present study the most common etiological factor leading to CRF was DM which constituted for 27.5% and it is followed by HTN which constituted for 22.5%. It is not substantiated with the study of L.Bajracharya et al where the

TABLE7: Visual Acuity:

commonest cause of CRF was HTN 43 out of 119(36.1%), followed by DM(27.7%) and glomerulonephritis(20.2%).

TABLE5: Staging Of Crf Patients UsingCockcrouft-Gault Formula:

Stage	No.Of Patients	Percentage(%)
Stage 1&2	52	26
Stage 3	52	26
Stage 4	47	23.5
Stage5	49	24.5

In our study stage 1,2 CRF accounted for 26%, stage3 CRF accounting for 26%, stage4 CRF for 23.5%,ESRD for 24.5%.

TABLE6: Ocular Symptoms:

Symptoms	No.Of Patients	Percentage (%)
Diminished Vision	124	62
Red Eyes	58	29
Irritable Symptoms	24	12

Most common complaints observered diminished vision accounted for 62% followed by red eyes for 29% and irritable symptoms for 12%.

WHO criteria	Visual acuity	Stage1 & 2104 eyes	Stage3 104 eyes	Stage4 94 eyes	Stage5 98 eyes	Total 400 eyes	%
Good vision	<6/18	50	32	36	72	190	47.5 %
Impaired vision	6/60 to 6/24	16	28	26	32	102	25.5 %
Legally blind	>6/60	20	36	18	34	108	27%
	Total eyes	86	96	80	138	400	

Chi-square value: 16.03342029

P value: 0.01357570722 Significant

2015

This table shows best corrected visual acuity.47.5% of the total patients were enrolled were with vision 6/18 or better. According to WHO criteria, 25.5%

were visually impaired and another 27% were in the category of legally blind.

TABLE 8: Causes Of Visual Impairment:

Causes	No.Of Eyes	Percentage Of Total Eyes (%)
Maculopathy	39	9.75
PDR	24	5.8
Cataract	15	3.75
Optic neuropathy	8	2.1
Corneal scar	2	0.4
Others	7	1.7
Total	95	23.75

In our present study the causes of visual impairment is mainly due to maculopathy 9.75%, followed by cataract which accounts for 5.8%,followed by PDR accounted for 3.75% .It is similar to the observation seen by L. Bajracharya et al which showed maculopathy as cause of visual impairment in 23 eyes out of 238 eyes(9.7%),followed by cataract in 14 (5.9%)eyes, PDR in 9 eyes(3.8%).

OCULAR MANIFESTATIONS:

TABLE9: Anterior Segment Manifestations:

	Stage (1&2)	Stage(3) 52	Stage (4)	Esrd(5)		Percentag	
Grades Of Crf	52 cases	cases	47cases	49cases	Total	e	P- Value
Lid edema	20	30	35	41	126	63%	0.0039 S
Conjuctival pallor	25	34	47	46	152	75.60%	0.0011 S
Corneal calcification	0	0	0	7eyes	7 eyes	1.75%	-
Pingecula	22	12	25	15	79	39.50%	0.0368 S
Red eyes	2eyes	3 eyes	3 eyes	0	8 eyes	2%	0.128 NS
Dry eyes	10 eyes	3 eyes	10eyes	7eyes	30eyes	7.50%	0.069 NS
Cataract	10eyes	7eyes	7 eyes	5 eyes	29 eyes	7.25%	0.048 S

Chi-square value: 44.76153211

P value: 0.000448 Significant

Lid puffiness was the most common sign observed in eyelid manifestations ie., 63% .it is in consistent with the findings observed by L. Bajracharya et al

which was 63% of total cases. Conjunctiva pallor was the most common sign observed in this study 75.6% ,followed by pingecula and dry eye which is

2015

in consistent with the observations of L. Bajracharya et al, where it was 75.6% of total cases.

being statistically significant they can be regarded as consistent finding in CRF.

TABLE 10:	Posterior Segment:
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Ocular	Stage1&2	Stage3	Stage4	Stage5	Total	(%)
Findings	(52 Cases)	(52 Cases)	(47	(49		
			Cases)	Cases)		
vitreous	0	7	3	3	13	6.5%
hemorrhage	-		-	-		
Diabetic						
proliferative		_	_			
vitreo	0	5eyes	2eyes	3eyes	10eyes	2.5%
retinopathic						
changes						
diabetic	22 out of 22	18 out of	12 out of	12 out of	64	88.8%
retinopathy		25	13	12		
Hypertensive	9	21	33	31	94	47%
retinopathy	-				<i></i>	1770
maculopathy	10	12	13	5	40	20%
Bullous RD	0	0	0	3eyes	3eyes	0.75%
BRVO	2eyes	0	2eyes	0	4eyes	1%
Pallor of disc	2eyes	0	3eyes	7eyes	12eyes	3%
Disc						
edema(grade	0	0	3	10	13	3.35%
4 HTN)						
glaucoma	0	2	2	0	4	1%
suspect		<i>–</i>	-		- T	1 /0

Chi square value: 30.6122296

P Value: < 0.00001 Significant

Hypertensive retinopathy:

In our study 47% of total patients with CRF had hypertensive retinopathy. Grade 4 hypertensive retinopathy with optic disc edema was present only in severe CRF. Grade 4 hypertensive retinopathy occurred in 7 patients with stage 4 and stage 5 CRF.

Diabetic retinopathy :

In the present study 89% of total diabetic patients with CRF had diabetic retinopathy.

Bullous retinal detachment:

There were 3 eyes of one bilateral, exudative type retinal detachment in patients with severe grade of renal disease.

2015

Grades	Stage1&2	Stage3	Stage4	Esrd(Stage5)	Total
Ι	5	10	7	8	30
II	2	3	2	8	15
III	2	8	22	10	42
IV	0	0	2	5	7
Total cases with HTN	9	21	33	31	94

TABLE11: Comparision Of Grades Of Htn Retinopathy With Crf:

Chi square value: 16.97757669

P Value: 0.049068283 Significant

In our study 47% of total patients with CRF had hypertensive retinopathy. Grade 4 hypertensive retinopathy with optic disc edema was present only in severe CRF. Grade 4 hypertensive retinopathy occurred in 7 patients with stage 4 and stage 5 CRF.

TABLE 12: Comparision Of Grades Of D	Dr Among Stages Of Crf:
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Grades	Stage 1&2	Stage3	Stage4	Stage5	Total	Percentage
	22 Cases	25 Cases	13 Cases	12 Cases	72 Cases	(%)
MILD	10	3	2	2	17	23.6%
MODERATE	2	7	3	4	16	22.2%
SEVERE	5	2	3	2	12	16.6%
VERY SEVERE	5	2	0	0	7	9.72%
PDR	0	2	2	2	6	8.3%
HR PDR	0	3	2	2	7	9.72%
TOTAL CASES WITH DR	22	19	12	12	65	

Chi square value: 14.50000561

P Value: 0.4879947398 No Significant

Mild diabetic retinopathy was mostly seen in stage 1 and 2 CRF but moderate, severe and PDR were seen in higher stages of CRF.

DISCUSSION

200 patients who were admitted to the nephrology unit of Kurnool medical college, Kurnool and met the inclusion and exclusion criteria were included in our study.

Admission rate: during our study period,total number of admissions in nephrology department were 1880.out of which CRF patients contributed for 1308.

Age incidence:

CRF can occur at any age group, in the present study ,age group of 40-80 years constituted 65% of total cases .

This is similar to the study done by L. bajracharya et al who observed that the maximum incidence was in the age group of 48.3 ± -14.9 years

Sex incidence:

In the present study male patients constituted for 143 and female patients constituted 57 out of 200 patients. Of the study group and the male to female ratio is 2.5: 1 and it is consistent with the study of L. bajracharya et al who observed the male to female ratio was 2.3:1⁵⁸. The reason for this may be due to faster rate of deterioration of kidney function in male with some forms of glomerulo nephritis and polycystic kidney disease.

Etiology of CRF at admission

In the present study the most common etiological factors leading to CRF was diabetes mellitus , it constituted 55 and it is followed by hypertension which constituted to 55.

These observations are not in consistent with the study of L. bajracharya et al where the commonest cause of CRF was hypertension ,43 out of 119 (36.1%), followed by diabetes mellitus (27.7%) and glomerulonephritis $(20.2\%)^{58}$.

Ocular symptoms in CRF patients :

Diminished vision is the most common ocular symptom observed in our study and it substantiates with L. bajracharya et al observation of 62% of patients having blurring of vision as most common symptom in CRF patients. In our study the most common reason for the visual impairment due to maculopathy was 9.75, followed by cataracts which accounts for 5.8% followed by PDR 3.75% and it is similar to the observations made by L. bajracharya et al which showed maculopathy as cause of visual impairment in 23(9.7%) eyes 238 eyes, followed by cataract 14 eyes (5.9%) and PDR in 9 eyes $(3.8\%)^{58}$.

A . Ocular manifestations:

1. Eye lid manifestations :

Lid puffiness (62.5%) was the most common sign observed in eye lids of CRF patients. It is consistent with the signs observed by L. bajracharya et al which was 63% of the total cases⁵⁸.

This observation is statistically significant and can be regarded as consistent finding in CRF.

2. Anterior segment manifestations :

Conjunctival pallor was the most common sign in anterior segment observed in this study ie.,

2015

75% followed by pingecula and dry eye and it is consistent with the observations made by L.bajracharya et al ; it was 75.6% of total cases. Being statistically significant it can be regarded as consistent finding in CRF⁵⁸.

Corneal and conjunctival calcifications were present only in ESRD group. calcification was near the nasal and temporal limbus with a lucid interval and did not affect the vision, were observed in 1.75% in our study this was not consistent with the observations of other studies by bourquia a et al ⁵⁹, they reported that 36.0% of patients in their study had corneal and conjunctival calcifications And the studies by d pahor et al and pa Michaud et al ^{70,71} showed that calcification occurs in 60.0 to 80.0% .A positive correlation of the soft tissue calcification with the duration of hemodialysis in studies done by bourquia et al ⁵⁹ and Brenner barry et al ⁶⁰.

3. Intra ocular pressure

Mean intra ocular pressure in patients of CRF was 12.7 ± 3.3 mmhg.2 cases in our study reported neovascular glaucoma with IOP of 43.4, 40.2 mm hg. In the study done in Italy, average IOP of CRF patients was slightly less than the control group(14.9±2mmhg versus 15.6 ± 1.9 mmhg with p=0.07).our study did not have control group

4. Posterior segment manifestations :

The most important and vision threatening findings were in the posterior segment

a. Hypertensive retinopathy :

In our study 47% of total patients with CRF had hypertensive retinopathy. It was more prevalent as the renal disease progressed and it is statistically significant with p value 0.0001. the findings in our study correlated well with the studies done by L.bajracharya et al , m popa et al ⁶¹ and stibor et al ⁶². Grade 4 hypertensive retinopathy with optic disc edema was present only in severe CRF . Grade 4 hypertensive retinopathy occurred in 7 patients with stage 4 and stage 5 CRF.

b. Diabetic retinopathy :

In the present study 89% of total patients with CRF had diabetic retinopathy . mild diabetic retinopathy was mostly seen in stage 1 and 2 CRF but moderate , severe and PDR were seen in higher stages of CRF. this study correlates with observations seen in other studies done by L. bajracharya et al , ley AM et al ⁶³ , T Schleiffer et al ⁶⁴ and M Goldstein et al ⁶⁵. diabetic retinopathy is invariably present in cases of diabetic nephropathy and that more severe forms of retinopathy are detected as renal disease progresses .

c. Clinically significant macular edema :

Overall 80 eyes had clinically significant macular edema, most of which 64 eyes (32 cases) were related to diabetic retinopathy and only16 eyes (8cases) were associated with hypertensive retinopathy. It correlated with observations seen by L. Bajracharya et al⁵⁸.

d. Maculopathy:

All types of maculopathy focal 26eyes , diffuse 24eyes and chronic 30 eyes were

2015

detected and correlated with observations seen by L. Bajracharya et al 58 .

e. Retinal detachment :

There were one case of bilateral, exudative type retinal detachment in patients with severe grade of renal disease , all the findings and management were similar with other case reports given by M Goldstein et al ⁶⁵, HP Liao et al ⁶⁶, I Steiness et al ⁶⁷, A Hornblass et al ⁶⁸ and P Sharpstone et al ⁶⁹.

All the cases of grade 3 and 4 hypertensive retinopathy were detected for the first time during this study. Grade 3 and 4 hypertensive retinopathy has bad prognosis and this may alert the physician for more aggressive management of blood pressure. Among the diabetic retinopathy patients there was 6 PDR , 12 severe diabetic retinopathy and 7 very severe diabetic retinopathy all never treated before and Several patients were advised urgent laser treatment in the retina.

SUMMARY

Our study was done from november 2011 to september 2013 on 200 consecutive patients, who were admitted in nephrology ward, Kurnool medical college, Kurnool.

In our study, we aimed to prospectively analyze the ocular manifestations among CRF patients .

A detailed history , detailed ophthalmic examination was done for all the cases and recorded.

When CRF patients were evaluated the patients in the age group of 40-80 years were commonly affected . There was a definite male preponderance among the cases. The most common aetiological factor leading to CRF in these patients is diabetes mellitus followed by hypertension and some are due to glomerulonephritis and Autosomal dominant polycystic kidney disease.

Patients with CRF were staged using CGF formula in to stage 1-5 as per

Staging. Most of the patients in the present study were with milder stages of CRF and ocular screening of CRF patients in their early stages is important observation in our study as many patients were advised necessary treatment before they become irreversibly visually impaired.

Diminished vision was the most common symptom seen with CRF patients and it was commonly attributed to maculopathy followed by cataract and PDR.lid puffiness and conjuctival pallor were the most common signs observed in CRF patients. These findings are statistically significant and can be regarded as consistent finding in CRF.

Among the posterior segment signs hypertensive retinopathy findings are most common followed by diabetic retinopathy. The severity of retinopathy was more as the renal disease progressed.

The following measures would help in preventing irreversible visual loss in CRF patients.

 A Detailed ophthalmic examination is important for all newly diagnosed cases of CRF.

2015

- A Strict metabolic control and ocular screening are important in all cases of diabetic nephropathy.
- A Strict blood pressure control is important in all cases of hypertension.

CONCLUSIONS

The following conclusions are drawn from our study.

- Ocular manifestations are common in CRF patients.
- The most frequently encountered manifestations in CRF is conjuctival pallor and lid edema.
- The most common cause of CRF in our study is diabetes mellitus.
- The most commonly observed reason for diminished vision in CRF patients is maculopathy.
- Hypertensive retinopathy progresses as renal disease progresses from grade1 to grade4.
- Diabetic retinopathy is present invariably in all cases of diabetic nephropathy and more severe forms of retinopathy are detected as renal disease progresses.
- Regular screening for hypertensive retinopathy in cases of CRF can alert physician for more aggressive managementofbloodpressure.
- Regular screening for diabetic retinopathy in cases of CRF can help patients with early intervention with laser

photocoagulation and alert physician for more aggressive management of diabetes.

- 9. Detailed ocular examination should be undertaken in patients with CRF.
- If the patient has positive history abnormal renal status, he should undergo close follow up because they are at an increased risk of visual loss.
- 11. Awareness is needed of the potential ocular complications of disease process.
- 12. Retinopathy is often asymptomatic in its most treatable stage, delay in diagnosis can result in significant increase in the patient's risk of visual loss.
- 13. Ocular condition is an indicator of the metabolic control of the disease process.

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2015

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Dr. G. Narendranath Reddy et al JMSCR Volume 3 Issue 3 March 2015

2015

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