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Ocular Fundus Abnormalities in Pre-Dialytic Chronic Kidney Disease Patients

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Abstract

Background: Chronic kidney disease (CKD) affects 10% - 16% of the adult population. Although ocular findings related to renal insufficiency include cataract, conjunctival calcification, lid edema, conjunctival pallor and xanthalesma, by far the most important is retinopathy. **Objective:** To evaluate the ocular fundus abnormalities in pre-dialytic chronic kidney disease patients of the adult population. **Methodology:** This cross-sectional observational study was conducted in the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from April 2012 to March 2014. A total of 100 hospital admitted CKD patients were purposively selected for this study. Age, gender, blood pressure, Body Mass Index (BMI), 24 hours Urinary Total Protein (UTP), haemoglobin level, serum creatinine, serum cholesterol, serum triglyceride and color fundus photography findings of both eyes were recorded for each patient. Inter-group comparisons were made between patients with retinopathy and those without retinopathy. **Results:** Out of 100 adult non-dialytic CKD patients, 43 (43%) had ocular fundus abnormalities, among them 27 (62.8%) were male and 16 (37.2%) were female. The risk of development of retinopathy was significantly higher among older patients ($p = 0.006$), those with low haemoglobin level ($p = 0.0001$) and high blood pressure. Retinopathy was significantly ($p = 0.0001$) increased with reduction of e-GFR. There was no relationship between BMI and high serum triglyceride level with retinal abnormality. Among 43 (43%) patients with retinal abnormality, 30 (69.76%) patients showed only hypertensive retinopathy and 5 (11.6%) patients showed only diabetic retinopathy. Mixed hypertensive and diabetic retinopathy was found in 8 (18.6%) patients.

Maculopathy was seen in 11 (25.58%) patients, of whom 3 (6.98%) had hypertensive retinopathy and 8 (18.87%) had diabetic retinopathy. Optic atrophy was seen in 2 (4.6%) patients and drusen like retinal deposits were seen in 2 (4.6%) patients. **Conclusion:** Ocular fundus abnormalities are common among adult pre-dialytic CKD patients. Retinopathy is significantly higher in advanced stages of CKD.

Keywords

Chronic Kidney Disease (CKD), Ocular Fundus, Retinopathy

1. Introduction

Chronic kidney disease (CKD) is an irreversible and progressive process. It affects 10% - 16% of the adult population in Asia, Australia, Europe and the United States [1]. CKD has been associated with many chronic conditions like anaemia, cardiovascular disease, bone and mineral disorder, dyslipidaemia, poor nutritional status, cognitive function etc. [2]. In some recent studies, it is also shown that, several types of ocular fundus abnormalities has been associated with CKD such as microvascular retinopathy, diabetic retinopathy, macular degeneration, retinal hemorrhage [3] [4]. Deterioration of vision in CKD is due to worsening of hypertensive or diabetic retinopathy, ischemic optic neuropathy, central retinal vein occlusion and cortical blindness [5]. At the time of end-stage renal disease (ESRD), 80.0% of patients developed secondary hypertension (HTN) [5]. Ocular abnormalities may be directly due to HTN, uremia and anaemia. Some are related to the causes leading to CKD.

In 1836, Richard Bright first discovered the association of renal disease with blindness. Later on, it was found that uremic retinitis is the manifestation of systemic hypertension [6]. A study among the Chinese population revealed that, the prevalence of overall ocular fundus pathology was 32% in patients with CKD, and was significantly higher than that of patients without CKD [7]. Another study among 1904 CKD patients in the United States indicated that the overall prevalence of ocular fundus pathology among CKD patients was as high as 45% [8]. The prevalence of occular pathology varied with races, indicating effects of genetic and socioeconomic differences [8].

Retinal hemorrhage occurs in renal failure as microvascular and diabetic retinopathy, and of macular degeneration, which is exaggerated by the bleeding tendency in uremia [9] [10] [11]. Retinal microvascular abnormalities are common because hypertension, renovascular disease, and diabetes account for more than half of all patients with renal failure and also represent "traditional" risk factors for macrovascular and microvascular disease. "Non-traditional" risk factors such as inflammation, calcification, and endothelial dysfunction may contribute to the increased vascular risk too [12] [13] [14]. Diabetes is the single most common cause of CKD world-wide, and many patients with diabetes-asso-

ciated renal failure also have retinopathy [15]. In addition, recent population-based studies suggest that macular degeneration is increased in renal impairment. Risk factors common to renal failure and macular degeneration include increasing age, smoking, diabetes and hypertension [15].

Hypertensive retinopathic changes are particularly severe in renal failure. This has been attributed to the effects of retained nitrogen products. Accelerated hypertension can result in optic disc edema [16]. Blindness due to proliferative retinopathy or maculopathy is approximately five times more common in diabetic patients with nephropathy compared with normo-albuminuric patients [17]. Diabetic retinopathy tends to deteriorate with falling renal function, poorly controlled blood pressure and in patients whom no retinal treatment has been given before [18].

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 [19]. 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. Therefore the aim of this study was to evaluate the ocular fundus abnormalities in pre-dialytic chronic kidney disease patients of adult population.

2. Materials and Methods

This hospital based cross sectional study was done in the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from April 2012 to March 2014 to evaluate the ocular fundus abnormalities in pre-dialytic chronic kidney disease patients of adult population. The study was approved by the Ethical Review Committee, BSMMU, Dhaka, Bangladesh. According to the statistical calculation, a total of one hundred (100) pre-dialytic CKD patients were selected purposively.

Inclusion criteria was adult patients (age > 18 years) of both sexes with any stage of CKD. Patient with clinical picture or investigations suggesting acute kidney injury (AKI), patient on maintenance haemodialysis, patient with renal transplant and patient with cataract were excluded from the study. Height, weight, blood pressure, other demographic, clinical and biochemical information were recorded in a pre-tested data sheets.

Laboratory investigations included complete blood count (CBC), serum creatinine, Urinary Total Protein (UTP), serum fasting lipid profile. Each patient's estimated glomerular filtration rate (e-GFR) was calculated by Cockcoft-Gault (CG) formula, and according to the e-GFR, patients were assigned different stages of CKD using *KDIGO, 2012 guideline.

Patients were sent for color fundoscopy photograph of both eyes to department of Ophthalmology, BSMMU, Dhaka, Bangladesh. One image of each eye was taken after dilation with 0.5% tropicamide using a KOWA 7 (Canon, Tokyo, Japan) retinal camera. After that the color fundus photograph of each patient was assessed by an ophthalmologist in department of ophthalmology, BSMMU

and comment was taken.

The participants were divided into two groups based on the presence or absence of retinopathy. The outcome variables analysed between the two groups were age, gender, blood pressure, BMI, Urinary Total Protein (UTP) in 24 hours, haemoglobin level, serum creatinine, serum cholesterol and serum triglyceride.

2.1. Results of Fundus Examination Were Evaluated as Follows

Retinopathy defined as vascular pathology as a result of diabetes, hypertension or other conditions. The presence of retinal microaneurysms only, dot and blot and/or flame hemorrhages only, hemorrhages and/or microaneurysms, cotton-wool spots, hard exudates, intra-retinal microvascular abnormalities, venous beading, arteriovenous nipping, new vessels on the disc and elsewhere, and pre-retinal and vitreous hemorrhages was defined as retinopathy. Arteriolar narrowing and arterio-venous nipping were also defined as retinopathy. Macular degeneration suggested by large drusen and pigmentary changes. Other fundus pathology, such as other macular abnormalities and optic nerve atrophy. "Any ocular fundus pathology" was defined by the presence of at least one of fundus abnormalities mentioned above.

2.2. Definition of CKD

According to *KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, CKD is defined as abnormalities of kidney structure or function, present for >3 months.

2.3. Stages of CKD

*KDIGO suggested the following stages of CKD

- Stage 1: normal e-GFR ≥ 90 mL/min per 1.73 m^2.
- Stage 2: e-GFR between 60 to 89 mL/min per 1.73 m^2 (mildly decreased renal function).
- Stage 3a: e-GFR between 45 to 59 mL/min per 1.73 m^2 (Mild to moderately decreased renal function).
- Stage 3b: e-GFR between 30 to 44 mL/min per 1.73 m^2 (Moderate to severely decreased renal function).
- Stage 4: e-GFR between 15 to 29 mL/min per 1.73 m^2 (Severely decreased renal function).
- Stage 5: e-GFR of <15 mL/min per 1.73 m^2 (Kidney failure).

[*KDIGO = Kidney Disease Improving Global Outcomes].

2.4. Hypertensive Retinopathy Stages

Hypertensive retinopathy is categorized into five (5) stages.

- Grade 0: No changes.
- Grade 1: Barely detectable arterial narrowing.
- Grade 2: Obvious arterial narrowing with focal irregularities.

- Grade 3: Grade 2 plus retinal hemorrhages, exudates, cotton wool spots, or retinal edema.
- Grade 4: Grade 3 plus papilledema.

2.5. Stages of Diabetic Retinopathy

- Microaneurysms: The earliest clinical sign of diabetic retinopathy; these occur secondary to capillary wall outpouching due to pericyte loss; they appear as small, red dots in the superficial retinal layers.
- Dot and blot hemorrhages: Appear similar to microaneurysms if they are small; they occur as microaneurysms rupture in the deeper layers of the retina, such as the inner nuclear and outer plexiform layers.
- Flame-shaped hemorrhages: Splinter hemorrhages that occur in the more superficial nerve fiber layer.
- Retinal edema and hard exudates: Caused by the breakdown of the blood-retina barrier, allowing leakage of serum proteins, lipids, and protein from the vessels.
- Cotton-wool spots: Nerve fiber layer infarctions from occlusion of precapillary arterioles; they are frequently bordered by microaneurysms and vascular hyperpermeability.
- Venous loops and venous beading: Frequently occur adjacent to areas of nonperfusion; they reflect increasing retinal ischemia, and their occurrence is the most significant predictor of progression to proliferative diabetic retinopathy (PDR).
- Intraretinal microvascular abnormalities: Remodeled capillary beds without proliferative changes; can usually be found on the borders of the nonperfused retina.
- Macular edema: Leading cause of visual impairment in patients with diabetes.

2.6. Statistical Analysis of Data

Data cleaning validation and analysis was performed using the SPSS (Statistical Package for Social Science) software. Categorical data was presented as frequency, percentage and continuous variable was expressed as mean ± SD (standard deviation). The statistics used to analyze the data were descriptive statistics and test done were Student's "t" test, Z-test, Chi-square test and Fisher exact test. The level of significance was set at 0.05 and p value < 0.05 was considered significant.

3. Observations and Results

To evaluate the pattern of ocular fundus abnormality in pre-dialytic CKD patients of different stages among the adult population, we have evaluated 100 patients (64 male and 36 female) and divided them into two groups: **Group-A** (with fundus abnormality being present; n = 43, male = 27, female = 16) and **Group-B** (having no fundus abnormality; n = 57, male = 37, female = 20) (**Table 1**).

Table 1. Basic data of the study patients.

Parameters	Group A (n = 43)	Group B (n = 57)	P value
Age (years)			
Mean ± SD	45.56 ± 13.79	37.46 ± 14.46	0.006**
Range	20.00 - 73.00	18.00 - 71.00	
Sex			
Male	27 (62.8)	37 (64.9)	0.827**
Female	16 (37.2)	20 (35.1)	
BMI (kg/m*)			
Mean ± SD	21.97 ± 3.53	21.76 ± 2.93	0.740**
Range	15.55 - 34.63	15.20 - 30.61	
Systolic blood pressure (mmHg)			
Mean ± SD	141.40 ± 23.46	128.77 ± 19.94	0.005**
Range	90.00 - 200.00	90.00 - 170.00	
Diastolic blood pressure (mmHg)			
Mean ± SD	87.56 ± 11.72	81.40 ± 11.75	0.011*
Range	60.00 - 120.00	60.00 - 100.00	

Group A: Ocular fundus abnormality present; Group B: Ocular fundus abnormality absent. Unpaired Student's "t" test/Chi-square test was done to determine the level of significance: ns = Not significant, * = Significant ($p < 0.05$), ** = Highly Significant ($p < 0.01$).

The mean (±SD) age of group-A (Ocular fundus abnormality present) was 45.56 ± 13.79, and that of group-B (Ocular fundus abnormality absent) was 37.46 ± 14.46 ($p = 0.006$). The difference was significant between these two groups ($p = 0.006$) (Table 1).

The mean (±SD) BMI of the patients with retinopathy (group-A) was 21.97 ± 3.53 kg/m^2 and the patients without retinopathy (group-B) was 21.76 ± 2.93 kg/m^2. The difference was not approaching to the level of significance ($p = 0.740$) (Table 1).

The mean (±SD) systolic blood pressure in retinopathy positive group-A was 141.40 ± 23.46 (mm of Hg) and that of group-B was 128.77 ± 19.94 (mm of Hg), the difference was highly significant ($p = 0.005$) (Table 1).

The mean (±SD) diastolic blood pressure in group-A was 87.56 ± 11.72 (mm of Hg) and that of group-B was 81.40 ± 11.75 (mm of Hg), the difference was statistically significant ($p = 0.011$) (Table 1).

Table 2(a) shows the laboratory investigation findings among the two groups. The mean (±SD) haemoglobin level of patient with retinopathy (group-A) was 9.51 ± 1.82 g/dl and that of patients without retinopathy (group B) was 11.16 ± 2.39 g/dl. The difference was highly significant ($p = 0.0001$).

It was observed that, the mean (±SD) urinary total protein (UTP) in patient with retinopathy (Group-A) was 2.47 ± 2.06 g/24 hour and in patients without

Table 2. (a) Laboratory investigation findings of the study patients; (b) Laboratory investigation findings of the study patients.

(a)

Parameters	Group A (n = 43)	Group B (n = 57)	P value
	Haemoglobin (g/dl)		
Mean ± SD	9.51 ± 1.82	11.16 ± 2.39	0.0001**
Range	5.80 - 15.10	6.70 - 18.90	
	No. (%)	**No. (%)**	
≥12.0/11.5 (Male/Female)	3 (7.0)	21 (36.8)	0.001**
<12.0/<11.5 (Male/Female)	40 (93.0)	36 (63.2)	
	Urinary total protein (g/24h)		
Mean ± SD	2.47 ± 2.06	4.16 ± 3.25	0.003*
Range	0.59 - 10.40	0.18 - 12.60	
	No. (%)	**No. (%)**	
≤0.3	0 (0.0)	1 (1.8)	1.000**
>0.3	43 (100.0)	56 (98.2)	
	Serum creatinine (μmol/L)		
Mean ± SD	422.57 ± 256.73	196.52 ± 161.55	0.0001**
Range	84.00 - 1228.00	62.00 - 961.10	
	No. (%)	**No. (%)**	
60 - 120	4 (9.3)	28 (49.1)	0.0001**
>120	39 (90.7)	29 (50.9)	

Group A: Ocular fundus abnormality present; Group B: Ocular fundus abnormality absent; Unpaired Student's "t" test/Chi-square test was done to determine the level of significance: ns = Not significant, * = Significant ($p < 0.05$), ** = Highly Significant ($p < 0.01$).

(b)

Parameters	Group A (n = 43)	Group B (n = 57)	P value
	Serum cholesterol (mmol/L)		
Mean ± SD	5.75 ± 2.69	8.18 ± 3.28	0.0001**
Range	2.40 - 13.70	2.30 - 14.70	
	No. (%)	**No. (%)**	
3.3 - 6.3	21 (48.8)	12 (21.1)	0.003*
>6.3	22 (51.2)	45 (78.9)	
	Triglyceride (mmol/L)		
Mean ± SD	3.05 ± 1.76	2.95 ± 1.47	0.761**
Range	1.20 - 8.30	1.20 - 7.60	
	No. (%)	**No. (%)**	
<2.3	25 (58.1)	26 (45.6)	0.215**
≥2.3	18 (41.9)	31 (54.4)	
	Dyslipidaemia		
	No. (%)	**No. (%)**	
Positive (TG ≥ 2.3/S. Chol > 6.3)	29 (67.4)	47 (82.5)	0.082**
Negative (TG < 2.3/S. Chol ≤ 6.3)	14 (32.6)	10 (17.5)	

Group A: Ocular fundus abnormality present; Group B: Ocular fundus abnormality absent. Unpaired Student's "t" test/Chi-square test was done to determine the level of significance: ns = Not significant, * = Significant ($p < 0.05$), ** = Highly Significant ($p < 0.01$).

retinopathy (Group-B) was 4.16 ± 3.25 g/24 hour. The difference was statistically significant (p = 0.003).

The mean (±SD) serum creatinine of patient with retinopathy (Group-A) was 422.57 ± 256.73 μmol/L and in patients without retinopathy (Group-B) was 196.52 ± 161.55 μmol/L. The difference was highly significant (p = 0.0001).

The mean (±SD) cholesterol level of group-A and group-B were 5.75 ± 2.69 mmol/L and 8.18 ± 3.28 mmol/L respectively, the difference was highly significant (p = 0.0001). The mean (±SD) triglyceride level of group-A and group-B was 3.05 ± 1.76 mmol/L and 2.95 ± 1.47 mmol/L respectively, the difference was not statistically significant (p = 0.761). Among the patients with retinopathy (Group-A); 29 (67.4%) had dyslipidaemia, and that was 47 (82.5%) in patients without retinopathy (Group-B), the difference was not significant (p = 0.082) (Table 2(b)).

Table 3 shows different types of ocular fundus abnormalities. Among the 43 (43%) patients with retinal abnormality, 30 (69.76%) subjects showed only hypertensive retinopathy and 5 (11.6%) subjects showed only diabetic retinopathy. Mixed hypertensive and diabetic retinopathy was found in 8 (18.6%) subjects. Maculopathy was seen in 11 (25.58%) subjects, among them 3 (6.98%) patients with hypertensive retinopathy and 8 (18.87%) patients with diabetic retinopathy. Optic atrophy was seen in 2 (4.6%) patients and drusen like retinal deposit was seen in 2 (4.6%) patients.

Table 4 shows the different types of hypertensive retinopathy. Among the 43 study subjects with retinal abnormality only hypertensive retinopathy was seen in 30 (69.76%) patients, mixed hypertensive and diabetic retinopathy was found in 8 (18.6%) patients. Among the total 38 (88.37%) [30 patients with only hypertensive retinopathy plus 8 patient with mixed hypertensive and diabetic retinopathy] patients with hypertensive retinopathy; Grade-I hypertensive retinopathy was seen in 4 (9.3%) patients, Grade-II hypertensive retinopathy was seen in 20

Table 3. Different types of ocular fundus abnormality (n = 43).

Types of ocular fundus abnormality	Frequency	% among total patients	% among fundus abnormality
Total study patients	100		
Ocular fundus abnormality	43		
Only hypertensive retinopathy	30	30%	69.76%
Only diabetic retinopathy	05	5%	11.6%
Mixed hypertensive and diabetic retinopathy	08	8%	18.6%
Maculopathy	11 (3 & 8)*	11%	25.58% (6.98% & 18.87%)*
Optic atrophy	02	2%	4.6%
Retinal deposit	02	2%	4.6%

*Among 11 (25.58%) maculopathy subjects, 3 (6.98%) patients with hypertensive retinopathy and 8 (18.87%) patients with diabetic retinopathy. NB: Some participants have more than one finding.

Table 4. Different types of hypertensive retinopathy.

Types of hypertensive retinopathy	Frequency	% among total retinopathy	% among *HTN retinopathy
Total study patients	100		
Total retinopathy	43		
Total hypertensive retinopathy	38	88.37%	
Only hypertensive retinopathy	30	69.76%	78.95%
Grade-I hypertensive retinopathy	04	9.3%	10.52%
Grade-II hypertensive retinopathy	20	46.51%	52.63%
Grade-III hypertensive retinopathy	11	25.58%	28.95%
Grade-IV hypertensive retinopathy	03	6.98%	7.89%
Hypertensive retinopathy with maculopathy	03	6.98%	7.89%
Hypertensive retinopathy with optic disc swelling	03	6.98%	7.89%
Hypertensive retinopathy with optic atrophy	01	2.32%	2.63%

*HTN = Hypertensive; NB: Some participants have more than one finding.

(46.51%) patients, grade-III hypertensive retinopathy was in 11 (25.58%) patients and 3 (6.98%) patients were diagnosed as grade-IV hypertensive retinopathy. Maculopathy associated with hypertensive retinopathy was seen in 3 (6.98%) patients. Hypertensive retinopathy with optic disc swelling was found in 3 (6.98%) patients. Only 1 (2.63%) patient with hypertensive retinopathy showed optic atrophy.

Table 5 shows the different types of diabetic retinopathy. Among the total 43 patients with retinopathy, diabetic retinopathy was seen in 13 (30.23%) patients. Only diabetic retinopathy was seen in 5 (11.6%) patients, mixed hypertensive and diabetic retinopathy was found in 8 (18.6%) patients. Background non-proliferative diabetic retinopathy was seen in 8 (61.54%) patients. Pre-proliferative diabetic retinopathy was observed in 2 (15.38%) patients and proliferative diabetic retinopathy was found in 3 (23.7%) patients. Diabetic maculopathy was seen in 8 (61.54%) patients. And only 1 (7.69%) patient with diabetic retinopathy showed optic atrophy.

Table 6 shows Ocular fundal findings in relation with estimated glomerular filtration rate (e-GFR). The mean (±SD) e-GFR of patients with retinopathy positive was 22.98 ± 18.16 ml/min per 1.73 m^2, and those who do not have retinopathy was 50.69 ± 24.95 ml/min per 1.73 m^2. The difference was highly significant ($p = 0.0001$). Thus it has been observed that retinopathy was significantly ($p = 0.0001$) increased with reduction of e-GFR.

Table 7 shows the comparative study of retinal abnormalities in CKD stages 4 - 5 and CKD stage 1 - 3. Here it has been observed that, among the total 43 subjects with retinal abnormalities, 32 (74.4%) was in CKD stage 4-5, and 11 (25.6%) in CKD stage 1 - 3 ($p = 0.006$). Among the total 30 patients with hypertensive retinopathy; 23 (76.7%) patients were in CKD stage 4 - 5 and 7 (23.3)

Table 5. Different types of diabetic retinopathy.

Types of diabetic retinopathy	Frequency	% among total retinopathy	% among diabetic retinopathy
Total study patients	100		
Total retinopathy	43		
Total diabetic retinopathy	13	30.23%	
Only diabetic retinopathy	05	11.63%	38.46%
Both diabetic and hypertensive Retinopathy	08	18.6%	61.54%
Background non-proliferative diabetic retinopathy	08	18.6%	61.54%
Pre-proliferative diabetic retinopathy	02	4.65%	15.38%
Proliferative diabetic Retinopathy	03	6.98%	23.06%
Diabetic retinopathy with Maculopathy	08	18.6%	61.54%
Diabetic retinopathy with optic atrophy	01	2.32%	7.69%

NB: Some participants have more than one finding.

Table 6. Ocular fundal findings in relation with estimated glomerular filtration rate (e-GFR).

e-GFR (ml/min per 1.73 m*)	Group A (n = 43)	Group B (n = 57)	P value
Mean ± SD	22.98 ± 18.16	50.69 ± 24.95	0.0001**
Range	5.47 - 76.00	7.39 - 88.89	
	No. (%)	No. (%)	
Stage 1, 2 (e-GFR ≥ 60)	4 (9.3)	26 (45.6)	0.0001**
Stage 3 (e-GFR 30 - 59)	7 (16.3)	14 (24.6)	
Stage 4 (e-GFR 15 - 29)	11 (25.6)	11 (19.3)	
Stage 5 (e-GFR < 15)	21 (48.8)	6 (10.5)	

Group A: Ocular fundus abnormality present; Group B: Ocular fundus abnormality absent. Unpaired Student's "t" test/Chi-square test/Fisher's exact test. ** = Highly significant ($p < 0.01$).

Table 7. Comparison of retinal abnormalities in CKD stages 4 - 5 and CKD stage 1-3 (n = 43).

Parameters	n	Stage 4 - 5 No. (%)	Stage 1 - 3 No. (%)	P value
Retinal abnormality	43	32 (74.4)	11 (25.6)	0.006*
Only hypertensive retinopathy	30	23 (76.7)	7 (23.3)	0.006*
Only diabetic retinopathy	5	3 (60.0)	2 (40.0)	0.625**
Mixed hypertensive plus diabetic retinopathy	8	4 (50.0)	4 (50.0)	1.000**

Z-test; ns = Not significant; * = Significant at $p < 0.05$.

patients were in CKD stage 1 - 3 ($p = 0.006$). On the other hand, among the 5 patients with only diabetic retinopathy; 3 (60%) patients were in CKD stage 4 - 5 and 2 (40%) patients were in CKD stage 1 - 3 ($p = 0.625$). Among eight (8) pa-

tients with both hypertensive and diabetic retinopathy; 4 (50%) patients were in CKD stage 4 - 5 and rest 4 (50%) patients were in CKD stage 1 - 3 (p = 1.00). Retinopathy was significantly higher in advanced stages of CKD (stage 4 - 5) compared to early stages (stage 1 - 3).

4. Discussion

Chronic kidney disease (CKD) affects different organs of the body including eye. To find out the ocular fundus abnormalities in CKD patients, we had evaluated 100 hospital admitted patients in Department of Nephrology, BSMMU, Dhaka, Bangladesh, who had not yet commenced dialysis.

A recent study by Bixia and Ling *et al.* among the Chinese population revealed that the prevalence of overall ocular fundus pathology was 32% in patients with CKD and was significantly higher than that of patients without CKD [7]. Also similar study Grunwald and Alexander *et al.* among 1904 CKD patients in the United States showed that the overall prevalence of ocular fundus pathology was as high as 45% [8]. In this study, out of 100 CKD patients, 43 (43%) patients showed ocular fundus abnormality. Therefore this finding has got similarity with studies mentioned above.

In the CRIC (Chronic Renal Insufficiency Cohort) study by Grunwald and Alexander *et al.* showed that male have significantly higher retinopathy than female (male = 48.10%, female = 42.15%, $p < 0.05$) [8]. In this current study, 64 (64%) patients were male and 36 (36%) were female. Among the 64 male patients, 27 (62.8%) patients and among the 36 female patients, 16 (37.2%) patients showed ocular fundus abnormalities. Thus there was no significant difference (p = 0.827) between male and female in development of retinopathy in this study.

In two different studies by Alexander *et al.* [8] and another Tien *et al.* [20], both observed retinopathy was high in older age groups. In this series, the mean (±SD) age of retinopathy positive and retinopathy negative patients were 45.56 ± 13.79 years and 37.46 ± 14.46 years respectively and p = 0.006, which showed similarity with previous study. Therefore it has been documented that retinopathy is higher in older age groups.

Bixia and Ling *et al.* showed significantly high BMI in patients with retinopathy [7]. Another study by Grunwald *et al.* showed significantly low BMI in patients with retinopathy [8]. In this current study, BMI showed no significant difference (p = 0.740) between retinopathy positive and retinopathy negative groups. So relationship between BMI with retinopathy remains unexplained.

Bixia *et al.* reported that, both systolic and diastolic blood pressures were significantly higher in patients with retinopathy than those who had no retinopathy [7]. In this current study, the mean (±SD) systolic blood pressure was significantly higher in patients with retinopathy than patients without retinopathy (141.40 ± 23.46 mm of Hg and 128.77 ± 19.94 mm of Hg, p = 0.005). Similarly the mean (±SD) diastolic blood pressure was significantly higher in patients with retinopathy than patients without retinopathy (87.56 ± 11.72 mm of Hg and 81.40 ± 11.75 mm of Hg, p = 0.011). Thus similar results were observed between

the current and previous studies.

In this study, low hemoglobin level was strongly associated with development of retinopathy. The hemoglobin level in retinopathy positive group was 9.51 ± 1.82 g/dl, and retinopathy negative group was 11.16 ± 2.39 g/dl, and the p value was 0.0001, which was highly significant. Qiao *et al.* in Finland studied on 1691 diabetic patients and found that, the diabetic patients with hemoglobin level lower than 12 mg/dl were two times more likely to develop diabetic retinopathy [21]. So the finding of our study was consistent with this previous study.

Proteinuria was found to be independently associated with retinopathy, which further supports that both retinopathy and proteinuria are markers of systematic microvascular abnormalities [7]. This association has also been found to exist among participants without hypertension or diabetes, suggesting that susceptibility to microvascular disease may be caused by mechanisms other than those directly stemming from hypertension or diabetes [7]. We had found the mean (±SD) urinary total protein (UTP) in patients with retinopathy was (2.47 ± 2.06 g/24hour), which was significantly lower (p = 0.003) than patients without retinopathy (4.16 ± 3.25 g/24hour). It may be due to sclerosis of renal vasculature in advanced stages of CKD. Therefore the association between proteinuria and retinopathy was not observed in this current study.

Current study showed that high serum creatinine levels associated with retinal abnormalities. The mean (±SD) serum creatinine of patient with retinopathy (422.57 ± 256.73 μmol/L) was significantly higher (p = 0.0001) than patients without retinopathy (196.52 ± 161.55 μmol/L) in this study. The possible explanation for this retinopathy-kidney link might be; the retinal microvascular abnormalities resulting from diabetes, hypertension, cigarette smoking, inflammation and other processes that provide a common pathophysiologic link for the development and progression of CKD [20] [22]. Grunwald *et al.* showed that, the prevalence of retinopathy was significantly higher among participants with CKD, compared with participants without CKD [8].

Evaluation of lipid profile showed that, the mean (±SD) cholesterol level of retinopathy positive and retinopathy negative patients were 5.75 ± 2.69 mmol/L and 8.18 ± 3.28 mmol/L respectively. It may be due to the maximum glomerulonephritis patients with proteinuria was in the group with no retinopathy. The mean triglyceride level of group-A and group-B was 3.05 ± 1.76 mmol/L and 2.95 ± 1.47 mmol/L, the difference was not statistically significant (p = 0.761). Dyslipidaemia was found in 29 (67.4%) patients with retinopathy (Group-A) and that was 47 (82.5%) patients without retinopathy (Group-B), the difference was not significant (p = 0.082). However in a study by Tien and Josef *et al.* documented that, retinopathy was associated with high cholesterol levels and higher triglyceride levels [20].

In this study, 43 patients showed retinal abnormality. Of them 30 (69.76%) patients showed only hypertensive retinopathy and 5 (11.63%) patients showed only diabetic retinopathy. 8 (18.60%) patients had both hypertensive and diabetic changes on their ocular color fundal examination. Optic atrophy was seen in 2

(4.65%) patients and drusen like retinal deposit was seen in 2 (4.65%) patients.

Among the 38 (30 patients with hypertensive retinopathy plus 8 patient with mixed hypertensive and diabetic retinopaty) patients with hypertensive retinopathy, the most common abnormality we had found was grade-II hypertensive retinopathy (20, 46.51%), then grade-III (11, 25.58%) and grade-I hypertensive retinopathy (4, 10.52%) respectively. The least we found was grade–IV hypertensive retinopathy (3, 6.98%). Soft exudates which was due to hypertensive retinopathy found in 32.55% (n = 14) patients. Maculopathy was seen in 3 (6.98%) patients. Only 1 patient (2.32%) with hypertensive retinopathy showed optic atrophy.

Among the 13 patients of diabetic retinal abnormality, 5 patients (11.63%) with only diabetic retinopathy, 8 patients (18.60%) showed combination of both diabetic and hypertensive retinopathy. Majority of those [8 patients (18.60%)] had non-proliferative background diabetic retinopathy, 2 patients (4.65%) showed pre-proliferative diabetic retinopathy and 3 patients (6.98%) showed vision threatening proliferative diabetic retinopathy with neovascularisation. Microaneurysm, which was the hallmark of diabetic retinopathy was found in 30.23% (n = 13 among total 43 patients with retinopathy) patients. More than half of the patients 61.54% (n = 8) showed diabetic maculopathy. Optic atrophy was seen in 7.69% (n = 1) patients with diabetic retinopathy.

In a study by Rajeev and Mohamad *et al.* showed that 41 (41 of 149, 28%) patients with CKD stages 3 to 5 had a moderate to severe diabetic retinopathy, compared with 16 (11%) patients with CKD stages 1 to 2 ($p = 0.001$) [23]. In addition, diabetic retinopathy became more common as renal function deteriorated in CKD stages 3 to 5 ($p = 0.001$). But they did not found any difference in level of hemoglobin A1c in patients with diabetic retinopathy with CKD stages 3 to 5 compared with CKD stages 1 to 2 (7.9% ± 1.81% and 8.5% ± 2.34%, respectively, $p = 0.30$) [23]. They also reported that proliferative diabetic retinopathy were more common in CKD stages 3 to 5 than CKD stages 1 to 2 (18 of 149, 12% compared with 2 of 150, 1%, $p = 0.001$) and similarly became more common as renal function deteriorated ($p = 0.001$). In this present study, diabetic retinopathy in CKD stage 1 - 3 and CKD stage 4 - 5 had no significant statistical difference.

Maculopathy in current study was seen in 11 (25.58%) patients, of them 3 (6.98%) were associated with hypertensive retinopathy and 8 (18.6%) were diabetic maculopathy. In a study [23], it was observed that macular degeneration was increased in patients with CKD stages 3 to 5 compared with patients with CKD stages 1 to 2. They had seen 62 (62 of 140, 44%) patients with CKD stages 3 to 5 had these changes compared with 43 (43 of 148, 29%) patients with CKD stages 1 to 2 ($p = 0.010$).

Grunwald and Alexander *et al.* observed that, lower e-GFR was associated with a much higher incidence of fundus pathology [8]. The percentage of participants with any eye pathology was 60% in those with e-GFR < 30 ml/min and 35% in participants with e-GFR ≥ 50 ml/min [8]. In the current study, it has

been observed that, the mean (±SD) e-GFR of patients with retinopathy positive was 22.98 ± 18.16 ml/min per 1.73 m^2 which was significantly lower ($p = 0.0001$) than those who do not have retinopathy (50.69 ± 24.95 ml/min per 1.73 m^2). The low e-GFR was a risk factor for development of retinopathy as retinopathy significantly increases with decreasing e-GFR. Therefore this current study concluded that retinopathy was significantly ($p = 0.0001$) higher in advanced stages of CKD than in early stages.

5. Conclusion

The current study suggests that, ocular fundus abnormalities are common among the pre-dialytic CKD patients of adult population. It has been observed that retinopathy is significantly higher in advanced stages of CKD than in early stages. Hypertensive retinopathy, non-proliferative diabetic retinopathy, vision threatening proliferative diabetic retinopathy and maculopathy are not uncommon in adult pre-dialytic CKD patients.

Limitations of Study

It was a single centre study with relatively small sample size.

Recommendations

To identify the correct incidence of retinopathy in pre-dialytic chronic kidney disease (CKD) patients in adult population, a large scale, multi-center study will be needed. Regular ocular follow up, early recognition of abnormality and intervention will provide better visual outcome.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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