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CHRONIC KIDNEY DISEASE;
HYPERTENSIVE AND DIABETIC RETINOPATHY IN PATIENTS

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ABSTRACT... Diabetes Mellitus and Hypertension are leading causes of chronic kidney disease (CKD). There is limited data on frequency of retinopathy attributed to diabetes mellitus or hypertension in CKD patients in local population. **Objective:** to determine the frequency of diabetic and hypertensive retinopathy in patients with CKD not on hemodialysis or peritoneal dialysis. **Study Design:** Cross Sectional. **Setting:** Nephorology ward at Sharif Medical City Hospital. **Period:** 6 Month. **Methods:** All patients between ages of 20-80 years with CKD not previously on renal replacement therapy (hemodialysis or peritoneal dialysis) who were admitted to nephrology ward at tertiary care facility over a 6 month period were included. Fundoscopic examination was performed by a qualified ophthalmologist after dilating pupils. **Results:** A total of 124 patients were included in the study. Stage V CKD was present in 85.7%. Diabetes Mellitus was present in 84 patients (67.7%). Of these patients, 39 (46.4%) had diabetic retinopathy. Non-proliferative diabetic retinopathy, proliferative diabetic retinopathy and macular edema were found in 27 (69.1%), 4 (10.2%) and 9 (23.1%) patients respectively. Hypertensive retinopathy was present in 51 (49.5%) out of 103 (83%) hypertensive patients. Of these patients, 16 (31.3%) had grade I, 21 (41.2%) had grade II, 11 (21.6%) had grade III and 3 (5.8%) had grade IV hypertensive retinopathy. **Conclusion:** A significant proportion of patients with advanced CKD have retinopathy. Patients with CKD and diabetes or hypertension should be encouraged to undergo a complete eye examination

Key words: Chronic Kidney Disease, Diabetic Retinopathy, Macular Edema, GFR.

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INTRODUCTION

Chronic Kidney Disease (CKD) is a growing worldwide public health problem and is associated with high morbidity and health care utilization.[1] Diabetes Mellitus and Hypertension are the leading causes of CKD.[2] Diabetes mellitus and hypertension affect multiple organs including eyes. Renal microvascular damage induced by diabetes mellitus and hypertension play an important role in pathogenesis of CKD.[2] Retinal vasculature which can be observed non-invasively allows a clinician to explore microvascular complications of diabetes mellitus and hypertension.

Several studies have shown correlation between diabetic and hypertensive retinopathy and nephropathy.[3-6] Etiology of CKD may be attributed to diabetes mellitus or hypertension if presence of diabetic or hypertensive retinopathy respectively is documented on funduscopic examination.[2] In addition, most patients with CKD due to diabetes Mellitus or hypertension will likely have retinal changes. Retinal examination in such patients, who may otherwise be asymptomatic, may help in early detection and institution of treatment for diabetic or hypertensive retinopathy.

Several international studies have explored relationship between fundoscopic abnormalities and presence of CKD in patients with diabetes mellitus and/or hypertension. Reported frequency of diabetic and hypertensive retinopathy has ranged from 22.8%-88.3% and 7.8%-68% in CKD patients.[7-13] There is limited information in local literature with one study found a frequency of diabetic retinopathy as 36% and that of hypertensive retinopathy as 22% but study population comprised of hemodialysis patients only.[14]

Patients with CKD in Pakistan seek medical advice at a much later stage due to lack of education, awareness, medical facilities and financial constraints.[15] Therefore; frequency of diabetic and hypertensive retinopathy in CKD patients who are not yet on hemodialysis or peritoneal dialysis in Pakistan may be different compared to the reported literature.

The objective of this study is to determine the frequency of diabetic and hypertensive retinopathy in patients with CKD not on hemodialysis or peritoneal dialysis.

METHODS

The study design was cross-sectional in nature. All patients between ages of 20-80 years with CKD not previously on renal replacement therapy (hemodialysis or peritoneal dialysis) who were admitted to nephrology ward at Sharif Medical City Hospital over a 6 month period and who gave informed consent for the study were included.

Sampling technique was non-probability consecutive sampling. Sample size of 96 was calculated with 95% confidence level, 10% margin of error and taking expected percentage of CKD patients with Diabetic or hypertensive retinopathy as 50%. The study was approved by institutional review board.

CKD was defined as estimated GFR (eGFR) of less than $<60ml/min/1.73m^2$ or presence of proteinuria for 3 or more months.[16] eGFR was calculated by CKD-EPI formula as follows: GFR $= 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female], Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.[17]

Patient's history, medical records and laboratory information were reviewed to obtain data on patient's age, sex, history of hypertension, diabetes mellitus, duration of hypertension and diabetes mellitus cardiovascular disease, heart rate, blood pressure, blood hemoglobin, serum creatinine, eGFR and urine protein to creatinine ratio. Cardiovascular disease was defined as known prior history of coronary artery disease, cerebrovascular disease or peripheral vascular disease based on history and review of prior medical records.

Fundoscopic examination was performed by a qualified ophthalmologist after dilating pupils. Diabetic retinopathy was categorized as non-proliferative, proliferative retinopathy and macular edema.[18] Non-proliferative diabetic retinopathy was characterized by presence of any of the following abnormalities:- cotton wool spots, intra-retinal hemorrhages, hard exudates or microvascular abnormalities (microaneurysms, occluded vessels or dilated/tortous blood vessel). Proliferative diabetic retinopathy was characterized by presence of neovascularization, pre-retinal or vitreous hemorrhage or retinal detachment. Macular edema was characterized by retinal thickening or edema involving macula.

Hypertensive retinopathy was classified by Keith Wagener Barker (KWG) grades.[19] Grade I was assigned if patient had arteriolar constriction/attenuation/sclerosis -`silver wiring` and vascular tortuosities. Grade II was assigned if patient had grade I findings and irregularly located, tight constrictions - Known as `AV nicking` or `AV nipping`. Grade III was assigned if patient had grade 2 findings and retinal edema, cotton wool spots and flame-hemorrhages. Grade IV was assigned if patient had grade III findings and optic disc edema.

Patients were divided into two groups based on presence or absence of retinopathy.

Statistical Analysis

Continuous parametric variables were reported as means ± standard deviation; and categorical variables were expressed as percentages. Categorical variables were compared using the chi-square test, and continuous variables were compared using t-test. All statistical analyses were performed using SPSS 20.0 (Chicago, IL USA). For all tests, p values of <0.05 were considered statistically significant.

RESULTS

A total of 124 patients were included in the study. Of these patients 72 (57%) had visual symptoms. Proportion of patients with stage III, IV and V CKD was 5.9%, 7.6% and 85.7% respectively. Diabetes Mellitus was present in 84 patients. Mean age of patients with diabetes mellitus and CKD was 52.3±11.4 years. Mean serum creatinine was 7.2±3.3 mg/dl, mean eGFR was 10.4±9.4 ml/min/1.73 m^2. Of these patients, 41 (48.8%) were males and 43 (51.2%) were females, 22 (26.2%) were smokers and 29 (35.5%) had known cardiovascular disease. of these 9 (10.7%) had cataracts in one or both eyes and 39 (46.4%) had diabetic retinopathy. Non- proliferative diabetic retinopathy, proliferative diabetic retinopathy and macular edema were found in 27 (69.1%), 4 (10.2%) and 9 (23.1%) patients respectively. Out of 39 patients with diabetic retinopathy, 17 patients (43.8%) were advised anti vascular endothelial growth factor therapy or laser photocoagulation.

Table-I. shows comparison of characteristics of diabetic CKD patients with and without diabetic retinopathy. of all CKD patients, 103 (83%) patients had hypertension. Mean age of these patients was 49.8±13.6 years. Mean serum creatinine was 7.3±3.4 mg/dl and mean eGFR was 10.4±7.5 ml/min/1.73 m^2. Hypertensive retinopathy was present in 51 (49.5%) out of 103 (83%) hypertensive patients. Of these patients, 16 (31.3%) had grade I, 21 (41.2%) had grade II, 11 (21.6%) had grade III and 3 (5.8%) had grade IV hypertensive retinopathy. A comparison of characteristics of hypertensive CKD patients with and without hypertensive retinopathy is depicted in table-II.

	Patients with Diabetic Retinopathy N=39	Patients without Diabetic Retinopathy N=45	P value
Mean age (years)	51.7±11.5	52.9±11.3	0.63
Males (%)	48.7	48.9	0.98
Hypertension (%)	87.2	91.1	0.50
Duration of Hypertension (months)	65.6±55.4	59.2±67.7	0.70
Duration of Diabetes Mellitus (months)	123±72.6	121.6±79.7	0.59
Cardiovascular Disease (%)	42.1	29.5	0.24
Smokers (%)	29.7	24.4	0.59
Dyslipidemia (%)	23.1	18.2	0.58
Mean Systolic Blood pressure (mm Hg)	125±27.2	134.7±31.6	0.14
Mean Diastolic Blood pressure (mm Hg)	86±19.3	89.1±13.6	0.41
Mean hemoglobin (g/dl)	9.2±2.1	8.8±1.7	0.32
Mean serum creatinine (mg/dl)	6.9±3.5	7.4±3.3	0.44
Mean eGFR (ml/min/1.73 m^2)	9.9±10.7	10.7±8.1	0.70
Mean urine protein to creatinine ratio (g/g)	4.6±4.4	3.8±4.0	0.53

Table-I. Comparison of characteristics of CKD patients with and without Diabetic retinopathy

	Patients with Hypertensive Retinopathy N=51	Patients without Hypertensive Retinopathy N=52	P value
Mean age (years)	50.3±14.5	49.3±12.4	0.71
Males (%)	57.9	53.1	0.61
Diabetes Mellitus (%)	77.2	63.3	0.12
Duration of Hypertension (months)	62.5±68.9	49.4±41.8	0.24
Duration of Diabetes Mellitus (months)	103.9±81.2	110.3±78.9	0.74
Cardiovascular Disease (%)	33.3	31.2	0.82
Smokers (%)	24.6	25.5	0.90
Dyslipidemia (%)	17.9	10.4	0.28
Mean Systolic Blood pressure (mm Hg)	130.5±27.8	128.6±32.9	0.76
Mean Diastolic Blood pressure (mm Hg)	87.6±16.9	87.6±16.5	0.99
Mean hemoglobin (g/dl)	8.8±2.1	8.8±1.8	0.18
Mean serum creatinine (mg/dl)	7.3±3.3	7.4±3.5	0.18
Mean eGFR (ml/min/1.73 m^2)	10.3±8.3	10.0±6.7	0.31
Mean urine protein to creatinine ratio (g/g)	3.7±3.7	3.9±3.9	0.35

Table-II. Comparison of characteristics of CKD patients with and without hypertensive retinopathy

DISCUSSION

Our study showed that nearly half of patients with CKD who had either diabetes and/or hypertension had funduscopic findings consistent with retinopathy. To our knowledge, this is the probably the first reported study of frequency of hypertensive and diabetic retinopathy in CKD patients in Pakistan.

In our study we found that 46% of patients with diabetes and CKD had diabetic retinopathy and 1/3rd of these patients had proliferative diabetic retinopathy or macular edema. Our results are consistent with study by Wong et. al which showed a frequency of diabetic retinopathy as 46% in a much larger cohort of CKD patients in Singapore.[10] Other studies have shown a lower frequency. In an Italian study by Giuseppe et. al. advanced diabetic retinopathy was found in 15.3% of all CKD patients (9). Similarly prevalence of any retinopathy was found to be 25% by Grunwald et al[11], 38% by Jasvidner S et al.[13] and 28% by Deva et al.[12] Our study has significantly higher proportion of patients with advanced CKD. In addition, late presentation and possible lack of prior funduscopic examination may be additional reasons for higher frequency of diabetic retinopathy in our patient population. In a regional study in another 3rd world country Nepal by Bajracharya et al, diabetic retinopathy was found in significantly higher (88.3%) proportion of patients with CKD.[7]

We also found that among hypertensive patients with CKD, nearly half of patients had funduscopic findings consistent with hypertensive retinopathy. Our results are consistent with study by Bajracharya et al. which found a frequency of hypertensive retinopathy as 47%.[7] Jasvinder et al has found a much lower prevalence of 7.8% in his study population which has significantly more patients with early stage CKD.[13] Vrabec R et al. showed a much higher frequency of 68% in his relatively small cohort of hemodialysis patients.[24] Our results differ since we have more patients with advanced CKD but we didn't include any patients on hemodialysis.

Discovery of retinopathy in CKD patients has several implications. First, it can lead to timely institution of treatment for diabetic retinopathy to prevent visual loss. In our study, nearly 44% of patients with diabetic retinopathy were advised treatment further treatment. In addition, retinopathy in CKD patients has prognostic significance. Several studies have shown that hypertensive or diabetic retinopathy in CKD patients is associated with rapid decline in eGFR and increased risk of cardiovascular events or death[21-23] There is also a strong association between severity of retinopathy and its features and level of kidney function after adjustment of traditional and non-traditional risk factors.[8]

Our study has several limitations including relative small sample size, single center and cross-sectional study design. In addition, our study included large number of patients with advanced CKD who were hospitalized. This may have resulted in over-estimation of frequency of retinopathy as hospitalized patients with advanced CKD are more likely to have underlying microvascular complications. However, our study population's characteristics are reflective of patient's profiles in tertiary care facilities in Pakistan.

In summary, our study shows that a significant proportion of patients with advanced CKD have retinopathy. Patients with CKD and diabetes or hypertension should be encouraged to undergo a complete eye examination.

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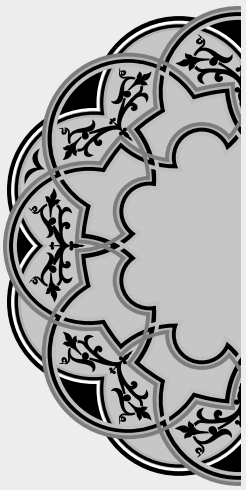

"Being defeated is often a temporary condition; giving up is what makes it permanent."

Unknown

AUTHORSHIP AND CONTRIBUTION DECLARATION

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4	Dr. Roshina Anjum	Data collection	
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