

ORIGINAL ARTICLE

Diabetes, Hypertension and Kidney Disease Combination “DHKD Syndrome” is common in India

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Abstract

Objective: The study was designed to find out frequency of (i) Diabetes mellitus (DM) as a cause Chronic Kidney Disease (CKD), (ii) Association between diabetic-CKD (diabetic patients who subsequently developed CKD as complication), hypertension (HT) and obesity. Further assessment was made to (iii) Identify percentage of diabetics attending medical and nephrology OPD had prior testing for proteinuria and or creatinine.

Methods: After ethical consideration this prospective observational study was conducted on consecutive 6175 patients who gave consent to participate in two major referral hospitals one in Delhi and other in Bhubaneswar (BBSR). Primary hypertension was defined as blood pressure of $\geq 140/90$ mmHg detected before onset of DM or detected together in the absence of CKD (elevated serum creatinine S Cr ≥ 1.7 mg/dL and or proteinuria $> 0.3g/24H$). Upper limit of serum creatinine was kept at 1.7 mg for this study. Mean value of three estimations on different days was recorded. Detail clinical history of DM and HT was taken.

Body Mass Index (BMI), ocular fundi examination, urine analysis, serum creatinine, lipid profile, blood glucose, HbA_{1c} tests were conducted in all patients. They were regularly followed up in renal clinic at about 2 month interval for repeat investigations. Blood pressure in nondiabetic-CKD patients was recorded for comparison.

Further, consecutive diabetic patients attending general medicine OPD for first time were examined, their previous investigations were carefully scrutinized and recorded. Urine for albuminuria and serum creatinine were tested every month over a period of one year.

Results: In Delhi diabetic-CKD was observed in 68.4% and the same was 56.2% in BBSR giving a combined figure of 62.3 percent. On close analysis of past record primary hypertension was observed in 75.4% who subsequently developed diabetes and CKD. Frequency of association between diabetic-CKD and HT were 88.2% and 69.3% in two cities respectively, combined frequency being 78.7 percent. Association of diabetic-CKD and obesity was 55.1 % and 55.9% in two cities respectively with combined frequency of 55.5 percent. In contrast obesity in non-diabetic-CKD patients in Delhi and BBSR was found in 43.1% and 18.5% respectively, combined frequency being 30.8%. Fifty four percent of diabetic patients who attended medical OPD for the first time were found to have proteinuria and elevated serum creatinine. However, they were not earlier tested for those parameters. Hence, they were unaware of CKD.

Conclusion: Diabetes was found to be a bigger cause (62.3%) of CKD than what has been reported thus far in India. At presentation association of diabetic-CKD with HT was recorded higher (78.7%) in India. Hence use of the syndrome “DHKD”, (complex of diabetes, hypertension and kidney disease) is justifiable. Our study shows 54.4% of diabetic patients attending medicine OPD were uninvestigated by either physician or GP for CKD because urine albumin and serum creatinine tests were lacking. Thus, progression to CKD in many patients went unnoticed. Syndromic diagnosis of “DHKD” therefore in our view is important to create general awareness for early detection and effective treatment of diabetic nephropathy.

Introduction

Diabetes and Hypertension two major causes of CKD are spreading like silent epidemic in India and other developing countries.^{1,2} It has reduced quality man days and has already put huge financial burden on families and government exchequer.³ ICMR study reported in 2011 revealed 64.4 and 77.2 million people had diabetes and prediabetes respectively.⁴ It is predicted that by 2030 India’s diabetic population would be nearly 87 million.⁵ Similarly, incidence of hypertension has been progressively rising at alarming rate. According to 2010 WHO report on global status of non-communicable diseases, prevalence of HT has increased from 16% in 2004 to 32.6% in 2008.⁶ Further more Jaipur heart watch study on urban Indians also revealed incidence of HT increased from 30% in 1994 to 51% in 2003 both in male and female population.⁷ An earlier study has shown several fold increase in incidence of hypertension among rural “Oraon” tribal people when they migrated to urban areas.⁸

Aims and Objective

However, there is no clear data on (i) how frequently diabetes is complicated by chronic kidney disease (ii) What is the frequency of association between diabetic-CKD and hypertension. (iii) What percentage of Indian diabetic patients in the society are aware of associated renal dysfunction (iv) What

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is the correlation between obesity and kidney disease. To find answers to above questions we prospectively studied consecutive diabetic patients attending renal clinic in two major referral hospitals in two different geographic regions and followed them over a period of 10 and 6 years respectively. The study also aimed at identifying frequency of renal dysfunction in diabetic patients attending medicine OPD for first time.

Material and Methods

Consecutive adult patients attending nephrology clinic of the author from 1994 -2003 in a premier teaching hospital of Delhi and 2006-2012 in an Eastern India referral Hospital in Bhubaneswar (BBSR) constituted subjects of this study. Patients, who gave informed consent to participate, were included. Most patients were admitted to indoor in order to complete the investigations.

Patients with unreliable history and serious complications were excluded. Similarly, those who had evidence of acute kidney injury were also excluded from the study. Detail history and physical examination, prior records of HT, DM and renal function tests were analysed. Blood Pressure was measured by sphygmomanometer and 14 cm Cuff by the same observer throughout the study. After giving 5 minutes rest three readings were taken in supine position. Mean figure of three readings was taken as the actual blood pressure. From analysis of history and record primary hypertension was defined as elevated blood pressure of $\geq 140/90$ mmHg detected earlier than onset of diabetes or both detected at the same time in the absence of CKD. CKD was defined for this study as serum creatinine \geq of 1.7 mg/dL (as per our lab standard) and or proteinuria $>$ 0.3 gm. Serum creatinine was measured on more than 3 occasions in 3 months (after correction of acute kidney injury factors if any). Body Mass Index was calculated from equation,

$$\text{Body weight in Kg}$$

$$(\text{Height in meter})^2$$

for correlation. After overnight fasting, morning blood sample was taken for serum lipid profile, uric acid, blood glucose, glycosylated hemoglobin (HbA_{1c}). Twenty-four hour urine protein estimation was done at the institute laboratories. ECG, chest X-ray

and ocular fundi examination were conducted as part of routine protocol for all CKD patients. They were followed in renal clinics at 2- 3 months interval for assessment and treatment. Consecutive non-diabetic CKD patients during 5 years at Delhi and 9 years at BBSR were examined for assessment of past or present hypertension. Author in collaboration with medicine consultant conducted simple tests like urine for albuminuria and serum creatinine in consecutive diabetic patients attending medicine OPD for first time over a period of one year.

Results

A total 6175 consecutive patients attending two nephrology units constituted our study population. There were 3050 subjects (Male=62 %, Female=38%) in Delhi group and 3125 subjects (Male=73%, Female=27%) in BBSR group. In them CKD was associated with diabetes in 68.4% among Delhi patients and 56.2% among BBSR patients (Tables 1 and 2). Among 2087 Delhi patients with diabetic-CKD, 14% had stage-I and II (proteinuria only) where as more advanced stage-III, IV, V were seen in 38.8 %, 30.2% and 16.7% respectively (Table 1). The same were seen in 21.2%, 27.7%, 26.7% and 24.4% in BBSR respectively (Table 2).

Frequency of association between diabetic-CKD and HT was seen in 88.2% (Delhi) and in 69.3% (BBSR) respectively. In contrast those figures in non-diabetic CKD in Delhi and BBSR were 56.8% and 53.8% respectively (Table 3). Frequency of association between diabetic-CKD and obesity was 55.1% (Delhi) and 55.9% (BBSR) respectively. In contrast those figures in nondiabetic-CKD were 43.2%, 18.5% respectively (Table 4).

It was revealed that as high as 54% of diabetic patients attending general medicine OPD were positive for heavy proteinuria and or abnormal serum creatinine unknown to them as their renal function was never tested before. In both centers, CKD associated with hypertension was observed in higher percentage in diabetics compared to non diabetics. Similarly diabetic CKD patients were more frequently associated with obesity than nondiabetics. This was true in all patients studied at different time period of study and were statistically

significant.

Discussion

Higher rate of diabetic renal disease is reported among Indo-Asians in UK, African-American,⁹ Mexican-Americans in USA and Pima Indians.¹⁰ These ethnic groups have shown not only higher incidence of Type-2 diabetes but also high incidence of hypertension suggesting genetic predisposition to hypertension. It is well known that combination of diabetes and hypertension leads to higher incidence of nephropathy. The same has been shown by current study. Hypertension, diabetes and hyperlipidemia are risk factors for life-threatening complications like CKD and CVD (Cardio Vascular Disease) which put huge financial burden on patients and on state exchequer for treatment.

Current study observed significant higher association between diabetes and CKD (62.3% mean value in two hospitals). This is much higher than incidences 22.3% - 30.3% reported in literature 11 years ago.^{11,12} Despite a possible bias factor as patients were seen in nephrology clinic, findings were relevant. Similarly, it revealed a much higher incidence of hypertension among diabetic-CKD patients (combined value 79.5%) compared to nondiabetic CKD; (55.0%) respectively (Table 3). Furthermore higher association of obesity was observed among diabetic-CKD patients than non diabetic-CKD, combined value of 55.6% against 25.5% respectively (Table 4).

Regarding association of CKD and hypertension, Bivariate analysis (Table 3) showed CKD due to diabetes was associated with higher incidence of hypertension (88.2%) and nondiabetic CKD associated with lower incidence (56.8%) at Delhi. At Bhubaneswar those figures were 69.3 percent and 53.8 percent respectively. These associations were statistically highly significant. Diabetes and hypertension have been co-prevalent in patients as high as 62%. Almost one- third of patients with hypertension developed diabetes later.¹³ Present study also confirm to the earlier observation, because when associated with hypertension incidence of DN rose to 79.5 percent.

In the present study fifty four percent of CKD was detected among

Table 1: Frequency of association between CKD and DM at AIIMS, New Delhi (year 1994-2003)

Year	Total no. of cases of CKD	Total no. of CKD cases with DM	Proteinuria > 0.3g	S. Cr ≤ 1.7 mg/dl		
				CKD III	CKD IV	CKD V
				1.7-3.5	3.6-6.5	6.6-15.8
1995	282	192	28	78	54	32
1996	316	208	32	73	66	37
1997	274	195	34	76	52	33
1998	253	182	26	79	54	23
1999	382	254	27	96	87	44
2000	396	273	34	102	86	51
2001	432	291	40	115	86	50
2002	228	157	26	61	47	23
2003	245	166	23	66	50	27
	3050	2087 (68.4%)	295 (14.1%)	811 (38.8%)	631 (30.2%)	350 (16.7%)

Table 3: Bivariate analysis showing association between diabetic CKD and hypertension

	Hypertension (HT) no. (%)	No HT no. (%)	Total	P value
A. AIIMS New Delhi (Year 1994-2003)				
Diabetic CKD	1840 (88.2)	247 (11.8)	2087	<0.0001
	Primary HT 565 (30.7)			
	Secondary HT 1275 (69.3)			
Non-diabetic CKD	547 (56.8)	416 (43.2)	963	
B. KIMS, Bhubaneswar (Year 2006-2012)				
Diabetic CKD	1218 (69.3)	540 (30.7)	1758	<0.0001
	Primary HT 354 (29.06)			
	Secondary HT 864 (70.94)			
Non-diabetic CKD	736 (53.8)	631 (46.2)	1367	

diabetic patients attending medicine OPD. It was revealed that they were unaware of presence of CKD in them. Moreover, what was observed in medical OPD was at a point of time. Those patients primarily attended for diabetes. Given longer time on longer follow up patients likely to develop proteinuria and or raised serum creatinine. Thus, it is clear that CKD occurs in higher proportion among Indian diabetic population.

Pathophysiologically CKD produces hypertension by several mechanisms such as salt and water retention, ischemic damage to renal medulla (producing less secretion of prostaglandin secretion). Several studies have suggested a genetic link between diabetes and hypertension. Interesting to note that 75.4% of our patients had primary hypertension before their serum creatinine was elevated or other parameters of CKD detected. Co-existence of HT and hyperglycemia dramatically and synergistically increase risk of microvascular diseases like renal retinal microangiopathy.¹⁴ Several studies have suggested sensitizing effect of hyperglycemia on vascular system leading to complication of

HT.¹⁵ What then is the relation between hypertension and diabetes. Prediabetics frequently have HT as one of the feature of metabolic syndrome.¹⁶

Genetic link: (i) Angiotensinogen: Among many candidate genes linking HT to DM/DN, genes of renin-angiotensin system have been of most interest. Pro-renin, renin, ACE and angiotensin level are elevated in diabetic nephropathy.¹⁷ (ii) Furthermore studies have implicated genes of renin-angiotensin system to be determinants for both hypertension and diabetic kidney damage as well as cardiovascular disease. (iii) Linkage of the M235T polymorphism gene has been demonstrated in essential hypertension.¹⁸ (iv) Although there are conflicting reports one study has clearly shown association TT genotype with elevated blood pressure in patients with diabetic nephropathy.¹⁹

Conclusion

Present study provides ample evidence confirming high association between diabetes, hypertension and kidney disease is like a nexus. More than 50% of diabetic patients of our country are unaware of existence of renal damage prior to presentation due

Table 2: Frequency of association between CKD and DM at renal clinic, KIMS, Bhubaneswar (year 2006-2012)

Year	Total no. of cases of CKD	Total no. of CKD cases with DM	Proteinuria > 0.3 g	S. Cr ≤ 1.7 mg/dl		
				CKD III	CKD IV	CKD V
				1.7-3.5	3.6-6.5	6.6-14.6
2006	235	125	32	39	43	35
2007	312	139	39	49	47	37
2008	340	153	40	54	46	42
2009	342	167	42	57	49	41
2010	349	180	34	50	54	48
2011	390	208	37	51	57	47
2012	393	240	41	55	61	51
2013	359	278	52	64	55	61
2014	405	268	55	68	58	67
	3125	1758 (56.2%)	372 (21.2%)	487 (27.7%)	470 (26.7%)	429 (24.4%)

Table 4: Bivariate analysis showing association between diabetic CKD and obesity

	Obesity number (%)	No obesity number (%)	Total	P value
A. AIIMS New Delhi (Year 1994-2003)				
Diabetic CKD	629 (55.1)	512 (44.9)	1141	<0.0001
Non-diabetic CKD	234 (43.2)	308 (56.8)	542	
B. KIMS, Bhubaneswar (Year 2006-2012)				
Diabetic CKD	983 (55.9)	775 (44.1)	1758	<0.0001
Non-diabetic CKD	253 (18.5)	1114 (81.5)	1367	

to lack of simple urine albumin test and or serum creatinine estimation. Thus CKD at the crucial early stage go unnoticed leading to more advanced stages. This is a serious mistake and therefore it is necessary to use the term "Diabetic Hypertension-Kidney Disease (DHKD) Syndrome" for creating awareness among patients and doctors for early detection of DN, at a stage when it can be effectively treated.

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