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Original Article

Internal Medicine Section

Diabetic Kidney Disease and Hypertension: A True Love Story

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ABSTRACT

Introduction: Diabetes Mellitus (DM) remains one of the commonest causes of structural and functional kidney abnormalities leading to End Stage Renal Disease (ESRD). The next most common cause is hypertension. It is utmost important to investigate the association between diabetic nephropathy and hypertension because it is a major causal factor of end-stage kidney failure in Type 2 Diabetes Mellitus (T2DM).

Aim: The aim of the present study was to investigate the association between albuminuria, hypertension and estimated glomerular filtration rate (eGFR) in a prospective cohort of T2DM patients in a developing country.

Materials and Methods: A total of 824 patients were enrolled from a tertiary healthcare center in central India. This study was performed in three groups: normal controls (232), type 2 diabetics without nephropathy (185) and type 2 diabetics with nephropathy (407). Diabetic nephropathy was clinically defined by the presence of persistent proteinuria of > 500mg/day in a diabetic patient in the absence of clinical or laboratory evidence of other kidney or urinary tract disease. Hypertension was categorized based on JNC 7 classification. Detailed clinical history was obtained from all subjects. Student's t-test was applied to see the difference in mean values of quantitative data in two groups. Chi-Square test was applied to see the difference in frequency of discrete variables in two groups.

Results: A 66.3% diabetic nephropathy patients and 51.9% type 2 diabetics without nephropathy were found hypertensive in present study; In contrast only 14.7% controls had hypertension. No association of hypertension was found with age and gender in either group. Serum creatinine and eGFR was found significantly different in hypertensive diabetic nephropathy patients than normotensive (p=0.002 and <0.0001 respectively).

Conclusion: Our study found that hypertension was an independent risk factor for the Diabetic Kidney Disease (DKD). Along with this, a proportional increase in the level of serum creatinine and eGFR was seen with an incidence of hypertension in diabetic nephropathy.

Keywords: Diabetes, Diabetic nephropathy, Proteinuria

INTRODUCTION

Microvascular and macrovascular complications are frequently encountered in type II Diabetes mellitus. Micro and macrovascular lesions can involve various organs and tissues resulting in significant morbidity and mortality. Data collected by United State Renal Data System (USRDS) in 2008 on End Stage Renal Disease (ESRD) including Diabetic Kidney Disease (DKD) has shown that incidence rates of treated ESRD have raised worldwide [1]. DKD is a clinical syndrome characterized by persistent albuminuria, arterial blood pressure elevation, a relentless decline in Glomerular Filtration Rate (GFR), and an associated high risk of cardiovascular morbidity and mortality.

Hypertension is common among patients with DKD. In diabetic patients, hypertension increases the risk for renal and cardiovascular morbidity and mortality [2]. The mechanism of hypertension in diabetic nephropathy is complex, incompletely understood and includes electrolyte imbalance, activation of Renin-Angiotensin Aldosterone System (RAAS), Endothelial Cell Dysfunction (ECD), and increased oxidative stress [3].

There are various reports which have been published from time to time indicating hypertension as a risk factor for the diabetic nephropathy [4,5]. With the advances and ongoing researches; newer and newer drugs have been evaluated. Therefore, it is recommended to evaluate the incidence of hypertension and other secondary complications encountered in diabetic mellitus so that early modality therapeutic approach can be done. Hence, this research was planned to observe the incidence of hypertension and dyslipidaemia in diabetes mellitus with and without nephropathy in patients from central India.

MATERIALS AND METHODS

Study Design: In this case control prospective study, a total of 824 cases were analysed which includes 592 diabetic patients and 232 were healthy controls. This study was conducted on patients getting admitted to Medicine Department of a tertiary care center, Indore from September 2013 to September 2015. Patients with type 2 diabetes mellitus or clinical features suggestive of diabetes mellitus (satisfying the ADA criterion for the diagnosis of diabetes mellitus) and age limit between 30 to 60 years were included in this study. Exclusion criteria includes patients with history of smoking, sepsis or acute infection, chronic liver disease, shock, body mass index (BMI) >30 kg/m^2 and those who were not willing to give consent. Exclusion criteria for controls were identical. Clearance was gained from our institutional ethical and research committee and written informed consent was taken from all patients.

Clinical Assessment: Detailed clinical history was acquired. Physical examination and necessary laboratory investigations were done. Patients with typical history of polyuria, polydipsia and polyphagia were subjected to diabetes screening. All screened patients were diagnosed according to American Diabetic Association (ADA) 2013 criteria [6]. Diabetic kidney disease (DKD) was clinically defined by the presence of persistent proteinuria (>500 mg/day) in a diabetic patient in the absence of clinical or laboratory evidence of other kidney or urinary tract disease [7].

Patients with systolic blood pressure more than 140 mmHg and diastolic more than 90 mmHg were diagnosed as hypertensive as per Joint National Committee (JNC) seven [8].

Laboratory Measurements: 5 ml of venous blood was collected in with EDTA. Fasting plain vial. Fasting and post prandial blood

sugar, glycosylated haemoglobin (HbA1c) and lipid profile, serum creatinine, blood urea nitrogen, serum protein and albumin were determined as per standard protocol. A 24 hour urine sample was also collected to measure 24 hour urinary protein.

eGFR was calculated by using Cockcroft-Gault formula [9]

eGFR(Males) = [(140 - age in years) x (weight in kg)] ÷ 72 x serum Cr

eGFR (Females) = 0.85 x {(140 - age in years) x (weight in kg)) ÷ 72 x serum Cr}

On the basis of eGFR stage of kidney disease were defined as per KDOQI guidelines [10].

STATISTICAL ANALYSIS

Data was entered in Microsoft excel 2007 and analysed on MedCalc Software (Trial Version). Chi-Square test was used to see the difference in the frequency of qualitative variables in two or more groups. Student's t-test and one-way ANOVA test was applied to see the difference in mean in two and more than two groups respectively. The p-value less than 0.05 was considered significant.

RESULTS

Out of 592 diabetic patients, renal involvement was observed in 407(68.86%) patients and they were grouped under the category diabetic kidney disease. Stage 1 CKD (GFR>90) was observed in 15, Stage II (GFR 60-89) in 35, stage III (GFR 30-59) in 75, and stage IV (GFR 15-29) in 94 and stage V (GFR<15) in 188(46.2) patients. We observed significant difference in the occurrence of hypertension in DM, DKD and controls with highest prevalence of hypertension in DKD group [Table/Fig-1]. The subjects was grouped into two groups namely hypertensive and normotensive and significantly higher levels of HbA1c, serum creatinine, albumin, triglyceride and total cholesterol were observed in hypertensive group as compared to normotensive group. eGFR was observed to be lower in hypertensive patients than the normotensive patients [Table/Fig-2]. The results show that incidence of renal involvement were higher in hypertensive patients.

Groups	Normotensive (n=424)	Hypertensive (n=399)	Total (n=823)	p-value
DM without DKD	89 (48.1%)	96 (51.9%)	185	< 0.0001
DM with DKD	138 (33.7%)	269 (66.3%)	407	
Controls	198 (85.3%)	34 (14.7%)	232	

[Table/Fig-1]: Frequency of hypertension in different studied groups.
DM: Diabetes Mellitus, DN: Diabetic Nephropathy

Parameters	Normotensive	Hypertensive	p-value
Age (Years)	56.11 ± 9.04	56.39 ± 9.10	0.44
BMI (Kg/m^2)	24.09 ± 4.51	24.69 ± 4.50	0.056
HbA1c (%)	7.53 ± 1.76	6.37 ± 4.08	<0.0001
Serum Creatinine (mg/dL)	4.04 ± 3.23	2.14 ± 2.13	<0.0001
eGFR(ml/min)	29.90 ± 26.76	61.81 ± 37.25	<0.0001
Blood Urea Nitrogen(mg/dl)	56.71±32.17	54.55±33.89	0.526
S. Protein(g/dl)	6.62±1.37	6.65±1.23	0.840
S. Albumin(g/dl)	3.53±0.77	3.33±0.87	0.026
24 hr Urinary protein(mg/24 hrs)	1818±1535	1994±1622	0.324
Total cholesterol (mg/dL)	167.29 ± 52.03	158.68 ± 4.12	0.013
High Density Lipoprotein (mg/dL)	39.46 ± 14.05	39.31 ± 17.27	0.897
Low Density Lipoprotein (mg/dL)	98.74 ± 59.32	97.01 ± 34.43	0.622
Triglyceride (mg/dL)	156.77 ± 111.84	120.36 ± 61.61	<0.0001

[Table/Fig-2]: Demographic and Biochemical parameters in relation to presence of hypertension.

Biochemical profile was also compared in relation to hypertension in DM, DKD and control groups separately. On observing the [Table/Fig-3] it is clear that the patients with diabetes mellitus without nephropathy but with hypertension bear a lower eGFR as compared to the normotensive patients in the same group. Similarly, in DKD group, both hypertensive and normotensive patients, have an elevated serum creatinine and a lower eGFR. However, patients with hypertension had significantly greater creatinine and lower eGFR values than normotensive DKD patients.

DISCUSSION

Hypertension and Type 2 Diabetes Mellitus are two most important and commonly encountered life-style diseases in the Indian population. Both of these are very closely related to kidney disease which goes unrecognized most of the times.

In our study, 68.6% of type 2 diabetes mellitus (T2DM) had diabetic kidney disease of which 46.2% were of stage V or ESRD patients. VanBuren et al., reported that self-reported diabetes is associated with a prevalence of CKD of 8.9% (stage I), 12.8% (stage II), 19.4% (stage III), and 2.7% (stage IV and V combined) [3].

In the present study, it was observed that 60.7% normotensive T2DM patients had DKD whereas, in hypertensive T2DM patients the incidence of DKD had increased to 73.6%. (p =0.001, OR= 1.807, 95%CI= 1.268-2.575). Agarwal et al., have studied 300 newly diagnosed type II diabetes and have found an incidence of 17.5% of nephropathy and reported hypertension as the most important associated factor contributing to development of kidney disease [11]. In a large cross sectional pathway study among, microabluminuria was reported in 731(24.62%) out of 2969 type 2 diabetes mellitus. Of these 731 patients hypertension was present in 44.9% of patients [4].

Hypertension in diabetes mellitus may be due to metabolic syndrome, secondary to complications of diabetes mellitus, endocrine disorders or coincidental (essential arterial hypertension, isolated systolic hypertension). In the case of DKD, the incidence of hypertension increases due to sodium retention and increased peripheral vascular resistance [12]. Various single nucleotide polymorphisms in the genes such as ACE, eNOS, etc have been shown to be associated with hypertension and DKD in various studies. ACE is the key enzyme in renin – angiotensinsystem, which can catalyze the conversion of angiotensin I to angiotensin II. The insertion (I)/deletion (D) polymorphism of this gene has been demonstrated to be associated with hypertension and DKD in many studies [13]. Endothelial Nitric Oxide Synthase (eNOS) produces Nitric Oxide (NO) from L-arginine. NO has a significant role in the regulation of vascular tone and in the control of blood pressure. Therefore, mutation in eNOS alters the NO production and leads to hypertension [14].

We observed a significant association of serum albumin in DKD patients. A prospective study of 1513 type 2 diabetic patients with diabetic nephropathy, had reported that the serum albumin was an independent risk factor in patients with ESRD [5]. Høstmark et al., reported a positive association between serum albumin and blood pressure irrespective of sex and age [15]. Oda did a longitudinal study to see the effect of serum albumin level on the development of hypertension in general population and shows that for each one SD increase in the serum albumin level, the hazard ratio for hypertension was 0.779 (0.696-0.872; p<0.001) suggesting decreased serum albumin level as a significant predictor of hypertension [16]. Viswanathan et al., also reported a positive correlation of serum albumin with severity of chronic kidney disease [17]. Since hypertension is associated with endothelial dysfunction, insulin resistance, inflammation and oxidative stress [3], and albumin possesses both, anti-inflammatory and antioxidant properties [18] therefore, higher level of serum albumin may protect the development of hypertension and CVD. Albumin

	DM without DKD			DM with DKD			Controls		
	Hypertensive	Normotensive	p-value	Hypertensive	Normotensive	p-value	Hypertensive	Normotensive	p-value
Age (Y)	56.74±10.28	55.74±10.28	0.487	55.95±8.5	56.95±8.8	0.757	55.62±9.19	56.79±9.12	0.489
BMI (Kg/m^2)	24.59±5.79	24.54±3.7	0.952	23.7±3.95	23.63±4.02	0.850	25.63±4.18	25.47±2.95	0.788
HbA1c (%)	7.58±1.45	7.02±8.15	0.671	7.7±1.74	7.77±1.80	0.738	5.112±0.42	5.25±0.045	0.226
Serum Creatinine (mg/dL)	1.97±1.78	1567±1.40	0.089	5.20±3.22	4.21±2.56	0.002	1.034±0.27	1.022±0.028	0.817
eGFR(ml/min)	44.41±25.09	66.90±32.53	<0.0001	20.10±14.90	26.81±22.57	<0.0001	81.67±33.7	82.18±29.81	0.932
Blood Urea Nitrogen(mg/dl)	61.46 ± 47.46	54.15 ± 41.62	0.629	53.28 ± 30.74	57.32 ± 29.70	0.466	29.24 ± 17.34	21.10 ± 19.2	0.373
S. Protein(g/dl)	6.85 ± 0.97	7.02 ± 1.31	0.510	6.62 ± 1.26	6.54 ± 1.37	0.630	6.02 ± 1.3	5.91 ± 0.87	0.914
S. Albumin(g/dl)	3.66 ± 1.09	3.62 ± 0.89	0.851	3.27 ± 0.82	3.51 ± 0.74	0.012	3.11 ± 0.89	3.01 ± 0.21	0.167
24 hr Urinary protein(mg/24 hrs)	334.3 ± 163.84	326.10 ± 164.81	0.894	2304.83 ± 1583.37	2163 ± 1504	0.241	198.4 ± 108.72	120.64 ± 100.24	<0.0001
Total Cholesterol (mg/dl)	172.62±51.27	151.75±40.18	0.003	167.43±54.56	169.27±51.15	0.750	152.18±27.1	154.75±41.89	0.730
High Density Lipoprotein (mg/dl)	39.16±8.06	37.37±9.38	0.179	39.69±16.26	42.98±28.65	0.166	38.59±8.82	37.9±7.77	0.640
Low Density Lipoprotein (mg/dl)	108.74±94.85	91.49±32.73	0.120	95.43±44.31	99.84±38.73	0.452	96.74±25.31	98.09±32.5	0.816
Triglyceride (mg/dl)	139.84±83.24	111.35±56.57	0.009	172.50±123.15	163.57±78.16	0.454	85.91±21.04	96.08±32.25	0.039

[Table/Fig-3]: Comparison of Demographic and Biochemical variables in hypertensive and normotensive patients in different groups.

also prevents hemolysis and copper-stimulated peroxidation by reducing the production of free hydroxyl radicals from systems containing copper ions and H_2O_2 [19].

LIMITATIONS

The present study is a cross-sectional study and did not follow the diabetic patients. Therefore, the incidence of hypertension and diabetic nephropathy may be different. Only the referral cases were recuited for the study. The incidence may be totally different when this type of study is carried out in a general population.

CONCLUSION

In conclusion, hypertensive patients were found to have a lower eGFR which it is a major contributing factor for the development of diabetic kidney disease. Low serum albumin levels were significantly associated with the occurrence of hypertension, therefore, measures to keep the albumin levels high should be adopted to reduce the incident of hypertension in diabetes patients.

REFERENCES

[1] United States Renal Data System. USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2008.

[2] Hypertension in Diabetes Study Group. HDS 1: Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardio-vascular and diabetic complications. *J Hypertens*.1993;11:309–17.

[3] Van Buren PN, Toto R. Hypertension in diabetic nephropathy: epidemiology, mechanisms, and management. *Adv Chronic Kidney Dis*. 2011;18(1):28-41.

[4] Young BA, Katon WJ, Von Korff M, Simon GE, Lin EH, Ciechanowski PS, et al. Racial and ethnic differences in microalbuminuria prevalence in a diabetes population: the pathways study. *J Am SocNephrol.* 2005;16(1):219-28. Epub 2004 Nov 24.

[5] Keane WF, Brenner BM, de Zeeuw D, Grunfeld JP, McGill J, Mitch WE, et al. RENAAL Study Investigators. The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: the RENAAL study. *Kidney Int*. 2003;63(4):1499-507.

[6] American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2013;36(Suppl 1):S67-S74.

[7] Parving HH. Prevalence and causes of albuminuria inNIDDM. *Kidney Int.* 1992;41(4):758-62.

[8] National High Blood Pressure Education Program. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2004 Aug. Classification of Blood Pressure. Available from: http://www.ncbi.nlm.nih.gov/books/NBK9633/

[9] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.

[10] KDOQI. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis*. 2007;49(2 Suppl 2):S12-154.

[11] Agarwal N, Sengar NS, Jain PK, Khare R. Nephropathy in Newly Diagnosed Type 2 Diabetics withSpecial Stress on the Role of Hypertension. *JAPI*. 2011;59:145-47.

[12] Djordjevic V. Hypertension and nephropathy in diabetes mellitus: what is inherited and what is acquired? *Nephrol Dial Transplant*. 2001;16:92–3.

[13] Shanmuganathan R, Kumaresan R1, Giri P. Prevalence of angiotensin converting enzyme (ACE) gene insertion/deletion polymorphism in South Indian population with hypertension and chronic kidney disease. *J Postgrad Med.* 2015;61(4):230-34.

[14] Shankarishan P, Borah PK, Ahmed G, Mahanta J. Endothelial nitric oxide synthase gene polymorphisms and the risk of hypertension in an Indian population. *Biomed Res Int*. 2014;2014:793040.

[15] Høstmark AT, Tomten SE, Berg JE. Serum albumin and blood pressure: a population-based, cross-sectional study. *J Hypertens*. 2005;23(4):725-30.

[16] Oda E. Decreased serum albumin predicts hypertension in a Japanese health screening population. *Intern Med*. 2014;53(7):655-60. Epub 2012 Mar 1.

[17] Viswanathan V, Snehalatha C, Kumutha R, Jayaraman M, Ramachandran A. Serum albumin levels in different stages of type 2 diabetic nephropathy patients. *Indian J Nephrol.* 2004;14:89-92.

[18] Halliwell B. Albumin: an important extracellular antioxidant? *Biochem Pharmacol.* 1988;37:569-71.

[19] Wayner DD, Burton GW, Ingold KU, Locke S. Quantitative measurement of the total, peroxyl radical-trapping antioxidant capability of human blood plasma by controlled peroxidation: the important contribution made by plasma proteins. *FEBS Lett*. 1985;187: 33-37.

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