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Diabetic kidney disease and hypertension: What is inherited and what is acquired?

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. 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 >500 mg/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. The Chi-Square test was applied to see the difference in frequency of discrete variables in two groups.

Results: 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 were 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.

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Introduction

Diabetes is the leading cause of Chronic Kidney Disease (CKD) and End-Stage Kidney Disease (ESKD worldwide. Diabetic Kidney Disease (DKD) is a complex and heterogeneous disease with numerous overlapping etiologic pathways including changes in glomerular hemodynamics, oxidative stress and inflammation, and interstitial fibrosis and tubular atrophy.

CKD is defined by the presence of kidney damage or decreased kidney function for three or more months, irrespective of the cause. The persistence of the damage or decreased function for at least three months is necessary to distinguish CKD from acute kidney disease. Kidney damage refers to pathologic abnormalities, whether established via kidney biopsy or imaging studies or inferred from markers such as urinary sediment abnormalities or increased rates of urinary albumin excretion. Decreased kidney function refers to a decreased Glomerular Filtration Rate (GFR), which is usually estimated (eGFR) using serum creatinine and one of several available equations [1].

➢ Kidney damage is identified in most cases by the presence of albuminuria, urinary sediment abnormalities, anatomic abnormalities discovered with imaging studies, pathologic abnormalities discovered with kidney biopsy, or a history of kidney transplantation.

➢ Decreased kidney function is identified in most cases by an eGFR less than 60 mL/min per 1.73 m^2.

"Diabetic nephropathy" is characterized pathologically by glomerular basement membrane thickening, endothelial damage, mesangial expansion and nodules, and podocyte loss. However, it has become clear that there are various forms of kidney disease due to diabetes including nonclassical glomerular lesions as well as tubulointerstitial disease. Thus, the term "diabetic kidney disease" is used to reflect the presence of albuminuria, decreased Estimated Glomerular Filtration Rate (eGFR), or both, but it is not intended to indicate a specific kidney disease phenotype in a patient with diabetes.

Diabetic kidney disease is a complex and heterogeneous disease with numerous overlapping etiologic pathways. Hyperglycemia results in production of Advanced Glycation End-products (AGE) and reactive oxygen species. While hyperglycemia undoubtedly plays a central role, hyperinsulinemia and insulin resistance also may incite pathogenic mechanisms, possibly accounting for variation in histopathology between type 1 and type 2 diabetes. Ultimately, alterations in glomerular hemodynamics, inflammation, and fibrosis are primary mediators of kidney tissue damage (Figure 1), although the relative contribution of these mechanisms likely varies between individuals and over the course of the natural history of diabetic kidney disease.

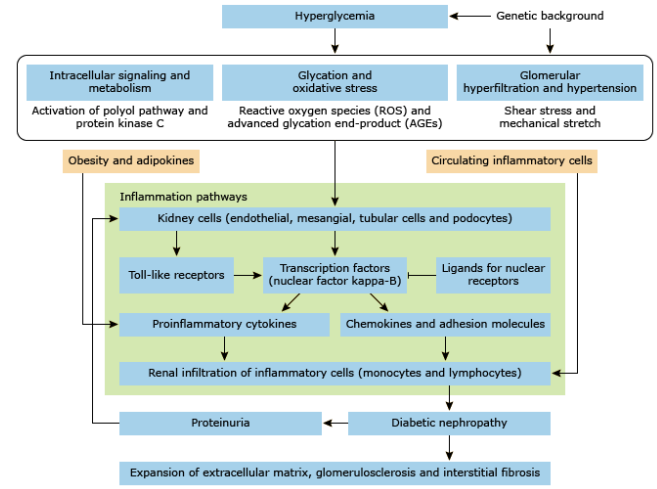

Figure 1: Inflammation and the pathogenesis of diabetic nephropathy.

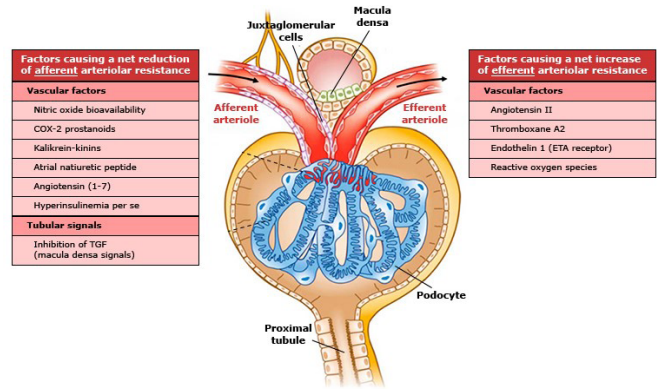

Figure 2: Glomerular hyperfiltration in diabetes.

Glomerular hyperfiltration in diabetes. Several vascular and tubular factors are suggested to result in a net reduction in afferent arteriolar resistance, thereby increasing (single nephron) GFR. Effects of insulin per se seem to depend on insulin sensitivity. A net increase in efferent arteriolar resistance—leading to increased GFR—is proposed for other vascular factors. Growth hormone and insulin-like growth factor-1 likely increase filtration by augmenting total renal blood flow, without specific arteriolar preference. Glucagon and vasopressin seem to principally act through TGF. Intrinsic defects of electromechanical coupling or alterations in signal transduction in afferent arterioles may impair vasoactive responses to renal hemodynamic (auto)regulation. Augmented filtration by increases in the ultrafiltration coefficient and net filtration pressure via reduction in intratubular volume and subsequent hydraulic pressure in Bowman's space are not depicted. Several vascular factors may be released or activated after a (high-protein) meal (e.g., nitric oxide, COX-2 prostanoids, angiotensin II), whereas TGF becomes (further) inhibited, through increased amino acid (and glucose)-coupled sodium reabsorption in the proximal tubule and/or increased glucagon/vasopressin-dependent sodium reabsorption in the thick ascending limb. These changes may collectively play a part in postprandial hyperfiltration (Figure 2).

A classification of type 1 and type 2 diabetic kidney disease was developed by the research committee of the Renal Pathology Society [2], which provides a systematic and uniform approach to classify pathology of the diabetic kidney and also promotes the study of pathogenesis and prognosis of disease. Scores are assigned to all three kidney compartments: the glomeruli; vasculature; and interstitium:

➢ Class I – Isolated glomerular basement membrane thickening. Basement membranes are greater than 430 nm in males and 395 nm in females over the age of nine years. There is no evidence of mesangial expansion, increased mesangial matrix, or global glomerulosclerosis involving >50 percent of glomeruli.

➢ Class II – Mild (Class IIa) or severe (Class IIb) mesangial expansion. A lesion is considered severe if areas of expansion larger than the mean area of a capillary lumen are present in >25 percent of the total mesangium.

➢ Class III – At least one Kimmelstiel-Wilson lesion (nodular intracapillary glomerulosclerosis) is observed on biopsy, and

there is <50 percent global glomerulosclerosis.

- Class IV – Advanced diabetic glomerulosclerosis. There is >50 percent global glomerulosclerosis that is attributable to diabetic nephropathy.

The clinical and prognostic significance of these glomerular classes has been evaluated in several retrospective cohort studies. Progression to ESKD is less common in classes I and IIa and more rapid in class IV. However, it is less clear whether class III (nodular glomerulosclerosis) carries a worse prognosis than class IIb (diffuse glomerulosclerosis) [3,4]. A limitation of this classification is that potentially important pathologic lesions are not included, such as the presence of focal and segmental sclerosis, mesangiolysis, capillary aneurysms, exudative lesions, and extracapillary hypercellularity [5,6].

Although progression to advanced CKD and ESKD is a major concern, cardiovascular events and death occur more frequently than the need for kidney replacement therapy, particularly in patients with a urine albumin excretion <1000 mg/g of creatinine or an eGFR above 45 mL/min/1.73m^2 [7-12]. Higher levels of albuminuria (even those below 30 mg/g) and lower levels of eGFR independently and additively increase the risk for cardiovascular events and death [11,13-16]. In patients at high cardiovascular risk, the incidence of cardiovascular events is approximately 2.5-fold higher for every 10-fold increase in urine albumin excretion and approximately twofold higher for every halving of eGFR [11,16]. Hypertension in diabetes mellitus may be due to one of the following reasons: The metabolic syndrome, it may be secondary to complications of diabetes mellitus, due to endocrine disorders and coincidental (essential arterial hypertension, isolated systolic hypertension). The natural history of hypertension differs markedly between type 1 and type 2 diabetes mellitus. Systemic hypertension is an early phenomenon in diabetic kidney disease. Furthermore, nocturnal blood pressure elevation (non -dippers) occur more frequently in patients with nephropathy. In type 1 ddiabetes patients the blood pressure is usually normal at presentation and remains normal for the first 5-10 years but increases with appearance of diabetic nephropathy. In contrast, type 2 diabetes patients, elevated blood pressure is usually present at diagnosis of diabetes or may develop thereafter. Exaggerated blood pressure response to exercise has been reported in long-standing type 1 ddiabetes patients with microangiopathy. Finally, the increase in glomerular pressure consequent to nephron adaptation may be accentuated with concomitant diabetes. Contributors to hypertension in patients with diabetes include kidney disease, extracellular fluid volume expansion, and increased arterial stiffness. Hypertension is common problem in patients with both type 1 and type 2 diabetes, but the time course in relation to the duration of diabetes is different. In type 1 diabetes, the prevalence of hypertension at the time of diagnosis is low, increasing subsequently over several decades. In type 2 diabetes, a substantial proportion of patients already have a hit at the time of diabetes diagnosis [17-20]. Among those with type 1 diabetes, the incidence of hypertension rises from 5% at 10 years, to 33% at 20 years, and to 70% at 40 years [18]. There is a close relation between the prevalence of hypertension and increasing albuminuria. The blood pressure typically begins to rise within the normal range at or within a few years after the onset of moderately increased albuminuria (the new term for what was previously called “microalbuminuria” and what is also sometimes called “high albuminuria”). Blood pressure then increases progressively as the kidney disease progresses.

These features were illustrated in a study of 981 patients who had type 1 diabetes for five or more years [21]. Hypertension was present in 19 percent of patients with normoalbuminuria, 30% with moderately increased albuminuria, and 65 percent with severely increased albuminuria (the new term for what was previously called “macroalbuminuria” and what is sometimes called “very high albuminuria”). The incidence of hypertension eventually reaches 75 to 85 percent in patients with progressive diabetic nephropathy [22]. The risk of hypertension is highest in Black individuals, who are also at much greater risk for kidney failure due to diabetic kidney disease.

The findings are different in patients with type 2 diabetes [23,24]. In a series of over 3500 newly diagnosed patients, 39 percent were already hypertensive [25]. In approximately one-half of these patients, the elevation in blood pressure occurred before the onset of moderately increased albuminuria. Hypertension was strongly associated with obesity, and not surprisingly, hypertensive patients were at increased risk for cardiovascular morbidity and mortality.

2017 American College of Cardiology/American Heart Association hypertension guidelines [26], as well as the American Diabetes Association guidelines suggest a goal blood pressure of less than 130/80 mmHg in patients with diabetes mellitus who have greater than a 10% 10-year cardiovascular risk [27].

For 20 years attention has focused on *genetic susceptibility* to renal injury from elevated blood pressure. The quest to identify specific genetic etiologies of diabetic kidney disease has been challenging. Several candidate genes were initially implicated in the susceptibility and progression of diabetic kidney disease, but subsequent studies failed to replicate the findings [28]. Several large genome-wide association studies identified genes and gene regions for various diabetic kidney disease phenotypes in both type 1 and type 2 diabetes [29-31]; however, consistent associations for only a few loci were replicated in subsequent studies. Complex conditions, particularly “diseases within diseases,” like development of kidney disease in ddiabetes, present major challenges for deciphering genetic associations [32]. However, genome-wide association studies using large data sets have yielded insights about genetic predisposition to diabetic kidney disease. As an example, one variant in the *Col4A3* gene (the same gene associated with Alport syndrome) was associated with protection from clinical diabetic kidney disease in individuals with type 1 diabetes; in the subset who underwent kidney biopsy, this variant was also associated with less severe glomerular pathology. Variants in other genes related to collagen pathophysiology and kidney fibrosis (*DDR1, COLEC11, BMP7*) are, similarly, associated with various phenotypes of diabetic kidney disease. The apolipoprotein 1 (*APOL1*) gene explains much of the disparity in nondiabetic ESKD among Black individuals but has not born out as a causative factor for diabetic kidney disease [33]. However, APOL1 variants are associated with an increased risk for progression of diabetic kidney disease in Black patients. According to Churchill et al [34], an experimental animal model of renal injury caused by hypertension suggests that nephropathy susceptible genes exist, but these genes have not yet been identified. In humans, the familial clustering of hypertensive renal disease and the identification of polymorphism in the renin-angiotensin- aldosterone system gene components support the idea of genetic susceptibility to hypertensive renal injury in diabetic kidney disease [35]. Krolewsky et al. [36] identified a region on the long arm of chromosome 3 in the vicinity of the angiotensin II type-1 recep-

tor gene that harbors a locus with major effects. In addition, they have demonstrated minor effects of the insertion allele in the ACE gene and the T-allele at position 235 in the angiotensinogen gene on the development of diabetic kidney disease. This finding must be confirmed in other family -based studies.

Is susceptibility to diabetic kidney disease the same as susceptibility to essential hypertension? According to Krolewsky et al. [36] there is some overlap. Essential hypertension has a significant genetic component with minor gene effects and these authors postulated that the expression and penetrance of one of these minor genes for essential hypertension is changed in the presence of hyperglycemia in such a way that carriers of that disease allele, which must be a common one, would develop diabetic kidney disease together with their hypertension. Overactivity of the Na^+/H^+ exchanger in the pathogenesis of DKD remains uncertain. Demaine ey al. [37] presented the results of an analysis of polymorphism in two areas of the aldose reductase gene in normal healthy controls and in type 1 diabetes patients with nephropathy. This finding is not confirmed by others [36].

Materials and methods

Study design

In this case control prospective study, a total of 824 cases were analyzed which includes 592 diabetic patients and 232 were healthy controls. This study was conducted on patients getting admitted to the Internal Medicine Department of a tertiary care center, from September 2013 to September 2023. 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 include 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 [38]. 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 [39]. Patients with systolic blood pressure of more than 140 mmHg and diastolic more than 90 mmHg were diagnosed as hypertensive as per Joint National Committee (JNC) seven [40].

Laboratory measurements

5 ml of venous blood was collected in with EDTA. Fasting plain vial. Fasting and post prandial blood sugar, glycosylated hemoglobin (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 [41]

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}

Based on eGFR stage of kidney disease were defined as per KDOQI guidelines [42].

Statistical analysis

Data was entered in Microsoft excel 2020 and analyzed 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 were applied to see the difference in meaning 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 1). The subjects were 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 2).

Table 1: Frequency of hypertension in different studied groups.

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 2: Demographic and Biochemical parameters in relation to the presence of hypertension.

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 hrs 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 3: Comparison of demographic and biochemical variables in hypertensive and normotensive patients in different groups.

	DM without DKD			DM with DKD			Controls		
	Hypertens	Normotens	p-value	Hypertension	Normotens	p-value	Hypertension	Normotens	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
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
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

The results show that incidence of renal involvement was higher in hypertensive patients. Biochemical profile was also compared in relation to hypertension in DM, DKD and control groups separately. On observing (Table 3) 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.

Discussions

Hypertension and type 2 Diabetes Mellitus are two most important and commonly encountered life-style diseases in the global population. Both 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 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) [43].

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 [44]. In a large cross sectional pathway study among, microalbuminuria was reported in 731(24.62%) out of 2969 type 2 diabetes mellitus. Of these 731 patients' hypertensions were present in 44.9% of patients [45]. 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 [46]. 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 – angiotensin system, 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 [47]. 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 [48]. 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 [49]. Høstmark et al., reported a positive association between serum albumin and blood pressure irrespective of sex and age [50]. 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 [51]. Viswanathan et al. also reported a positive correlation of serum albumin with severity of chronic kidney disease [52]. Since hypertension is associated with endothelial dysfunction, insulin resistance, inflammation and oxidative stress [43], and albumin possesses both anti-inflammatory and antioxidant properties [53], therefore, higher level of serum albumin may protect the development of hypertension and CVD. Albumin also prevents hemolysis and copper-stimulated peroxidation by reducing the production of free hydroxyl radicals from systems containing copper ions and H_2O_2 [54].

Conclusions

In conclusion, in our study hypertensive patients were found to have a lower eGFR which 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.

Hypertension and albuminuria play a critical role in initia-

tion and progressions of diabetic kidney disease. The ACE genes may predict diabetic kidney disease in some groups. Insulin resistance contributes to diabetic nephropathy, but mostly indirectly. Also, ACE genes may predict the rate of progression and the antiproteinuric response to ACE inhibitors. Diabetic kidney disease does not develop in the absence of hyperglycemia, but other factors exist that interact with poor glycemic control to produce nephropathy and hypertension. Genetic susceptibility is one of the most factors.

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