Review Article

Diabetic kidney disease its pathogenesis and management an Indian prospective

Abstract-

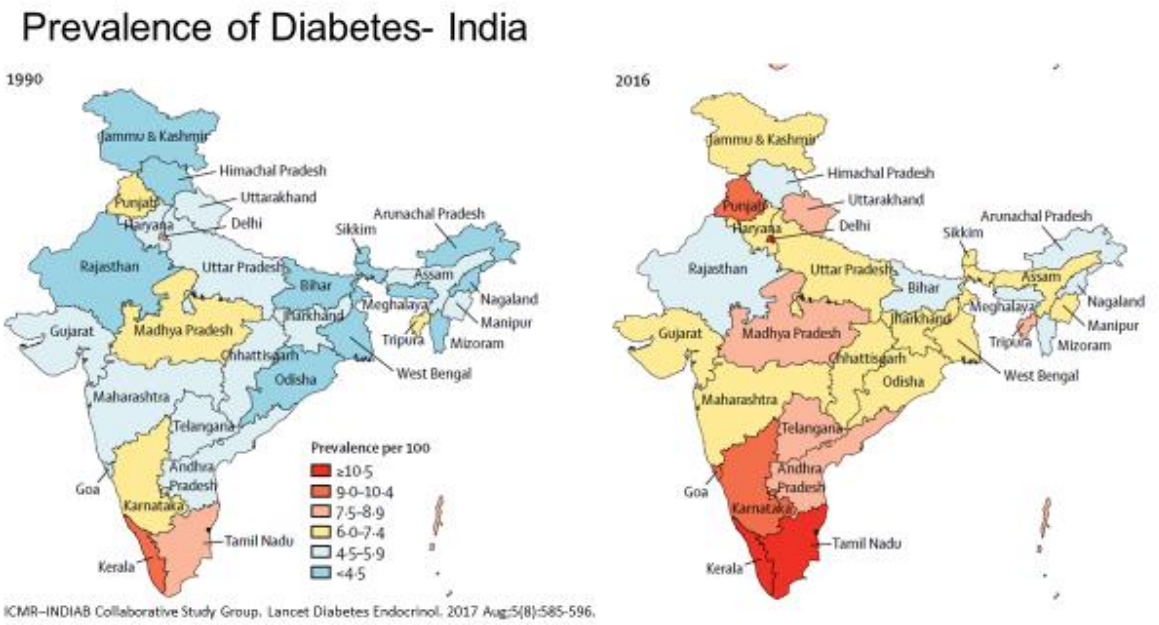
As the prevalence of diabetes is increasing in India so there is equally rise in the number of the patients with micro and macro vascular complications related to diabetes. The prevalence of diabetic kidney disease is increasing in Indian population because of genetic and non-genetic reason. Because of paucity of data we don't have exact numbers but it is the leading cause of end stage kidney disease in Indian population. Early screening for kidney disease and aggressive control of blood pressure and glycemic control can prevent or slow down the progression of diabetic kidney disease.

Introduction:

Epidemiology

Diabetes is turning out to be global emergency. Estimated people living with diabetes worldwide in year 2015 was 414 million and it's expected that by year 2040 that number is about to grow to 642 million. If we look at the numbers in south East Asia there were estimated 78.3 million diabetic patients in year 2015 and it's expected that by year 2040 that number will swell down to 140.2 million. Things are even worse in India the overall incidence of diabetes have increased in almost all the states of the country. Overall prevalence of diabetes in 15 states of India is 7·3% (95% CI 7·0–7·5). Its higher in urban India (11.2%, 10.6-11.8) compared to rural India (5.2%, 4.9 -5.4). Prevalence is higher in mainland states 8.3% as compared to northeast states 5.9% [1].As the prevalence of diabetes is increasing in India so there is equally rise in the number of the patients with micro and macro vascular complications . The prevalence of diabetic kidney disease is increasing in Indian population because of genetic and non-genetic reason. Because of paucity of data we don't have exact numbers but it is the leading cause of end stage kidney disease in Indian population

Fig 1: Prevalence of Diabetes-India



Definition

Renal disease specific to diabetes is called diabetic nephropathy. The characteristic features of diabetic nephropathy are albuminuria and progressive decline in glomerular filtration rate [2]. However, recently the term diabetic kidney disease (DKD) has been suggested instead of diabetic nephropathy. This is because diabetic nephropathy is a histopathological diagnosis and renal biopsy is routinely not indicated in patients with diabetes and renal dysfunction.

Incidence

Approximately 5-40% of patients with Type 2 diabetes develop DKD 20% of these individuals have DKD at diagnosis and 30- 40% at 10 years [3, 4]. However 25-40% of patients with Type 1 diabetes develop DKD after 5 years of duration of disease.

Risk factors

A variety of risk factors promotes the development and progression of diabetic nephropathy, including high glucose levels, obesity, dyslipidemia, elevated blood pressure, oxidative stress, and others [5,6]. Most of these risk factors are modifiable. Therefore, their intensive management is essential for preventing and delaying the decline in renal function. Many of these risk factors are also associated with a higher incidence of cardiovascular events, further supporting the importance of their management. New (genetic) markers for diabetic nephropathy are being investigated. Their determination may contribute to an early and improved treatment and probably to an early identification of individuals at risk of developing the disease.

Table 1: Risk Factors of Diabetic Nephropathy

Risk Factors of Diabetic Nephropathy

Risk factors	
Modifiable	**Non-modifiable**
Hypertension	Diabetes duration
Poor glycaemic control	Genetic susceptibility (familial clustering)
Degree of proteinuria	Male gender
Smoking	Ethnicity (higher risk in Black, Asian, Hispanic populations)
RAAS activation	
Elevated cholesterol	

RAAS: renin–angiotensin–aldosterone system

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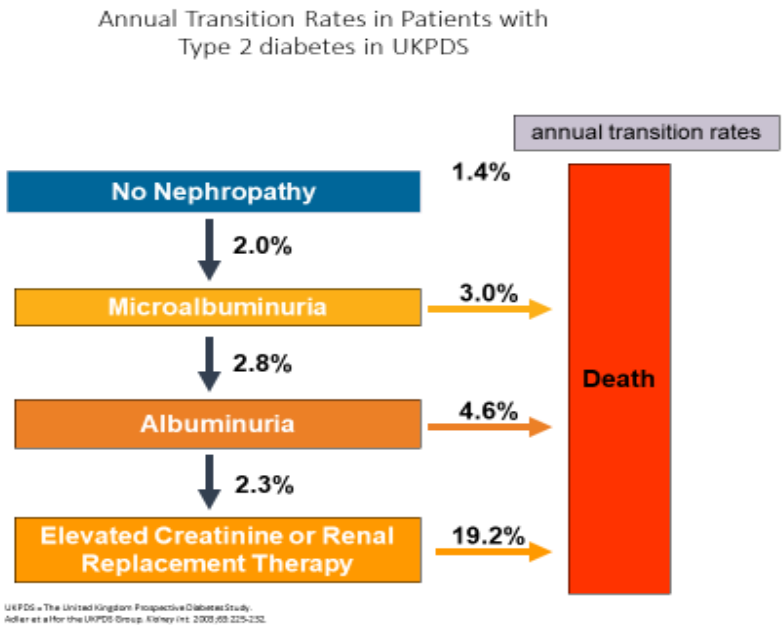
3 Shields J. Clin Med. 2020;10(5):500-4.

Mortality

Diabetic kidney disease progress from microalbuminuria to overt proteinuria leading progressive decline in GFR and ultimately leading to end stage renal disease. Mortality is directly proportion to progress of diabetic kidney disease as was shown in UKPDS trial [6].

Fig 2: Annual Transition Rates in Patients with Type 2 diabetes in UKPDS



Pathogenesis of Diabetic kidney disease –

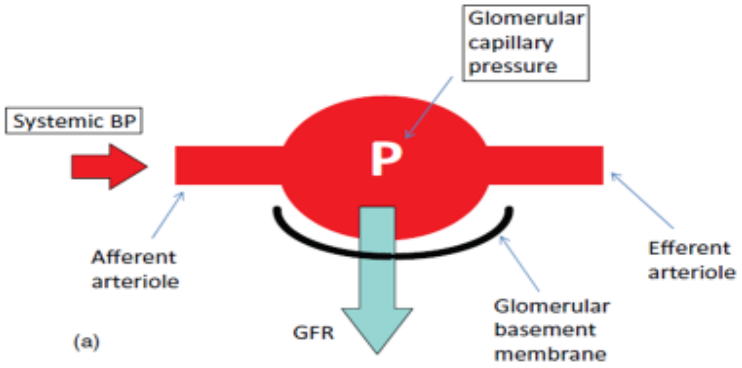
Normal intraglomerular pressure is 30-50mmHg, and this is required for optimal filtration across the glomerular basement membrane. Intraglomerular hypertension is the earliest abnormality in the pathogenesis of diabetic nephropathy and is caused by increased renal plasma flow exaggerated differential efferent arteriolar constriction, and mesangial proliferation. The consequence of intraglomerular hypertension is hyper filtration.

Increased renal plasma flow is due to hyperglycemia and elevated level of GH/IGF1, glucagon, angiotensin II , and nitric oxide. Differential efferent arteriolar constriction is a physiological phenomenon due to increased expression of AT_1 receptors on efferent arterioles as compared to afferent arteriole. However, activation of renal RASS results in increased levels of local angiotensin II, leading to increased intraglomerular pressure [7}. In addition, mesangial proliferation due to cytokines like TGF –B, and VEGF-A leads to increase in extracellular matrix deposition and also contributes to intraglomerular hypertension.

Fig 3: Glomerular hemodynamic changes in diabetic nephropathy
Normal glomerular capillary pressure and glomerular filtration

Glomerular hemodynamic changes in diabetic nephropathy

Normal glomerular capillary pressure and glomerular filtration



Ang = angiotensin; BP = blood pressure; GFR = glomerular filtration rate

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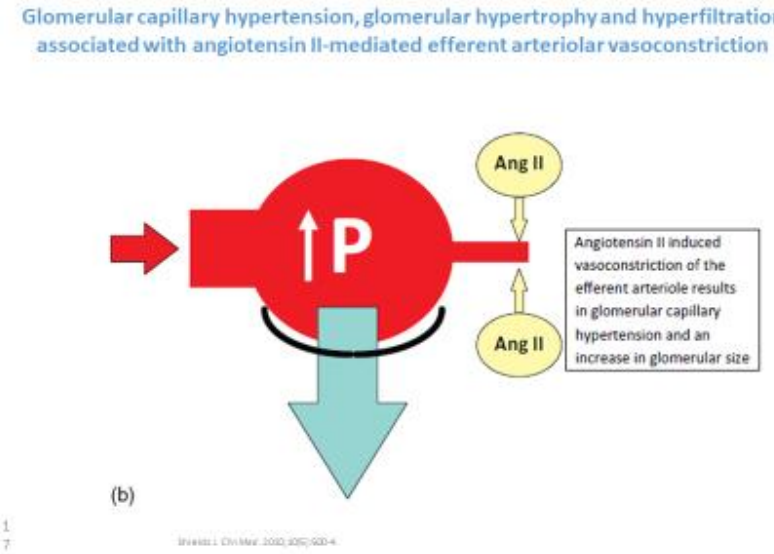
6 Shields J. Clin Med. 2010;105(5):920-4.

Fig 4: Glomerular capillary hypertension, glomerular hypertrophy and hyperfiltration associated with angiotensin II-mediated efferent arteriolar vasoconstriction



Intraglomerular hypertension is associated with structural abnormalities that result in proteinuria in patients with diabetic kidney disease .Podocytopathy, thickening of glomerular basement membrane (GBM), and mesangial proliferation are the early structural abnormalities associated with proteinuria in patients with diabetic kidney disease. Podocytes are the visceral epithelial cells present in bowman's space and determine the size of of the filtration slit .Local increase in angiotensin II causes podocyte injury i.e. effacement of podocytes and detachment and apoptosis, resulting in increased size of filtration slit and consequently proteinuria. In addition, nephrin, a key protein required for podocyte integrity is downregulated by angiotensin II [8]. Further, overexpression of VEGF-A in podocytes increases vascular permeability and worsen proteinuria. Increased expression of angiotensin II leads to reduced expression of heparin sulfate proteoglycans in GBM .This results in loss of negative charge on GBM, facilitating free passage of negatively charged albumin across GBM that's the reason for selective proteinuria. Further, there is thickening of GBM due to increased protein synthesis (collagen 4) and impaired protein degradation as result of non –enzymatic glycation, and consequently leads to worsening of proteinuria and renal function. Increased angiotensin II leads to expression of various growth factors including TGF-B; this results in increased deposition of extracellular matrix (collagen 4 and fibronectin) in mesangium and mesangial cell hypertrophy.

Fig 5: Development of micro albuminuria associated with thickened but 'leaky' glomerular

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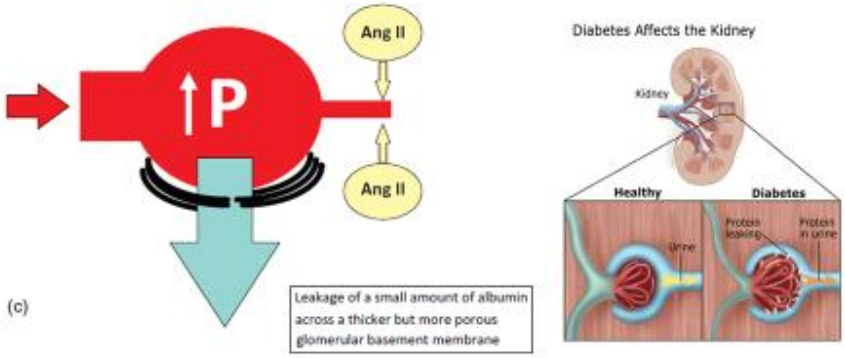

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Screening -

Screening for kidney damage (albuminuria) can be most easily performed by urinary albumin to creatinine ratio UACR in spot urine. Normal UACR is defined as 30mg/gm Cr .Increased urinary albumin exertion is defined as >30mg/gm Cr. Non diabetic causes of microalbuminuria include fever, exercise, hypertension ,congestive heart failure, urinary tract infections, pregnancy and drug like captopril and tolbutamide. Uncontrolled hyperglycemia per se can lead to increased urinary albumin excretion .Therefore it is important to look for persistent microalbuminuria. It is defined as presence of urinary albumin in range of 30-299mg/day on two occasions at least 1 month apart, over period of 3-6 months. It's important to confirm persistence of microalbuminuria as patient with diabetes may have transient albuminuria due to fever, exercise, and uncontrolled blood glucose. Persistent microalbuminuria in range of 30-299mg/day is an early indicator of diabetic kidney disease. Serum creatinine should be used to estimate the GFR.

Treatment

UKPDS trial has shown that More intensive blood glucose control resulted in both a 33 % reduction in relative risk of development of microalbuminuria or clinical grade proteinuria at 12

years, and significant reduction in the proportion doubling their plasma creatinine (0.91 vs 3.52% , P=0.0028). Tighter blood pressure control also reduced microalbuminuria and clinical grade proteinuria; but at 6 years there was no effect on plasma creatinine levels [6]. These data underline the importance of glycemic control and blood pressure control in type 2 diabetes in order to prevent diabetic nephropathy. Therefore following guidelines should be followed to stop or slow down the progression of diabetic kidney disease

Optimize the blood glucose control to slow down the progression of diabetic kidney Disease

Optimize blood pressure control (<140/90 mmHg) to reduce the risk or slow the progression of diabetic kidney disease

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For people with non-dialysis-dependent diabetic kidney disease, dietary protein intake should be 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered.

Drugs to slow the progression of diabetic kidney disease

- **ACE OR ARB** -Either an ACE inhibitor or an angiotensin receptor blocker is recommended for the treatment of no pregnant patients with diabetes and modestly elevated urinary albumin excretion (30–299 mg/day and is strongly recommended for those with urinary albumin excretion >300 mg/day and/or estimated glomerular filtration rate <60 mL/min/1.73 m2 [9].
- **Sodium-glucose cotransporter 2 inhibitors** — It is recommend the use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, such as canagliflozin, dapagliflozin, or empagliflozin, in patients with type 2 diabetes with nephropathy (estimated or measured urine albumin excretion >300 mg per day) and an estimated GFR (eGFR) ≥30 mL/min per 1.73 m^2.

- These drugs reduce the risk of kidney disease progression in such patients [10,-11], as well as the incidence of cardiovascular disease. The best data come from the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, which compared canagliflozin with placebo in 4401 diabetic patients with an eGFR between 30 and 89 mL/min per 1.73 m^2 and urine albumin-to-creatinine ratio (ACR) >300 mg/g (median, 927 mg/g) despite taking an ACE inhibitor or ARB [10]. At 2.6 years, canagliflozin reduced the incidence of end-stage renal disease, doubling of serum creatinine, hospitalization for heart failure, cardiovascular death, and all-cause mortality, although the effects on cardiovascular death and all-cause mortality were not statistically significant.

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- **Atrasentan-** It is a selective endothelin A receptor antagonist that can reduce albuminuria in patients with diabetic kidney disease but that may produce edema and heart failure. In a trial that enrolled more than 5000 diabetic patients with a urine albumin-to-creatinine ratio of at least 300 mg/g, randomization (to atrasentan or placebo) was performed only among those patients who, during a six-week open-label period receiving the drug, had a 30 percent or greater reduction in albuminuria and no substantial development of edema; only about half of enrolled patients were randomized [1]. At approximately two years, atrasentan reduced the incidence of a doubling of serum creatinine; there was also a trend toward a lower rate of end-stage renal disease. However, the number of renal events was small and serious adverse events were more common among those receiving the drug. The trial was stopped prematurely and atrasentan is not being marketed for use in diabetic kidney disease.

When estimated glomerular filtration rate is <60 mL/min/1.73 m2, evaluate and manage potential complications of chronic kidney disease. On basis of GFR chronic kidney disease is divided into following stages

Table 2: GFR concentration varies with different kidney disease

Stage	Description	GFR (mL/min per 1.73 m^2 body surface area)
1	Kidney damage* with normal or increased GFR	≥90
2	Kidney damage* with mildly decreased GFR	60–89
3	Moderately decreased eGFR	30–59
4	Severely decreased eGFR	15–29
5	Kidney failure	<15 or dialysis

*Kidney damage defined as abnormalities on pathologic, urine, blood, or imaging tests.

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Diabetes Care 2012;35(suppl 1):S35. Table 13.

Patients should be referred for evaluation for renal replacement treatment if they have estimated glomerular filtration rate <30 mL/min/1.73 m2.In brief the management of diabetic kidney diease according to GFR is as under

Table 3: Management of CKD in diabetes

Management of CKD in diabetes

GFR (mL/min/1.73 m^2)	Recommended management
All patients	Yearly measurement of Cr, UACR, potassium
45–60	Referral to a nephrologist if possibility for nondiabetic kidney disease exists (duration of type 1 diabetes <10 years, persistent albuminuria, abnormal findings on renal ultrasound, resistant hypertension, rapid fall in eGFR, or active urinary sediment on urine microscopic examination) Consider the need for dose adjustment of medications Monitor eGFR every 6 months Monitor electrolytes, bicarbonate, hemoglobin, calcium, phosphorus, and parathyroid hormone at least yearly Assure vitamin D sufficiency Consider bone density testing Referral for dietary counseling
30–44	Monitor eGFR every 3 months Monitor electrolytes, bicarbonate, calcium, phosphorus, parathyroid hormone, hemoglobin, albumin, and weight every 3–6 months Consider the need for dose adjustment of medications
<30	Referral to a nephrologist

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Diabetes Care 2016;39(Suppl. 1):S72–S80

Conclusion- Incidence of diabetic kidney disease is increasing alarmingly. Early screening for kidney disease using UACR can pick up early disease. Aggressive blood pressure and glycemic control and judicious use of drugs like ACE Inhibitors or ARB blockers along with newer drugs like SGLT2 inhibitors can slow down the progression of diabetic kidney disease

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