

Diabetic kidney disease : its pathogenesis and management.

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Abstract-

As the prevalence of diabetes is increasing in India, there is equal 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 reasons. 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 slow down and even prevent the progression of diabetic kidney disease.

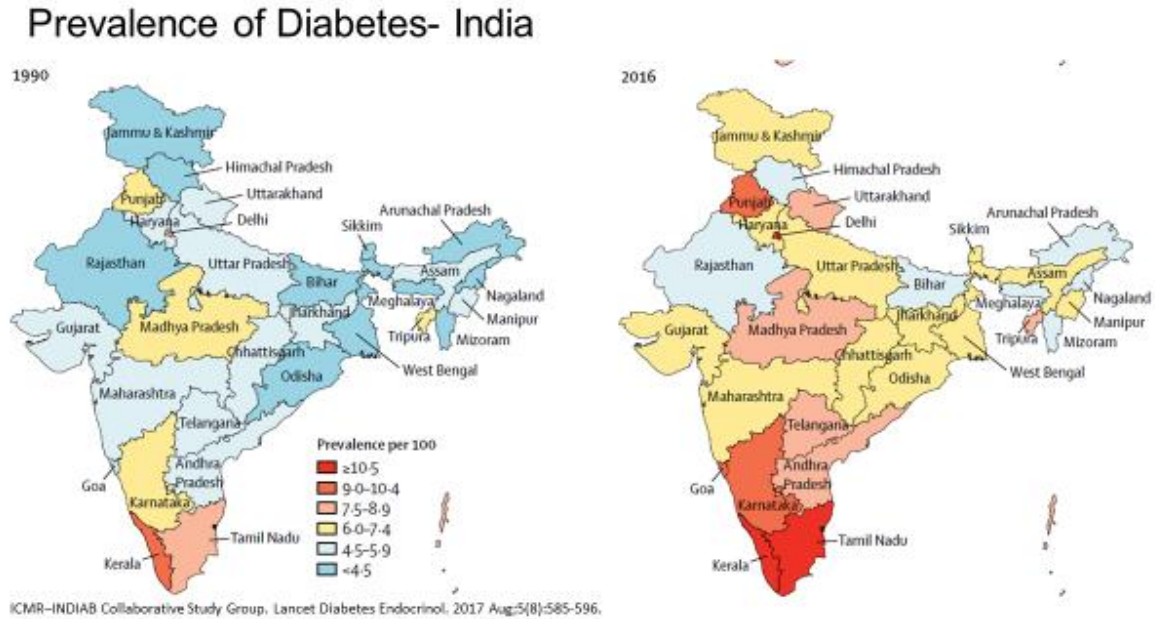
Introduction:

Renal disease specific to diabetes is called diabetic nephropathy. The characteristic features of diabetic nephropathy are albuminuria and progressive decline in glomerular filtration rate [1]. 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.

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 up to 140.2 million. Things are even worse in India. The overall incidence of diabetes has increased in almost all the states of the country. According to study published in Lancet in 2017, 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) as 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%) [2]. There were large differences in the prevalence of diabetes between states in India. As the results from the study described shows evidence of an epidemiological transition, with a higher prevalence of diabetes in low SES groups in the urban areas of the more economically developed states. The spread of diabetes to economically disadvantaged sections of society is a matter of great concern, warranting urgent preventive measures. As the prevalence of diabetes is increasing in India so there is equal 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 reasons. 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



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

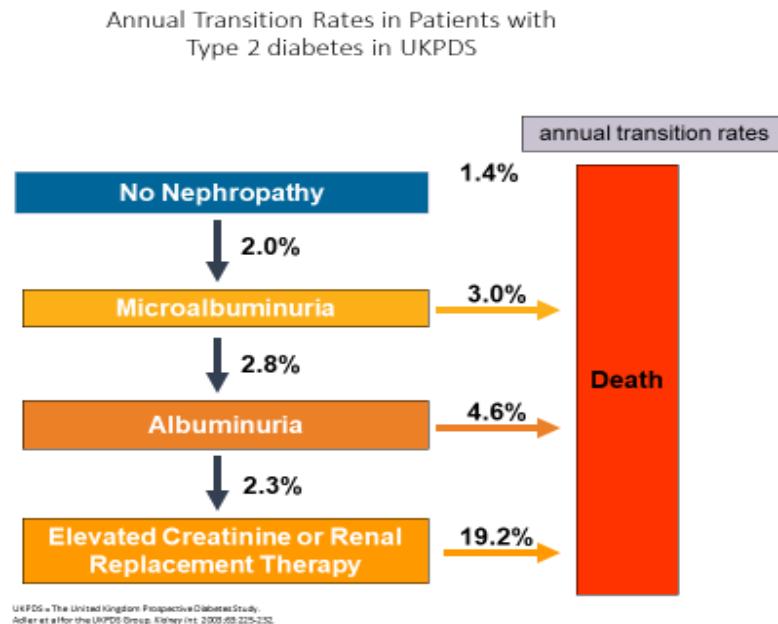
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3 Shields J. Clin Med. 2020;20(5):500-4.

Mortality

Diabetic kidney disease progress from microalbuminuria to overt proteinuria, leading to progressive decline in GFR and ultimately end stage renal disease. Mortality is directly proportional to progression 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 –

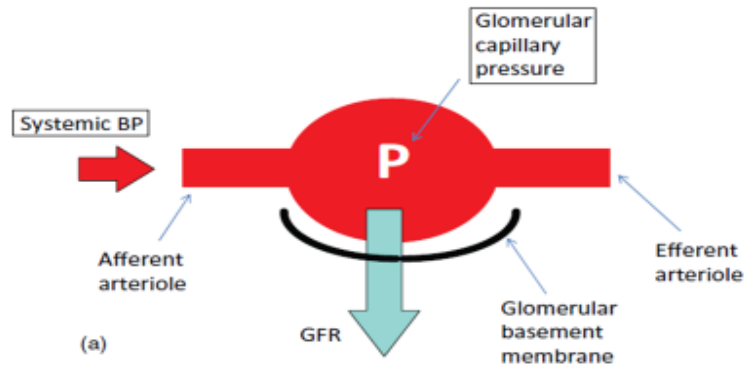
Normal intraglomerular pressure is 30-50mmHg, and this is required for optimal filtration across the glomerular basement membrane. Intraglomerular hypertension is the earliest abnormality in the pathogenesis of diabetic nephropathy and is caused by increased renal plasma flow exaggerated differential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

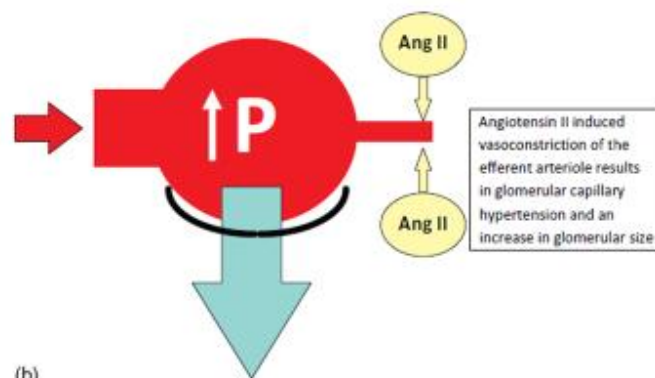
Glomerular hemodynamic changes in diabetic nephropathy
Normal glomerular capillary pressure and glomerular filtration



Ang=angiotensin; BP= blood pressure; GFR= glomerular filtration rate
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6 Shields J. Clin Med. 2020; 20(5):503-4.

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

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



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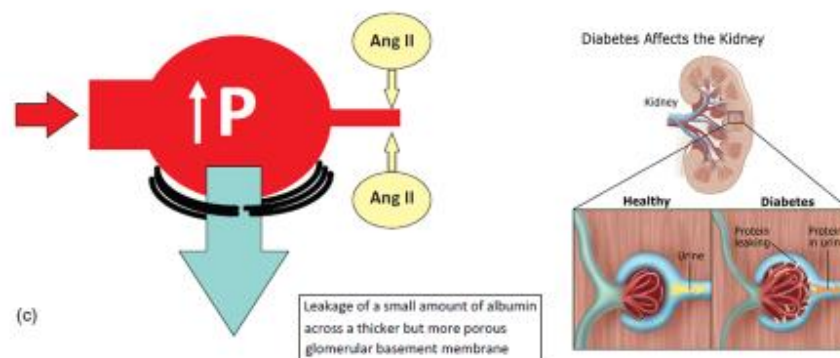
Stavros I. Christou. 2020;2020:2020-4

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 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 worsens 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- β ; 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

Development of micro albuminuria associated with thickened but 'leaky' glomerular



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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 excretion 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.

Management

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.

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 non-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 recommended 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 m².
- 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 m² 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.

- **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.

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 disease according to GFR is as under

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

Oral hypoglycemic agents in diabetic kidney disease

Biguanide - Metformin

- Metformin is contraindicated in DKD because it undergoes renal excretion
- Its most serious adverse effect is the development of lactic acidosis
 - although this is a very rare occurrence, with approximately 5 cases per 100,000 patient years
- **NICE guideline** on the treatment of T2DM allows metformin use up to a **GFR of 30 mL/min/1.73 m²**, with dose reduction advised at 45 mL/min/1.73 m²
- In the USA, metformin is contraindicated for men with serum creatinine ≥ 1.5 mg/dL and for women with serum creatinine ≥ 1.4 mg/dL

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Recent FDA Alert on usage of Metformin in Renal impairment

- FDA is requiring manufacturers to revise the labeling of metformin-containing drugs to indicate that these products may be safely used in patients with **mild to moderate renal impairment**.

The labeling recommendations:

- Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m².
- Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m² is not recommended.
- In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m², assess the benefits and risks of continuing treatment.
 - Discontinue metformin if the patient's eGFR later falls below 30 mL/minute/1.73 m².

Accessed on Aug 15, 2016 <http://www.fda.gov/Drugs/DrugSafety/surm082014.htm>

Evidence with Metformin in Renal Impairment

- **REduction of Atherothrombosis for Continued Health (REACH)** Registry 2004 showed decreased mortality associated with metformin use, even in patients with moderate kidney disease¹.
- Studies based on experimental and cell culture models have a **potential renal protective effect** for metformin^{2,3}.
 - In these studies, metformin prevented glucose-induced oxidative stress in podocytes by inhibiting NAD(P)H oxidase;
 - decreasing 8-hydroxydeoxyguanosine (8-OHdG), a supposed marker of total systemic oxidative stress and DNA damage in vivo;
 - and also improving the free-radical defense system
- Nonetheless, the use of metformin is still **avoided** in patients with **CKD stages 3–5** with other associated risk factors for lactic acidosis.

1. Mayo Clin Proc. 2011;86(10):960-7

2. Exp Diabetes Res. 2012; 2012:210821

3. Biochem Biophys Res Commun. 2010;393(2):268-73

Sulfonylureas

- **Glipizide** is metabolized by the liver into several inactive metabolites and its clearance and elimination half-life are not affected by a reduction in the estimated GFR (eGFR).
- So dose adjustments are not necessary in patients with CKD
 - Therefore, glipizide is the **SU of choice** in patients with CKD
- **Glibenclamide** or glyburide are each metabolized by the liver and are eliminated equally in the bile and urine.
 - Avoid use in patients with eGFR <60 mL/min/1.73 m²
- **Glimepiride** is metabolized by the liver into two main metabolites, one of which has hypoglycemic activity. In patients with renal impairment, these metabolites can accumulate.
 - Initiate conservatively at 1 mg daily
 - Avoid use if eGFR <60 mL/min/1.73 m²

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Sulfonylureas

- **Gliclazide** has inactive metabolites that are eliminated mainly in the urine (80%) and presents a lower risk of severe hypoglycemia than glibenclamide and glimepiride do.
 - This drug can be considered in renal impairment if appropriate attention is paid to the dose.

Glipizide	No dose adjustment required
Glimepiride	Initiate conservatively at 1 mg daily Avoid use if eGFR <60 mL/min/1.73 m ²
Gliclazide	Reduce dose if eGFR <30 mL/min/1.73 m ² Not recommended if eGFR <15 mL/min/1.73 m ²
Glyburide	Avoid use in patients with eGFR <60 mL/min/1.73 m ²

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Glinides

- **Nateglinide** (but not repaglinide) is hepatically metabolized, with renal excretion of active metabolites that are retained in DKD
 - so it should be used with caution in patients with advanced renal injury
- **Repaglinide** is considered a safe option until the GFR falls to <30 mL/min/1.73 m²
- In advanced renal disease, treatment with repaglinide should begin cautiously, with 0.5 mg daily, to avoid hypoglycemia.

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Alpha-glucosidase inhibitors

- **Acarbose**
 - Avoid if eGFR <30 mL/min/1.73 m²
- **Miglitol**
 - Avoid if eGFR <30 mL/min/1.73 m²
- Given their modest efficacy in glycemic control and the lack of long-term trials in patients with kidney disease, these medications should be avoided in CKD stages 4 and 5

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Glitazones

- Post hoc analysis from the PROspective pioglitAzone Clinical Trial In macro-Vascular Events (PROactive) identified a **greater decline** in the eGFR with pioglitazone (between-group difference of 0.8 mL/min per 1.73 m²/yr) than with placebo.
- These medications may cause **fluid retention** and thus should be used with caution in patients with heart failure (HF) as well as in those with CKD and a significant decrease in the GFR.

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Dipeptidyl peptidase-4 inhibitors

- **Sitagliptin** is mostly eliminated unchanged in the urine and can be used with appropriate dose reduction in all chronic kidney stages.
 - The usual dose of 100 mg once per day should be adjusted to 50 mg/day for patients with moderate renal impairment.
 - In severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease (ESRD) requiring dialysis, the dose is further reduced to 25 mg once daily
- **Vildagliptin:**
 - In T2DM Patients with moderate-to-severe CKD, dose reductions for vildagliptin are required, a reduction by half (to 50 mg/day) for both moderate, severe CKD & ESRD.

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- **Saxagliptin** is metabolized, mainly in the liver, into an active metabolite that is eliminated in the urine.
 - The normal dose (5 mg once daily) should be reduced to 2.5 mg once daily in patients with moderate or severe renal impairment.
- **Linagliptin** is the only DPP-4 inhibitor that is eliminated nearly entirely via the bile
 - used in all stages of CKD, without dose adjustments

Carmelina reinforce the long term safety profile of linagliptin

- Demonstrated a long term CV safety profile in patients with T2DM ,CV/Kidney disease
- No increase in risk of hospitalization for heart failure even in patients at high risk of heart failure
- CARMELINA thus provides unique clinical evidence for patient population that is highly relevant in clinical practice

Incretin mimetics

- **GLP-1 receptor agonists:**

- **Exenatide**

- Avoid if eGFR <30 mL/min/1.73 m².
- When eGFR between 30 and 50 mL/min/1.73 m² dose should not exceed 5 mcg

- **Liraglutide**

- Avoid if eGFR <60 mL/min/1.73 m²

- **Lixisenatide**

- Avoid if eGFR <50 mL/min/1.73 m²

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Sodium-glucose cotransporter 2 inhibitors

- This therapeutic class has been approved for the treatment of patients with T2DM with an eGFR of >45 mL/min/1.73 m²

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Insulin particularly short acting ones like lispro, aspart, and regular can be used in all stages of diabetic kidney disease

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

UNDER PEER REVIEW

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