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Review Article

# Diabetic Kidney Disease: Paradigm Shift in Comprehensive Management

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**Abstract:**

Being the country with highest Diabetic patients we also have higher prevalence of Diabetic Kidney Disease. It is the commonest microvascular complication yet not addressed intelligently. DKD mainly comprises reduced Glomerular filtration and Proteinuria. Dysglycaemic and raised blood pressure are two principal therapeutic targets in these patients. A comprehensive approach is the consensus in today's era as dictated by recent landmark trials. ACE-i/ARB have been the cornerstone of management of DKD since long but now SGLT-2 inhibitors and Non-steroidal MRA are the benchmark for management and reversal of DKD and its complications. This review highlights the past and present era of DKD management and how the paradigm shift has taken place in approach worldwide.

**Keywords:** MRA, ACE-i/ARB



## Introduction

India has highest diabetic population worldwide and it has jumped from position 2 to position 1 in 2022. In 2019 there were 77 million diabetic populations in India and current data is showing more than 100 million diabetics living in India. [1] One third population with Diabetes is under the risk of development of Diabetic Kidney Disease (DKD) during their course of disease. [2] Due to higher number of diabetic patients India has highest CKD burden as well. [3] According to Indian data nearly 45% of dialysis patients lost their kidney function due to diabetic kidney disease(Figure 1) and 27% patients reached to state of dialysis due to hypertensive nephrosclerosis, hence 2/3 rd of dialysis patients progressed to End Stage Renal Disease(ESRD) due to these two major problems. [4]

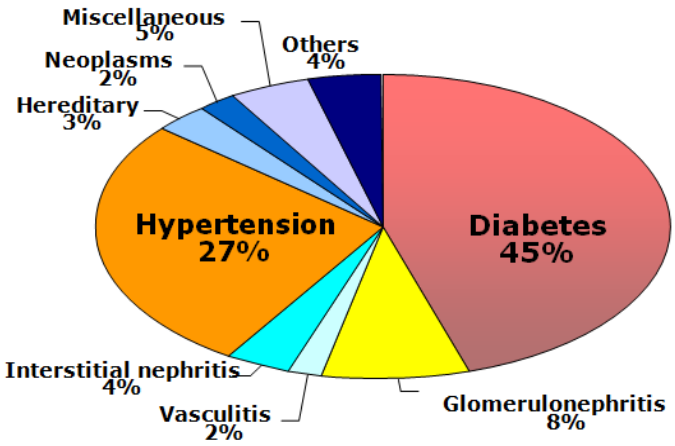


**Figure 1: Various factors responsible for ESRD in Indian population**

Majority of diabetic patients are type 2 diabetes (> 80 %) in India and worldwide. [5] Long duration of diabetes may produce microvascular (retinopathy, neuropathy, and nephropathy) or macrovascular (ASCVD and CVA) complications which may lead to premature morbidity and mortality. In all clinical senses diabetes is not merely hyperglycemia rather it is a systemic disorder which can affect every part of body and all emphasis should be given to prevent micro and macrovascular complications.

**Definition and terminology**

Previously used term Diabetic Nephropathy is not used now because no consensus definition was available for it. Now, we use the term Diabetic Kidney Disease (DKD), which indicates any kidney dysfunction induced by diabetes.

Diagnostic criteria of DKD includes

1. Diabetic patient with albuminuria > 300 mg /day
2. Presence of retinopathy as additional criteria
3. Absence of other glomerular disease

**Screening and diagnosis of DKD**

Each diabetic patient should be screened for DKD annually and it should be started 5 years after diagnosis in case of Type 1 and right at the time of diagnosis in Type 2.

Screening for DKD should include

1) Albumin Creatinine Ratio (ACR) in spot urine sample
2) Serum Creatinine for eGFR estimation

When we find albuminuria and renal dysfunction in a diabetic patient, it does not mean that it is always DKD. Renal dysfunction has heterogenous causes and albuminuria may be due to other glomerular diseases. All diabetic patients with renal dysfunction should undergo ultrasonography to see for renal size, shape, echotexture and to rule out any obstructive uropathy. When obstructive causes are ruled out every diabetic-albuminuric patient must undergo ocular fundus examination. If fundus shows changes of Retinopathy, it means that renal dysfunction and albuminuria in diabetic patient is due to DKD and no further workup is warranted. Retinopathy and nephropathy both are microvascular complications and go hand -in -hand, thus presence of retinopathy confirms DKD. Nearly 3% of patients having DKD may present without retinopathy, hence absence of retinopathy does not rule out DKD.

Albuminuria and renal dysfunction in diabetic patient may be due to DKD or any other glomerular disease, where DKD is relentlessly progressive while many other glomerular diseases are reversible hence it is mandatory to confirm whether patient is suffering from DKD or any other glomerular disease.

**Kidney biopsy in Diabetic kidney disease**

Kidney biopsy is not routinely performed for diagnosis of DKD. It is recommended in diabetic-albuminuric patients when

1. Patients of T2DM have albuminuria and renal dysfunction in absence of retinopathy
2. Type 1 DM with albuminuria and renal dys-function within 10 years of diagnosis
3. Patients with atypical urinary findings
4. Sudden onset heavy proteinuria

**Morphological features of DKD in Kidney biopsy**

Glucose derived metabolites, Glyoxal, Methylglyoxaland 3-deoxyglucose combines with amino group of intracellular and extracellular proteins. [5] This is a non-enzymatic process and forms Advanced Glycation End products (AGE ‘s).This formation of AGE ‘s takes place in non -diabetic persons also but in less amount without any untoward effects, while in chronic hyperglycemia levels of AGE increases to pathological quantity. Increased AGE’s is an important metabolic change for development of microvascular and macrovascular complications in diabetes. [6]

What this AGE does actually is interesting. Endothelial cells, macrophages T cells, vascular smooth muscle cells have receptors for AGE, named as RAGE. Binding of AGE to RAGE receptor leads to release of cytokines and growth factors. Most important of these is TGF-B, which is responsible for deposition of excess basement membrane material which results in basement membrane thickening. Other growth factors like VEGF also have role in pathogenesis of Diabetic Retinopathy.

This interaction between AGE and RAGE generates reactive oxygen species (ROS) in endothelial cells and causes increased procoagulant activity. [7] Growth factors also cause proliferation of vascular smooth muscle cells and extracellular matrix synthesis. All these changes results in damage to vessels and causes microangiopathy.

All the above-mentioned actions are receptor mediated effects of AGE’s but they can act without receptors as well, those effects are called non -receptor mediated effects of AGE’s. AGE’s can directly cross link extracellular matrix proteins and they do not need any receptor to do this, for example they cross link Type -1 Collagen of large vessels and reduces elasticity of that blood vessel. When elasticity of any vessel reduces, it is predispose to sheer stress and endothelial injury. When they cross-link Typev-4 collagen of basement membranes, these results in decreased endothelial cell adhesion and subsequently increased extravasation of fluids. Apart from this, when cross- linking of AGE with

collagen occurs they trap non-glycated plasma proteins or interstitial proteins as LDL. This leads to increased cholesterol deposition in tunica intima of vessel wall leading to increased atherosclerosis in diabetic patients. Morphological changes seen in biopsy are results of the above written pathological sequelae and affects all 4 comparts of kidney i.e. glomerulus, vessels, tubules and interstitium as shown in (Figure 2).

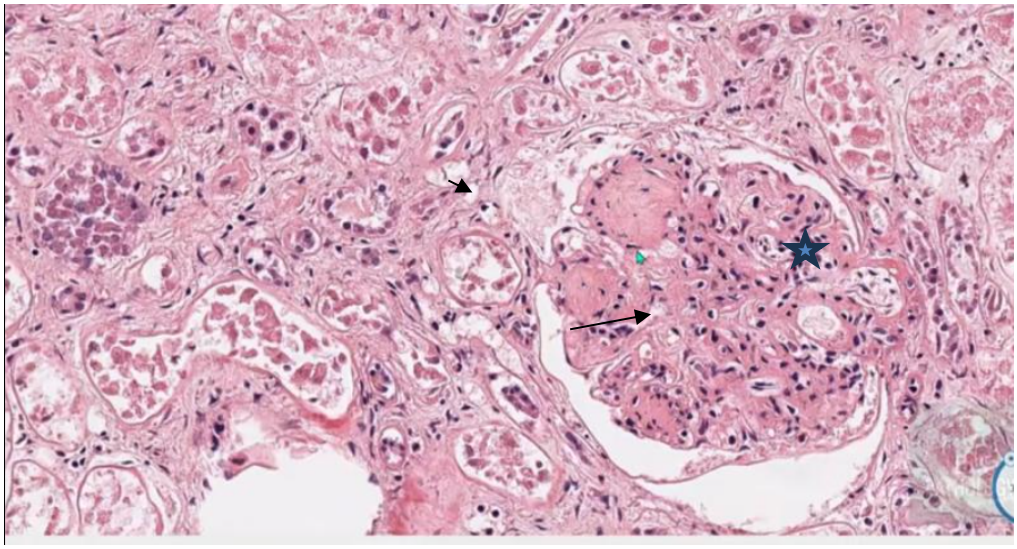

**Figure 2: Capillary basement membrane thickening and increased mesangial matrix (black arrow), nodular glomerulosclerosis (KW lesion) in interstitium (black arrowhead).Tubular atrophy and hyaline sclerosis in vessels (star)**

**Natural history Diabetic kidney disease:** Diabetic kidney disease is a relentlessly progressive disease. There is inverse relationship in e-GFR and albuminuria in DKD. (Figure 3)

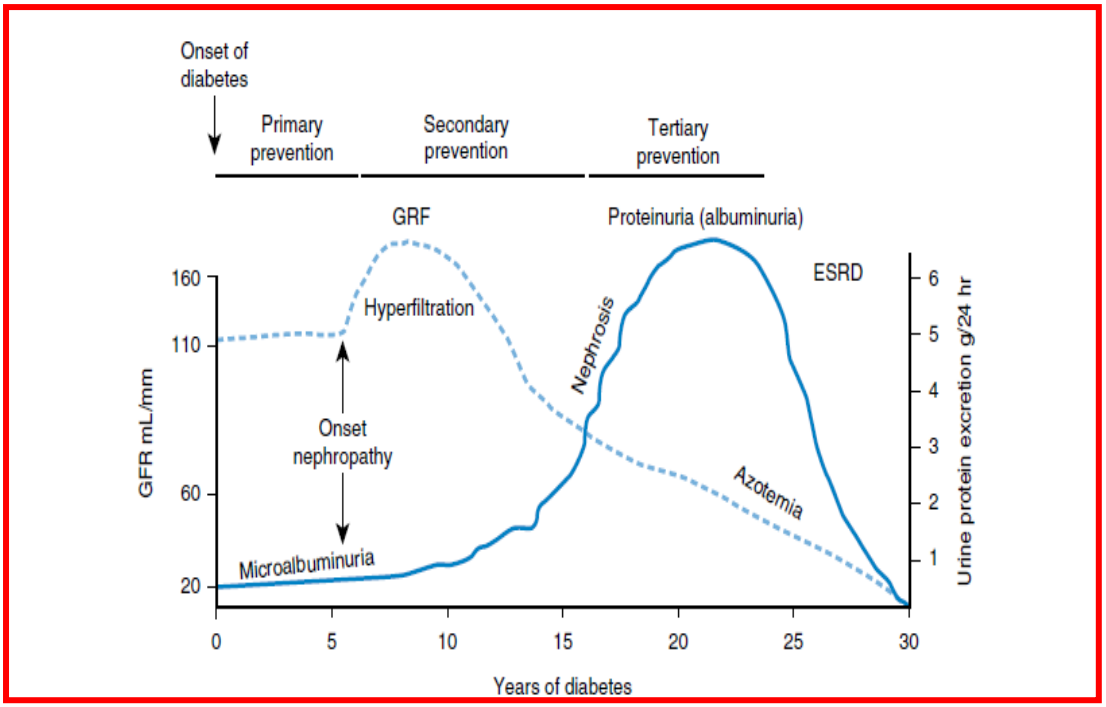


**Figure 3: Natural history of progression of Diabetic kidney disease (DKD)**

As shown in the graph that dotted line is showing e GFR and solid line showing albuminuria. After onset of nephropathy in initially few years e GFR increases, this is stage of hyper filtration and when albuminuria increases there is gradual decline of GFR thereafter. [8] Stopping occurrence of microalbuminuria is primary prevention, stopping of macroalbuminuria is secondary prevention and delaying renal failure is tertiary prevention. Hence it is obvious that retardation of progression of DKD

can be achieved by reducing albuminuria. [9] It has been decades since the introduction of ACEi/ARBs, still we do not have any significant medication which can reduce albuminuria in DKD. But in recent years high quality information was generated by landmark trials indicating that SGLT 2 inhibitors (SGLT 2i) and Non-steroidal Mineralocorticoid Receptor Antagonists (ns-MRA) can not only reduce the progression of DKD but have a cardio protective role as well. These medications have made paradigm shift in comprehensive care of DKD. [10]

### Comprehensive strategy for DKD

Diabetes not only requires glycaemic control, but comprehensive care because diabetes is a systemic disorder and hyperglycaemiais only a part of the disease process. DKD patients also need comprehensive care as they are at increased risk of progression to ESRD, ASCVD and heart failure. [11]

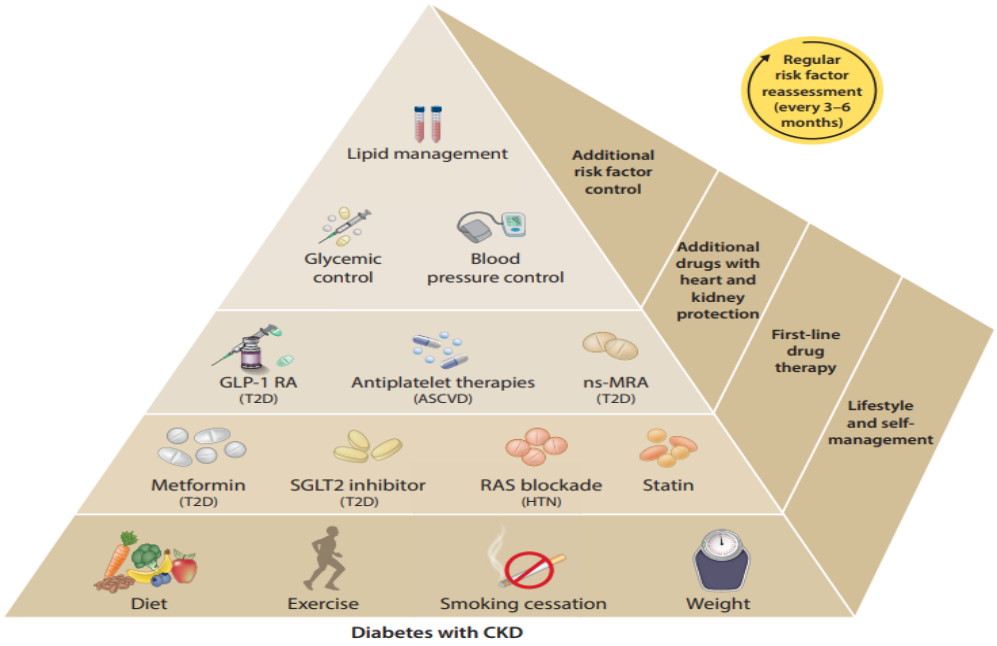


**Figure 4: Model for comprehensive care for treatment of DKD**

This pyramid in Figure 4 shows methods for comprehensive care of diabetic kidney disease. [12] Base of pyramid is formed by life style modification and self-management methods and probably is most important part of care, this includes weight reduction, smoking cessation, exercise and healthy diet.

Second layer of pyramid is related to good glycemic control by appropriate medications, which can be achieved by insulin in T1DM and by metformin and SGLT2i in T2DM.RAS inhibition for cardiovascular protection and reduction of albuminuria and statins should be given in both types of diabetes. [13]

Third layer of pyramid includes pharmacotherapy for renal and cardiac protection and if glycemiccontrol not achieved by metformin and SGLT2i, GLP1Receptor Agonist (GLP 1RA) should be added as add-on therapy. Non-steroidal MRA should be added to T2DM patients with high residual risk of kidney disease progression. [14] At top of pyramid lipid management good glycaemic control and BP control comes by additional drugs. Thus comprehensive management of DKD Includes

1. Good glycaemic control
2. Antihypertensive treatment
3. Renoprotection
4. Cardio protection

### Glycaemic control in DKD

Land mark trials of UKPDS [15,16] and DCCT 17has shown that good glycaemic control not only reduces microvascular complications but also has favourable effects on macrovascular complications as well. AS a result good glycaemic control is utmost necessary for renoprotection and cardio-protection. New high quality information has emerged after KDIGO 2022 which reviewed several landmark RCTs and thus SGLT2i and ns -MRA has been included in comprehensive care plan of DKD.18Metformin is still first line therapy in DKD if eGFR is > 30 ml /min /1.73 m2 or if Cr < 1.5 mg/dl in males or < 1.4mgh /dl in females. [19]

### SGLT2 inhibitors

SGLT2i is no longer a mere oral hypoglycaemic agent. Its status has been upgraded to a complete Cardio-reno protective agent due to Its pleotropic effects. Patients with DKD are at increased risk of

cardiovascular events and progression to kidney failure.

There is substantial evidence that SGLT2i's have a significant heart and kidney protective effects. There is high grade recommendation by KDIGO 2022 that SGLT2i should be started in any diabetic patient with renal dysfunction if eGFR > 20 ml/min /1.73 m2. [20]

**Mechanism of action of SGLT2i -** 90% of all the filtered glucose load is reabsorbed by SGLT2 receptors in S1 segment of Proximal Convoluted Tubule (PCT) and remaining 10 % by SGLT1 receptors in S3 segment of PCT. SGLT2i's reduces this tubular reabsorption of glucose and produces glycosuria and serum glucose lowering (Figure 5). [21]

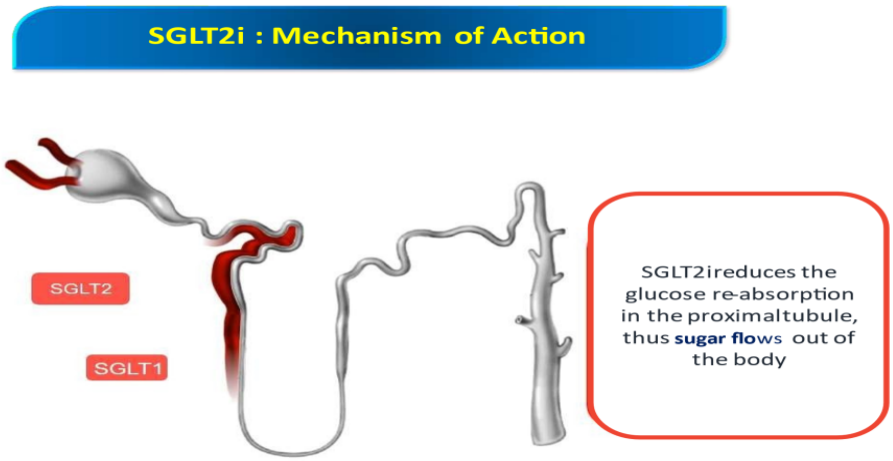


**Figure 5: Mechanism of action of SGLT-2 inhibitors**

They have an osmotic diuretic effect because of glycosuria and they shift fuel metabolism from carbohydrate breakdown to ketogenesis. Also a modest SBP reduction (4-5 mm of Hg) and modest HBA1c reduction (0.7 mg %) is seen with these agents.

As evidenced by EMPAREG [22], DICLARE-TIMI [23], CREDENCE [24], CANVAS [25], DAPA-HF [26] and DAPA CKD [27] trials, they reduce cardiovascular death, hospitalization by heart failure and progression of CKD. These cardiovascular and kidney benefits are independent of glucose lowering effects of SGLT2i's, probably by reducing intraglomerular hypertension and by reducing single nephron hyper filtration.

SGLT2i 's should be prescribed to all diabetic patients with renal dysfunction even if they have good glycaemic control because their benefit has been shown in non -diabetic CKD patients also. They should be started if eGFR is > 20 ml/min /1.73 m2 and once initiated they should be continued even if GFR < 20 ml/min /1.73m2 if they are well tolerated. If glycaemic control not achieved by metformin or SGLT2i in T2DM, GLP1-RA is addon therapy of choice for glycaemic control , if GLP1RA not tolerated well then other hypoglycaemic agents or insulin can be added .

**Non-steroidal MRA**

Mineralocorticoid receptor Agonists (MRA) may be steroidal as Spironolactone or Eplerenone or non-steroidal as Finerenone.

Ns-MRA is another breakthrough molecule in comprehensive care of DKD. It been evidenced by 2 large trials FIDELIO-DKD [28] and FIGARO DKD [29] that ns-MRA FINERENONE slows progressive loss of eGFR and decreases cardiovascular events on top of ACEi/ ARBs treatment. Ns-MRA benefit should be provided to all diabetic patients with renal dysfunction if eGFR is >25 ml/min /1.73 m2, albuminuria > 300 mg /day despite maximum RAS blockage and normal serum potassium levels.

Steroidal MRA are a standard practice in Heart Failure with reduced Ejection Fraction (HFrEF) but they have poor side effect profile such as hyperkalaemia and gynaecomastia. Ns- MRA produces less hyperkalaemia and does not cause Gynaecomastia. Their cardiovascular protective effects are similar to steroidal-MRA and they give renoprotection in addition.

If e-GFR is > 60ml/min /1.73m2, dose of Finerenone is 20 mg per day and if GFR <30 ml/min dose is 10 mg per day. Finerenone should not be started if Serum Potassium (SK+) is more than 5 mEq/l. Finerenone should be stopped if SK+ > 5.5 mg/dl and anti-hyperkaliaemic measures should be started.

**Antihypertensive treatment in DKD**

ACE inhbitors/ARBs are drug of choice for BP control in DKD patients, as evidenced by IDNT30, RENAAL31and several other trials. They not only provide renoprotection by reducing albuminuria but are cardioprotective as well. As other CKD patients, diabetic renal disease patients may require several

drugs for BP control, so Diuretics, Calcium Channel Blockers, Sympatholytics, Beta -blockers can be used according to need.

## Summary

Diabetic kidney disease is a relentlessly progressive disease and carries a risk of ASCVD, Heart Failure and progression to ESRD. We now know from long term experience and concrete data that reduction of proteinuria, intra glomerular pressure and reducing single nephron hypertension can retard the progression of DKD.

But since last couple of decades scientific progress was stagnant and we had ACE-i/ARBs only for this purpose, which is not the case now. In recent years after availability of SGLT2-I's we can hit 3 birds with single stone. It helps in getting good glycemic control as wellas reno and cardioprotective benefits. Ns -MRA's also gives similar systemic benefits with lesser side effects. These two drugs have made a paradigm shift in comprehensive care of Diabetic Kidney Disease.

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