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Diabetic Nephropathy: An Overview on Stages, Natural History, Biomarkers and Treatment

G. Bhavya*[a], A. Santhosh Kumar[b], Srtp. Ramya[c], M. Rishitha[d].
[a] *Students of pharm D 5th year, Nalanda Institute of Pharmaceutical Sciences, Kantepudi, Sattenapalli, Guntur-522438, Andhra Pradesh, India.*
[b,c,d] *Students of pharm D 5th year, Sri Venkateshwara college of pharmacy, Etcherla, Srikakulam-532001 Andhra Pradesh, India.*

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ABSTRACT:

Diabetic nephropathy is a chronic disease characterized by proteinuria, glomerular hypertrophy, decreased glomerular filtration and renal fibrosis with loss of renal function, the progression of disease is known to occur in a series of stages and is linked to glycemic control and blood pressure control. DN develops in approximately 422 million people who are diabetic and is leading cause of CKD worldwide. Increased blood pressure, poor glycemic control, dyslipidemia and smoking are the main risk factors for the development of DN. Genetic predisposition, elevated serum lipids and the amount of dietary proteins also seem to play a role as risk factors. Screening for microalbuminuria, serum creatinine, urine test should be performed yearly after diagnosis of diabetes. Using drugs with blockade effect on renin angiotensin-aldosterone system, lipid lowering, controlling blood pressure and blood sugar, lifestyle modifications are effective strategies for preventing development of microalbuminuria and delaying the progression of DN.

Keywords: diabetic nephropathy, biomarkers, albuminuria, diabetic kidney disease.

I. INTRODUCTION:

Diabetic nephropathy (DN) is the most common complication and leading cause of mortality associated with diabetes[1] and also increased risk of cardiovascular mortality. DN is more prevalent among African, Americans, Asians and native Americans than Caucasians[2]. The average incidence of DN is high during the first 10 to 20 years after the diabetes onset. Typically, it takes 15 years for small blood vessels in organs like kidney, eyes and nerves to get effected[3]. In 1959, Gellman et al., first reported an overview and clinical correction of findings on renal biopsien from patients with DN[4]. It is now a leading cause of end stage renal disease (ESRD). Chronic hypoxia and tubulointerstitial fibrosis are presently considered to be a common pathway for various progressive kidney disease including DN and hypoxia inducible factor (HIF-) 1 alpha plays an important role in these pathological mechanisms[5].

Sodium glucose cotransporter 2 (SGLT2) inhibitors, a novel class of anti-diabetic medication target the proximal tubules to reduce reabsorption, leading to increased urinary glucose secretion and produce hypoglycemic effects. Recent clinical trials have demonstrated that SGLT2 inhibitors have Reno protective effect in DN[6].

Most commonly used markers of renal disease and progression of CKD are estimated glomerular filtration rate (GFR) and proteinuria. Estimation of GFR reflect late functional changes and not early structural alternations in the kidney. Albuminuria has long been used to monitor onset and progression of DN[7].

DEFINITION:

DN is a chronic disease characterized by proteinuria, glomerular hypertrophy, decreased glomerular filtration and renal fibrosis with loss of renal function and Hyperglycemia is the driving force for the development of DN[8]. DN defined by macroalbuminuria (>300mg in a 24hours collection) or microalbuminuria and abnormal renal function as represented by abnormality in serum creatinine, calculated creatinine clearance and a high risk of cardio vascular morbidity and mortality[9]. A glomerular filtration rate (<60ml/min/1.73m2) is also an independent risk factor for cardiovascular event and death[10].

EPIDEMIOLOGY:

WHO estimated that there were around 422 million people living with diabetes[11]. India is the new diabetic capital in the world with a large increase in subject with Type II diabetes in the last decade and an approximate prevalence of 11.6%

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and 2% in urban and rural population respectively[12]. A population-based study reported 2.9% prevalence of DN among Chinese Rural residents. A population-based study from UAE found 11.4%. The highest prevalence rate of DM and CKD-DM were observed in the Eastern Mediterranean region. Diabetes clinical data management study in Japan revealed that 15.3% of T2DM patient had low GFR. Findings of United Kingdom (U.K) prospective study in corporating for 4006 T2DM patient revealed that 28% patient develop renal impairment. The prevalence of DKD in the United States (U.S) population was found to be 2.2% according to cross sectional analysis of third national health and nutrition examination survey[13].

SYMPTOMS:

In early stages it may be asymptomatic, later stages of signs and symptoms include Worsening blood pressure control, Protein in the urine, Swelling of feet, ankles, hands or eyes, Increased urination, Confusion, Shortness of breath, Loss of appetite, Nausea and vomiting, Persistent itching, Fatigue.

ETIOLOGY:

A variety of forms of chronic kidney disease in diabetes can be seen which including DN, ischemic nephropathy related to vascular disease, hypertensive nephrosclerosis, as well as other renal diseases that are unrelated to diabetes[14]. DN (complication of type 1 and type 2 diabetes) caused due to poorly controlled diabetes which leads to blood vessel clusters and increased blood pressure damages the blood vessels that filter waste from body in kidney.

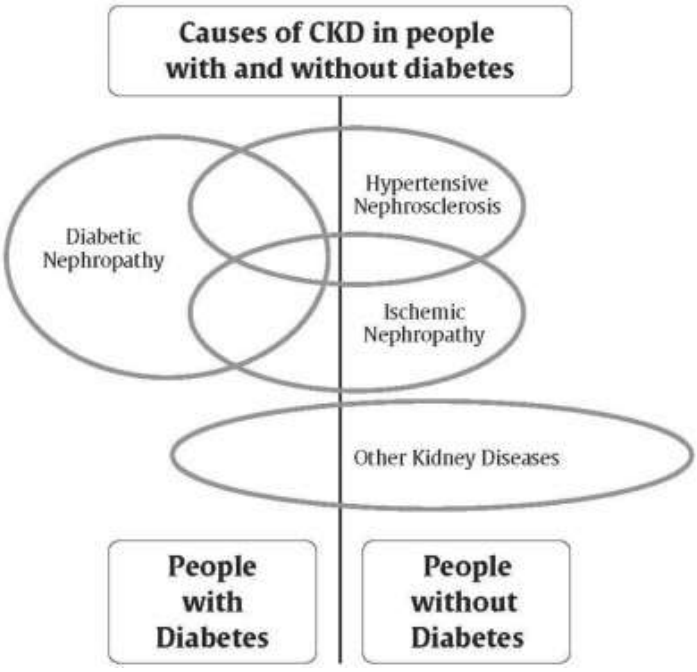

Figure 1 : Causes of CKD in patients with and without diabetes.

RISK FACTORS:[15]

Not all diabetic develops DN and in those who do, progression is variable. The main modifiable risks are hypertension, glycemic control and dyslipidemia and smoking. The main unmodifiable risks are age, race and genetic profile. DN is more likely to develop in patients with a family history of DN. One study suggested that males had an increased risk of DN.

NATURAL HISTORY:

A period of hyperfiltration followed by microalbuminuria (30–300 mg/day) and then by overt proteinuria accompanied by a decline in GFR in type 1 diabetic patients with DN (Fig 1). Similar progression of DN in T2DM Remarkably similar to that in type 1 diabetes, but confounding comorbidities, including hypertension and obesity, make a progressive pattern less clear[16,17].

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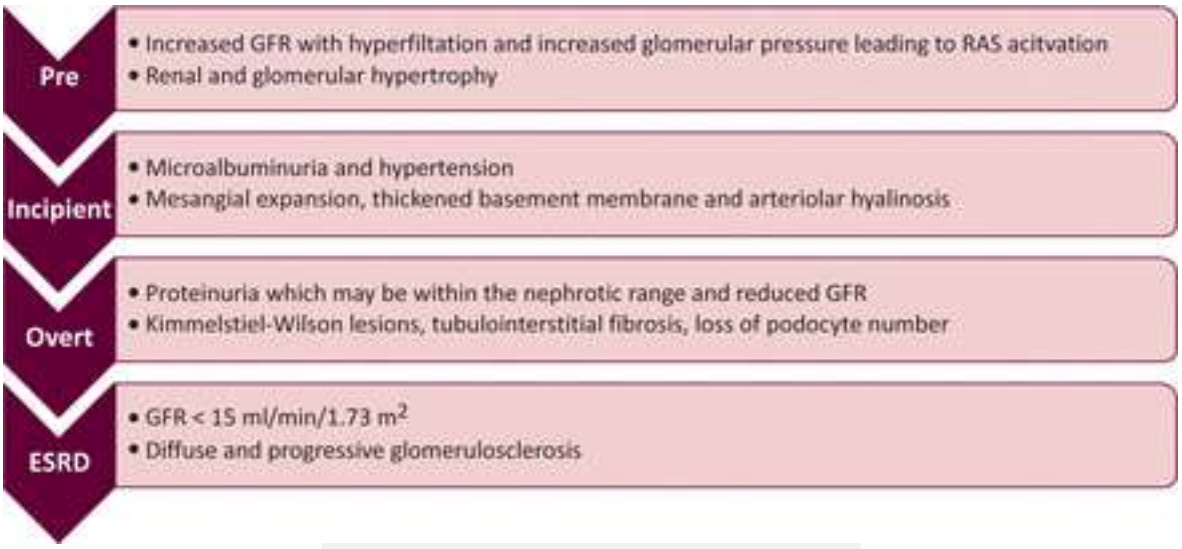

Figure 2: Natural history of diabetic nephropathy.

ESRD-end-stage renal disease; GFR-glomerular filtration rate; RAS-renin-angiotensin system.

In patients with T1DM was initially characterized in the late 1970s by Kussman. Proteinuria appears 11 to 23 years after the T1DM diagnosis, serum creatinine concentration begins to increase after 13 to 25 years, and end-stage kidney disease develops after 18 to 30 years[18].

The natural history of DN in T1DM is heterogeneous and is predominantly associated with atherosclerosis[19]. The timing of DN onset in patients with T2DM is difficult to assess[18].Progression from microalbuminuria to overt nephropathy occurs in 20-40% of Caucasians within a 10 year period, 20% of this overt nephropathy progressing to ESRD over a period of 20 years[20].

STAGES:[21,3]

Stage 1:Glomerular basement membrane thickening

It is preclinical stage characterized by early changes in function (hyperfunction) and size (hypertrophy) during diagnosis or before insulin. This stage is Usually from onset to 5 years. Borderline GFR (>90ml/min/1.73 m2), no albuminuria, hypertension but kidney size increased by 20% along with an increase in renal plasma flow.

Stage 2:Mild or severe mesangial expansion

Develops silently over many years (From 2 years after onset) and is characterized by basement membrane thickening and mesangial proliferation, intermittent microalbuminuria without signs of clinical disease. Shows normal GFR (60-89ml/min/1.73 m2), a number of patients continue in stage 2 throughout their lives.

Stage 3:Nodular sclerosis

Incipient diabetic nephropathy, clinical stage and its Main characteristic are Glomerular damage (GFR- 30-59) and persistent microalbuminuria (30–300 mg/day). A slow, gradual increase over the years (5–10 years after onset with or without hypertension) is a prominent feature in this very decisive phase of diabetic nephropathy. Increased blood pressure increases the rate of albumin excretion (measured by radioimmunoassay).

Stage 4:Advanced diabetic glomerulosclerosis that includes tubulointerstitial lesions and vascular lesions

Overt diabetic nephropathy or macroalbuminuria, the classic entity characterized by Irreversible proteinuria, sustained hypertension, persistent albuminuria >300 mg/24hrs and GFR (15-29 ml/min/1.73 m2). Long-term antihypertensive treatment reduces the fall rate by about 60%.

Stage 5:End-stage kidney disease

It is characterized by GFR < 15 ml/min/1.73 m2. Nearly 25% of diabetic population presently entering the end-stage kidney disease in the United States.

PATHOPHYSIOLOGY:

The pathophysiological mechanisms in the development of DN are multifactorial[22,23] inducing hemodynamic changes, inflammation, fibrosis and mesangial expansion, endothelial and podocyte

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injury, leading to albuminuria and reduced renal function[24].

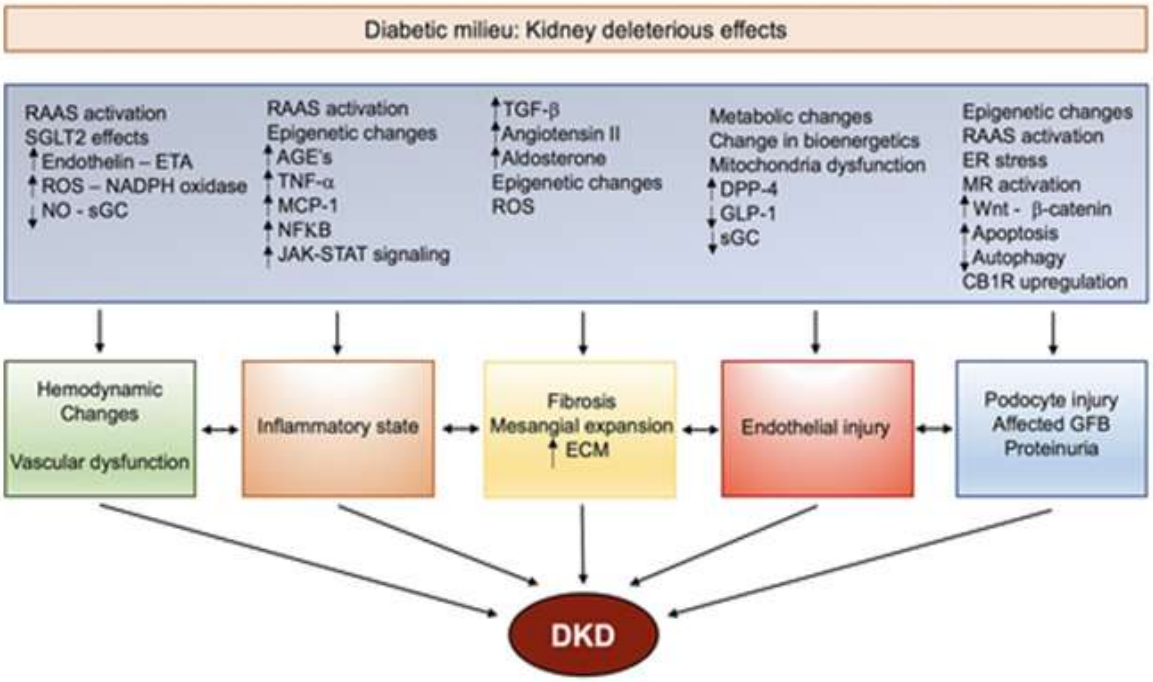

Figure 3: Several Pathway involved in the development of diabetic nephropathy[24].

BIOMARKERS:

Early identification and treatment of this chronic complication may reduce the rates of morbidity and mortality. Screening of chronic kidney disease (CKD) in diabetic patients recommends at least once a year. Standard biomarkers for DN are Creatinine and Albuminuria as we already discussed in screening. Recently, certain potential biomarkers (tubulointerstitial biomarkers) such as cystatin C, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), angiotensinogen, periostin, and monocyte chemoattractant protein-1 (MCP-1) were initially identified in acute kidney injury (AKI), also evaluating patients with CKD. Biomarkers

Tubulointerstitial biomarkers:

Cystatin C:[25,26]

Cystatin-C is produced from nucleated cells/proximal tubular cells in the body. It has a molecular weight of 13 kDa which is easily filtered by the glomeruli, and is reabsorbed and catabolized by the proximal tubule. T2DM with rapid renal progression had significantly increased levels of urine cystatin C. Urine cystatin C is a tubular marker and an independent predictor of CKD progression in T2DM. Serum cystatin is a glomerular filtration markers.

Neutrophil gelatinase-associated lipocalin (NGAL):[27,28]

NGAL is 25 kDa protein of the lipocalin family and it is synthesized in renal tubular, intestinal, hepatic, and pulmonary tissue. Predicted the renal progression of type 2 diabetes. Increased in response to tubulointerstitial injury. It is secreted in low concentrations by the thick ascending limb of the renal tubule and can be measured in the serum and urine. Increased NGAL synthesis and decreased reabsorption in proximal tubular injury occur causing increased urinary levels. Whereas circulating NGAL is filtered by the glomerulus to be reabsorbed in the proximal tubule.

Kidney injury Molecule-1 (KIM-1):[29,30,31]

KIM-1 is a urinary proximal tubular marker expressed on the apical membrane of proximal tubule cells. Its ectodomain is cleaved and released in the lumen of the tubule and finally appears in urine. This KIM-1 biomarker is undetected when the kidneys are normal, thus it serves as a specific and sensitive biomarker for proximal tubule damage. Serum and urine KIM-1 predicted the rapid decline of GFR. Urinary KIM-1 (uKIM-1) was higher in patients with proteinuria and normal renal function than in non-proteinuria individuals, and antiproteinuric drugs decreased

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uKIM-1. Baseline KIM-1 in proteinuria (>500 mg/day) patients predicted rate of eGFR loss and ESRD during 5–15 years of follow-up.

Angiotensinogen:[32]

Changes in angiotensinogen could influence renin angiotensin aldosterone system (RAAS) activity. Renal angiotensinogen is formed primarily in Proximal tubular cells. The activated intrarenal RAS was involved in the progression of renal injury in multiple models of hypertension and in kidney diseases including DN, immunoglobulin A (IgA) nephropathy, and radiation nephropathy. Urinary angiotensinogen level correlates with intrarenal angiotensinogen levels and independently associated with albuminuria and rapid GFR decline in T2DM. Some studies proposed that angiotensinogen could serve as a potential urinary biomarker to diagnose DN.

Periostin:[33]

Periostin, osteoblast-specific factor 2, firstly expressed in bone, is undetected in other main organs including the kidney, plays a major role in tissue regeneration, fibrosis and wound healing. It is involved in the fibrosis process and tissue remodeling, kidney development, and tubular dedifferentiation in experimental models. Urinary periostin levels were more significantly elevated among patients of normoalbuminuria, microalbuminuria, and macroalbuminuria. Predicted the renal progression of type 2 diabetes

Monocyte Chemoattractant Protein-1 (MCP-1):[34,35]

The infiltration of inflammatory cells in diseased kidneys is a hallmark of the progression of DN. MCP-1 as a member of the CC chemokine family is a major factor influencing macrophage accumulation. Rise in urinary MCP-1 levels correlates with the extent of interstitial inflammatory infiltrate. Urinary levels of MCP-1 among patients with overt nephropathy were also more significantly elevated when compared with levels among patients with normal albuminuria. Urine MCP-1 is a glomerular and tubular marker. Predicted the albuminuria and renal progression of type 2 diabetes.

Others:

Galectin-3 (Gal-3):

Gal-3 is a multifunctional 29-35 kDa belongs member of the lectin family and widely distributed in lungs, stomach, intestine and uterus[36,37,38]. Gal-3 is produced by activated mononuclear and contributes to macrophage phagocytosis through an intracellular mechanism playing a pivotal role in both innate and adaptive immunity by contributing to phagocytic clearance of microorganisms and apoptotic cells[38].

The main biological function of Gal-3 is regulation of cell-cell cooperation, extracellular interactions during self/non-self-antigen recognition and cellular activation, as well as mediating proliferation, differentiation, migration and apoptosis. Elevated level of galectin-3 was found in diabetic patients and these increased Gal-3 expression has been associated with renal fibrosis. Gal-3 is considered not only as a marker of tissue injury, but also as a mediator of the cell damage due to its pro-fibrotic and pro- inflammatory actions. In this context, Gal-3 could be useful for therapeutic targeting of individuals with T2DM[38].

Growth differentiation factor-15 (GDF-15):[39,40,41]

GDF-15 belongs to the transforming growth factor-beta family. It was originally identified by Bootcov etal. in 1997 and also called as macrophage inhibitory cytokine-1. Metformin was shown to cause increased levels of GDF-15. This pleiotropic protein has been linked to inflammation, metabolism, and oncogenesis regulation. Poorly expressed in healthy individuals, this molecule is upregulated in many pathological conditions such as following injury, ischemia, and other forms of oxidative and/or metabolic stress, raising interest in its potential utility as a biomarker in human disorders.

Fibroblast growth factor-23 (FGF-23):[42]

Fibroblast growth Factors (FGFs) are multifactorial proteins classified as intracrine, paracrine, endocrine, by their action mechanisms. Many tissues express FGF-23 such as bone tissue, bone marrow vessels, ventrolateral thalamic nucleus, thymus and lymph nodes. Its principle target is kidney. It regulates phosphate reabsorption and production of $1,25(OH)_2D_3$. In the past decades, FGF23 has emerged as a possible marker and therapeutic target in several conditions.

Platelet-derived growth factor (PDGF):[43]

Platelet-derived growth factors (PDGFs) are synthesized by platelets (wound repair and angiogenesis), smooth muscle cells, activated macrophages and endothelial cells upon activation, regulate cell growth and division. The PDGF has a

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dimeric structure and it is composed of A and B subunits. PDGF-B mRNA expression was upregulated in renal biopsies from type 2 diabetic patients with overt DN. However, the predictive value of urinary PDGF-BB for early diagnosis of DN is still limited.

SCREENING AND PRIMARY PREVENTION OF DIABETIC NEPHROPATHY:

Early detection of diabetic nephropathy can prevent or delay of end stage renal disease.

- **Microalbuminuria:** Earliest marker of DN and is used for screening. Not all patients with microalbuminuria will progress to nephropathy. Albuminuria screening should be beginning at 5 years diabetic duration among patients with type 1 diabetes and at the time of diagnosis among patients with T2DM based on the clinical practice guidelines for diabetic kidney disease outlined by the Kidney Disease Outcomes Quality Initiative (KDOQI)[44]. It is a standard biomarker used as Glomerular damage markers. 20–40% of diabetic patients with renal impairment exhibited normal albuminuria. It cannot detect injury in tubulointerstitial region[45].

2012 kidney disease improving global outcomes **(KDIGO)** definition of albuminuria category[46].

Measure	**A1**	**A2**	**A3**
Albumin excretion ratio	<30	30-300	>300
Albumin to creatinine(mg/g)	<30	30-300	>300
Albumin to creatinine(mg/mmol)	<3	3-30	>30

A1-Normal or mildly increased, A2-Moderate increased, A3-Severely increased

- **Annual urine test**: Perform annual urine test in type 1 diabetic patients with diabetes duration of >5 years and in all type 2 diabetic patients[47]. Spot urine samples (Early morning urine sample) or 24 hrs urine collection are used[48]. To confirm the microalbuminuria or proteinuria, two out of three tests should be positive because unstable glucose control, intercurrent acute illnesses, symptoms of urinary tract infection can alter day-to-day albumin excretion. The rate of change of albuminuria over one year independently predicts mortality and cardiovascular events.
- **Serum creatinine**: Even though serum creatinine is normal, it should be monitor in patients with high microalbuminuria/proteinuria. Once the serum creatinine is outwitting the normal reference range progress towards end stage renal disease should be monitor[46]. It is used as Glomerular filtration markers, Factors affecting creatinine generation are extremes of muscle mass, extremes of body size, diet and nutritional status: high protein diet and creatine supplements, muscle wasting diseases[44].
- **Blood glucose control**: Good glycemic control helps for effective reducing of diabetic microvascular complications. The blood glucose should be <7.5% on insulin and <6.5% not on insulin[47].
- **Blood pressure control**: In the United Kingdom Prospective Diabetes Study (UKPDS). The lower the blood pressure, the lower the risk of developing microalbuminuria. The upper limit of acceptable blood pressure has generally been agreed at 140/80 mm Hg to reduce cardiovascular disease mortality (CVD) and slow down the diabetic nephropathy progression[49].
- **Smoking cessation**

Advised to stop Smoking in individuals with diabetes as it leads to oxidative stress, increased blood pressure, increased TGF- β level and impaired vasodilation, all of which are associated with the development and progression of diabetic nephropathy. Moreover, studies have shown that in smokers nephropathy progression increases and leads to Immunoglobulin A (IgA) nephropathy[50]

TREATMENT:

MULTIDISCIPLINARY TREATMENT:

Multidisciplinary treatment, such as blood glucose control, blood pressure control with RAS inhibitor, lipid control, and lifestyle modifications, significantly reduced cardiovascular events in DKD patients and, as a secondary endpoint, suppressed renal events.

Blood pressure control and renin- angiotensin system blockade:

The patients with hypertension and DN are recommended to treated in an individualized manner, targeting a SBP to 130 mmHg and <130 mmHg if tolerated, but not <120 mmHg. In older people (aged >65 years) the SBP goal is to a range

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of 130-139 mmHg[51]. According to ADA First line antihypertensives are recommended if albuminuria present[52]. A RAAS blocker (ACEI or ARB) is first choice of drugs in the treatment of hypertension in patients with DN, particularly in the presence of proteinuria, microalbuminuria, or LVH[51]. Combination of ACEIs and ARBs may further reduce both blood pressure and proteinuria. Current guidelines recommend that normotensive patients with microalbuminuria should also be treated with an ACEI[16].

Glycaemia control:[53]

Both the DCCT [Diabetes Control and Complications Trial] and UKPDS [UK Prospective Diabetes Study] have demonstrated that intensive diabetes therapy can significantly reduce the risk of developing microalbuminuria and overt nephropathy in people with diabetes. Reduction in glucose leads to improved glomerular function. In the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) rates of hypoglycemia were twice as high in patients with CKD compared to patients without CKD. Presence of moderate or severe renal impairment offers significant challenges in the management of glycemic control. Insulin therapy can be used at all stages of CKD. **Table-1** details common medications used in type 2 diabetes and recommended dose adjustments in CKD.

Anaemia:[54,55]

Anemia is a frequent complication of DN develops at younger age and with greater severity. One in five patients with diabetes have anemia. All DN patients should be monitored for anemia. Anemia has also been shown to increase risk of progression of DKD by reduced oxygen delivery and heart failure. Treatment of anemia with iron replacement and erythropoietin has been shown to improve quality of life but overtreatment leads to worsened cardiovascular outcomes (heart failure and ischemic heart disease). Therefore, the target for Hb suggested by NICE is between 100 and 120 g/l.

Metabolic bone disease:[56,54]

Metabolic bone disease is mostly asymptomatic. Potential symptoms Anemia include pain and stiffness in joints, spontaneous tendon rupture, predisposition to fracture, and proximal muscle weakness are occurring late in the course of the condition. Abnormalities of parathyroid hormone (PTH) and vitamin D metabolism are also found along with abnormalities of bone disease. Serum calcium, phosphate and PTH should be monitored regularly. Persistent elevated phosphate levels can be treated by diet (phosphate restriction). Alfacalcidol may be indicated to a patient with hypocalcemia and raised PTH.

Lipid management:

Statins are recommended as the first-choice lipid lowering treatment[51]. Statin does not affect progression of kidney disease, but reduces cardiovascular disease risk in people with diabetes and chronic kidney disease. Therapy with a Statin should be considered if the LDL cholesterol is >100 mg/dl. The treatment goal of <100mg/dl[57]. High-intensity statin for all patients aged 50-70 years with multiple CV risk factors Moderate intensity statin for patients aged 40-75 years without additional CV riskfactor[52].

Diet:[15]

Advised to take diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweetened beverages. Low protein diet (0.6-0.8 g/kg/day) was recommended to patients with diabetic nephropathy. Normal protein intake defined as 1.0-0.8g/kg/day. Dietary sodium intake <2300 mg/day.

Exercise:[58]

Physical activity (>150 min/week aerobic activity) improves insulin sensitivity, lowers inflammatory markers, and improves endothelial function and can acutely increase urinary protein excretion but there is no evidence that vigorous exercise increases the rate of progression of diabetic kidney disease and likely no need for any specific exercise restrictions for people with DKD.

Weight loss:

Many patients with T2DM are overweight or obese which increases the incidence of rate of progression of DN. Weight loss will not only improve glycemic control but also will reduce the risk of cardiovascular disease. The national kidney foundation (NKF) recommends target BMI of 18.5-24.9 for patients with diabetes and CKD.

PHARMACOLOGICAL TREATMENT:

Here we divided pharmacological treatment into Newly approved, Drugs in phase III clinical trials and Potential drugs required further validations[59].

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Newly approved drugs:

Sodium-glucose co-transporter 2 (SGLT2) Inhibitors: Empagliflozin, Canagliflozin, Dapagliflozin

Sodium-dependent glucose co-transporters (SGLT) are found in the intestinal mucosa of the small intestine (SGLT1) and the proximal tubules (SGLT1 and SGLT2) of the nephrons[60]. SGLT2 inhibitors have emerged as a novel class of medications for the treatment of type 2 DM[57], inhibit proximal tubular glucose reabsorption and promote urinary glucose excretion, resulting in hypoglycemia. Treatment with an SGLT2 inhibitor is associated with a lower risk of renal endpoints and is recommended if eGFR is 30 to <90 mL/min/1.73 m2 and in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events[51]. The adverse effects caused by SGLT2 are fatigue, hypoglycemia, increased urine output, increased hematocrit, and mycotic genital or urinary tract infections[60].

SGLT2 inhibitor	Dose	Kidney function eligible for inclusion in pivotal randomized trials	Dosing approved by the US FDA
Canagliflozin	100–300mg once daily	CANVAS: eGFR≥30ml/min per $1.73m^2$ CREDENCE: eGFR 30–90ml/min per $1.73m^2$	No dose adjustment if eGFR >60 ml/min per $1.73m^2$ 100 mg daily if eGFR 30–59 ml/min per $1.73m^2$ Avoid initiation with eGFR <30 ml/min per $1.73m^2$, discontinue when initiating dialysis
Dapagliflozin	5–10mg once daily	DECLARE-TIMI 58: CrCl ≥60ml/min DAPA-HF: eGFR ≥30 ml/min per $1.73m^2$ DAPA-CKD: eGFR 25–75 ml/min per $1.73m^2$	No dose adjustment if eGFR ≥45 ml/min per $1.73m^2$ Not recommended with eGFR <45 ml/min per $1.73m^2$ Contraindicated with eGFR <30 ml/min per $1.73m^2$
Empagliflozin	10–25mg once daily	EMPA-REG: eGFR≥30ml/min per $1.73m^2$ EMPA-KIDNEY: eGFR 20–90ml/min per $1.73m^2$ EMPEROR-Reduced: eGFR≥20ml/min per $1.73m^2$	No dose adjustment if eGFR≥45 ml/min per $1.73m^2$ Avoid use, discontinue with eGFR persistently <45 ml/min per $1.73m^2$

Table 1 : SGLT2i with established kidney and cardiovascular benefits and dose adjustments as approved by the US FDA

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Promising drugs in phase III clinical trials

Glucagon-like peptide 1 receptor agonists (GLP-1RAs): Liraglutide, Semaglutide

Treatment with the GLP1-RAs is associated with a lower risk of renal endpoints, and should be considered for DN treatment if eGFR is >30 mL/min/1.73m2[60]. The inhibition of oxidative stress, inflammation, fibrosis, and induction of natriuresis have been mainly implicated as mechanisms underlying the attenuation of DKD. GLP-1RAs have beneficial effects on renal outcomes, especially in patients with T2D who are at high risk for CVD[61].

GLP-1 RA	Dose	CKD adjustment
Dulaglutide	0.75mg and 1.5mg once weekly	No dosage adjustment Use with eGFR >15ml/min per $1.73m^2$
Exenatide **Exenatide extended-release**	10µg twice daily 2mg once weekly	Use with CrCl >30ml/min
Liraglutide	0.6mg, 1.2mg, and 1.8mg once daily	No dosage adjustment Limited data for severe CKD
Lixisenatide	10µg and 20µg once daily	No dosage adjustment Limited data for severe CKD
Semaglutide(injection) **Semaglutide(oral)**	0.5mg and 1mg once weekly 3mg, 7mg, or 14mg daily	No dosage adjustment Limited data for severe CKD

Table 2: Dosing for available GLP-1 RA and dose modification for CKD. CKD, chronic kidney disease; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

Endothelin-1 receptor A antagonist (ET-1): Avosentan, Atrasentan

ET-1 system is complicated, consisting of a converting enzyme and two active receptors (ETA-R, ETB-R) and can exerts several physiological effects, (control of water and sodium homeostasis). Plasma ET-1 Levels are increased in diabetic patients also increased by the aging process, growth factors, inflammatory cytokines, and proteinuria which contribute to endothelial dysfunction. It is certified that endothelin receptor (ER) antagonists could reduce albuminuria in patients with DN[62]. Safe at low dosages. These are contraindicated during pregnancy. The adverse effect among ET blockers is fluid retention (most common), hepatotoxicity (specific side effects) and Testicular toxicity (rare but serious)[63].

Mineralocorticoid Receptor Antagonists: Apararenone (MT-3995), Esaxerenone, Finerenone

The main physiological mineralocorticoid (steroid hormones) is aldosterone, synthesized in the outer layer of the adrenal gland in response to hyponatremia and hyperkalemia, through the activation of the renin–angiotensin system[64]. Hyperkalemia, gynecomastia and vaginal bleeding are the common side-effects[65]. The MRAs spironolactone and eplerenone increase the risk of hyperkalemia so finerenone is recommended in Patients with CKD and heart failure[66].

Antifibrotic Agents: Pirfenidone, Pentoxifylline[15]

Pirfenidone inhibits Transforming growth factor beta (TGF-β) production and Transforming growth factor alpha(TNF-α) production. The exact mechanism of action is unclear. In a small randomized trial of 77 type 1 and 2 diabetics with established DN, pirfenidone at 1,200 mg/day for 1-year improved eGFR from baseline compared to placebo whereas at higher dose of 2,400 mg/day

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did not demonstrate a similar benefit and the dropout rate was high. Pirfenidone did not lower albuminuria.

Other drugs which require further validation are Anti-Advance Glycation end products (Pyridoxamine), Nuclear factor erythroid 2-related factor 2(Bardoxolone methyl), JAK-STAT inhibitor (Baricitinib), Nox1/4 inhibitor (GKT137831 APX-115), Inhibitor of chemokines cytokines (NOX-E36)

II. CONCLUSION:

Diabetes is the common cause for DN and ESRD. DN is asymptomatic initially so early screening helps us to prevent ESRD. There is a need to develop new biomarkers for DN. The main treatment involves blood pressure control, glycemic control and lifestyle modifications.

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