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Review Article

A REVIEW ARTICLE ON DIABETIC NEPHROPATHY**Dr. B. Aruna *, B. Vasundhara**

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Abstract:

Diabetic nephropathy is one of the most feared diabetic chronic microvascular complications of type 1 and type 2 diabetes. It is also known as diabetic kidney disease and is defined by increased urinary albumin excretion in the absence of other renal diseases. The chronic hyperglycaemia and high blood pressure are the main risk factors for the development of DN. The stages of diabetic nephropathy: Stage 1 kidney damage present but normal kidney function and a GFR of 90% or above and stage 2 kidney damage with some loss of function and a GFR of 60-89%. Stage 3 mild to severe loss of function and a GFR of 30-59%. Stage 4 severe loss of function and GFR of 15-29%. The major causes of end-stage renal disease. If what happens to the kidney in diabetic nephropathy is high blood glucose level can damage the small blood vessels and tiny filters in your kidneys. The mechanism of proteinuria is may be initiated by promoting increased production of reactive oxygen species. The induction of AGE-induced proinflammatory signaling and increased glomerular capillary pressure and hypofiltration. Pathogenesis of DN is progressive nerve fiber loss. The aim of this discuss the methods of early screening and diagnosis of diabetic nephropathy and the therapeutic strategies that promote renal and cardio protection in this high risk group of patients, in order to reduce the incidence of diabetic nephropathy and its associated cardiovascular mortality. The prevention of DN is the treatment of known risk factors hypertension, hyperglycaemia, smoking and also CV disease should be vigorously treated. The review focus on the role of inflammation and oxidative stress in pathogenesis of DN, approaches to diagnose in classic and NP-DN, current and emerging and therapeutic interventions.

Keywords: Diabetic nephropathy, albumin excretion hyperglycemia, cardiovascular mortality, proteinuria.

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INTRODUCTION:

Diabetic nephropathy is a common complication of type 1 and type 2 diabetes. DN is one of the most feared diabetic chronic microvascular complications. The diabetic nephropathy is also known as diabetic kidney disease. The term diabetic nephropathy is a syndrome characterized by the presence of pathological quantities of urine albumin excretion, diabetic glomerular lesions, and loss of glomerular filtration rate in diabetics^[1] The nephropathy is the deterioration of kidney function. The major causes of end stage renal disease. Diabetic kidney disease is a global challenge and a significant social and economic. The disorder presents with persistent albuminuria and a progressive decline in the glomerular filtration rate. There is a substantial evidence that early treatment can delay or prevent the progression of the disorder. Diabetic nephropathy (DN) is a major disorder of diabetes mellitus (DM) which ends up in chronic renal failure. People with DM are ten times more prone to end-stage kidney failure. The International Diabetes Federation (IDF) reports that 40% of diabetic people might develop final stage renal failure. Furthermore, diabetes and hypertension, either in combination or separately lead to about 80% of end-stage kidney failure. Microalbuminuria is the early evidence for detecting DN.^[2] About 20% of patients develop nephropathy from microalbuminuria within a decade and nearly 20% of patients reach end-stage kidney disease. On one hand, around 20% of T1DM patients suffer from end-stage kidney failure in just a decade, and 75% of patients in less than two decades as there is no treatment available to date. On the other hand, T2DM patients show evidence of microalbuminuria and nephropathy within a short period of DM.

The main objective of diabetic nephropathy targets four areas:

- Cardiovascular risk reduction.
- Control of blood pressure.
- Inhibition of the renin-angiotensin system (RAS)
- Glycemic control.

Epidemiology

The prevalence of diabetes is phenomenal and the projections are staggering.^[3] When one considers the morbidity, mortality, and cost of health care, the burden of the diabetes epidemic becomes apparent. Worldwide, the prevalence of diabetes was estimated at 171 million in 2000, increasing to 382 million in 2013; and is projected to reach 592 million by 2035. This represents 8%–10% of the global population, resulting in at least 548 billion dollars in health

expenditure on diabetes care. Type 2 diabetes constitutes about 85%–95% of all diabetes cases.^[4] In the US alone for 2011, 25.8 million children and adults have diabetes with another 79 million having a prediabetic state. The diabetes epidemic has resulted in DN becoming the most frequent cause of end-stage renal disease (ESRD) in most countries. In 2009–2011, diabetes was the primary cause of ESRD in about 60% of patients in Malaysia, Mexico, and Singapore. Countries with an ESRD incidence of 40%–50% include Israel, Korea, Hong Kong, Taiwan, Philippines, Japan, the US, and New Zealand.^[5] The incidence of ESRD due to diabetes also rises in the older age group. In 2011, the incident rates of ESRD due to diabetes in the US were 44, 266, and 584 per million for the age groups 20–44, 45–64, and 65–74 years, respectively. A similar finding was noted in the AusDiab study of 11,247 diabetic Australians.^[5] Thus, the reason for this boom in diabetes-associated ESRD is the increasing prevalence of diabetes and the aging population.

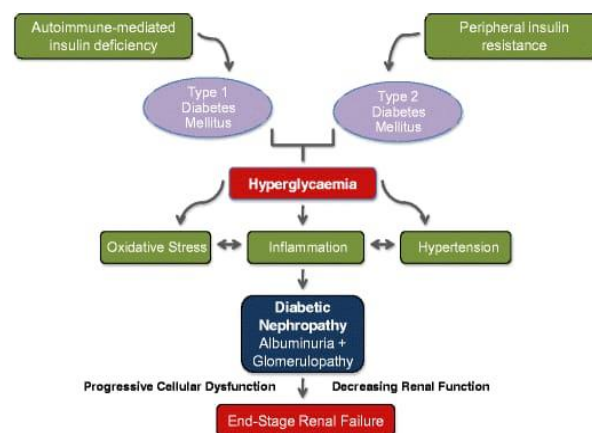


Table:1 epidemiology of diabetic nephropathy

Etiology

The exact cause of diabetic nephropathy is unknown, but various postulated mechanisms are hyperglycaemia (causing hyperfiltration and renal injury) advanced glycation products and activation of cytokines. Many investigators now agree that diabetes is an autoimmune disorder, the pivot role of innate immunity and regulatory T-cells.^[6] Hyperglycemia also increases the expression of transforming growth factor-beta. In the glomeruli and of matrix proteins, specifically stimulated by this cytokine. TGF-beta and vascular endothelium growth factor may contribute to the cellular hypertrophy and enhanced collagen synthesis and may induce the vascular changes observed in persons with diabetic

nephropathy. Hyperglycaemia also may activate protein kinase C, which may contribute to renal disease and other vascular complications of diabetes.

Classification of diabetic nephropathy

Diffuse neuropathy	Mononeuropathy	Radiculopathy	Other neuropathies
DPN primarily small fiber	Isolated cranial or peripheral neuropathy	Thoracic radiculoneuropathy	Pressure neuropathies
DPN primarily large fiber	Mononeuritis multiplex	Radiculoplexus neuropathy	CIDP
DPN mixed small and large fiber			Acute treatment induced neuropathy
DPN and autonomic neuropathy			

Signs and symptoms

Signs and symptoms of type 1 and type 2 diabetes are :

- Feeling more thirsty than usual
- Urinating often
- Losing weight without trying
- Presence of ketones in the urine
- Feeling tired and weak
- Feeling irritable or having other mood changes
- Having blurry vision
- Having slow healing sores.

Risk factors

1. Uncontrolled high blood sugar, also called hyperglycemia.
2. Uncontrolled high blood pressure, also called hypertension.
3. Smoking.
4. High blood cholesterol.
5. Obesity.

Stages of diabetic nephropathy

The initial phase of DN starts with the glomerular basement membrane (GBM) thickening. Normal glomerular filtration rate (GFR), lack of albuminuria, and hypertension are often observed in this stage for five years from the onset of GBM thickening.^[7] The next stage involves the

development of mild to severe mesangial expansion. Two years from the onset of the GBM thickening and mesangial proliferation, normal GFR were still observed and no other clinically significant symptoms were recorded. The third stage is the damage of glomerular and elevated microalbuminuria of 30 to 300 mg day⁻¹. The stage was observed in diabetic patients with or without the condition, hypertension. The third stage is called nodular sclerosis and starts after 5 to 10 years from GBM onset. The advanced diabetic glomerulosclerosis is the fourth stage of DN in which tubulointerstitial and vascular lesions are prominent. The end-stage is the total kidney failure with a GFR below 15 mL min⁻¹ per 1.73 m².

MECHANISMS OF DKD (DIABETIC KIDNEY DISEASE)

Hyper aminoacidemia, a glomerular hyperfiltration promoter, and hyperglycaemia are the metabolic modifications that change renal hemodynamics and facilitate fibrosis and inflammation in diabetes' initial stage (fig 2). In this study, the pathways that drive the development of chronic kidney disease (CKD) in DM patients are studied to provide a conceptual basis for identifying effective therapeutic targets. DN is a significant DM microvascular

disorder responsible for 50% of all ESRD populations.

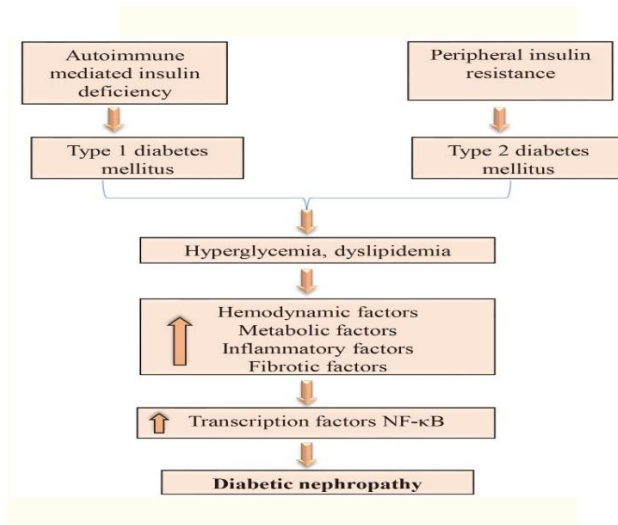


Table 2: The inflammatory mechanisms in the pathophysiology of diabetic nephropathy:

In hypertensive patients, DKD is also a significant reason for cardiovascular risk. Microalbuminuria acts as the first clinical expression of DKD and almost 50% of microalbuminuria patients will

advance to macroalbuminuria without an early diagnosis.^[8] The chance of ESRD progression is almost ten times greater than the patients with normal urinary albumin levels. The crucial factors for the existence of microalbuminuria in T2DM patients are high urinary albumin to creatinine ratio, high HbA1c level, older age hypertension, and increased blood glucose levels. Hemodynamic factors such as eGFR may not play a part.^[9] Roughly 30% of T1DM patients are associated with microalbuminuria and rely on blood glucose control and drug compliances to explore the initial and later consequences of hyperglycaemia on the kidney.^[10]

How do you control diabetic nephropathy?

The first step in treating diabetic nephropathy is to treat and control diabetes and high blood pressure. Treatment includes diet, lifestyle changes, exercise and prescription medicines. Controlling blood sugar and blood pressure might prevent or delay kidney issues and other complications.

PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY.HYPERGLYCEMIA:

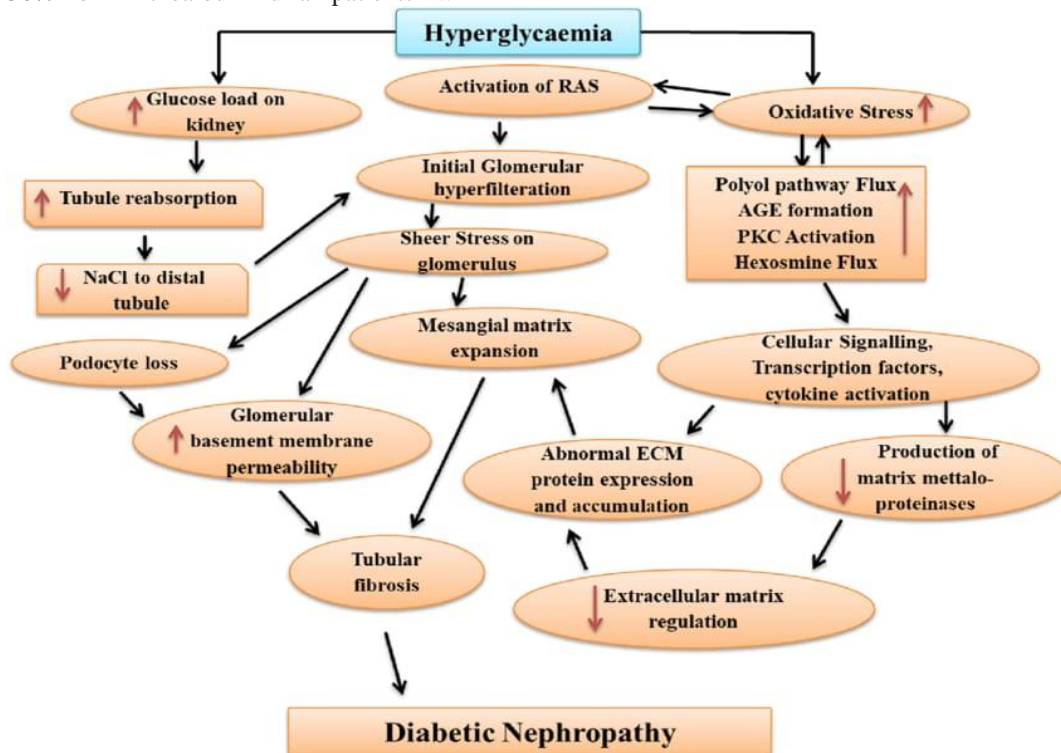


Table 3: The pathogenesis of diabetic nephropathy

CONVENTIONAL PATHOGENESIS

Renal fibrosis the final common pathway in the pathophysiology of DKD is caused least renal hemodynamic changes, Ischemia and glucose and their metabolism^[11] abnormalities associated with oxidative stress increases, inflammatory processes and overactive renin-angiotensin-aldosterone system (RAAS).

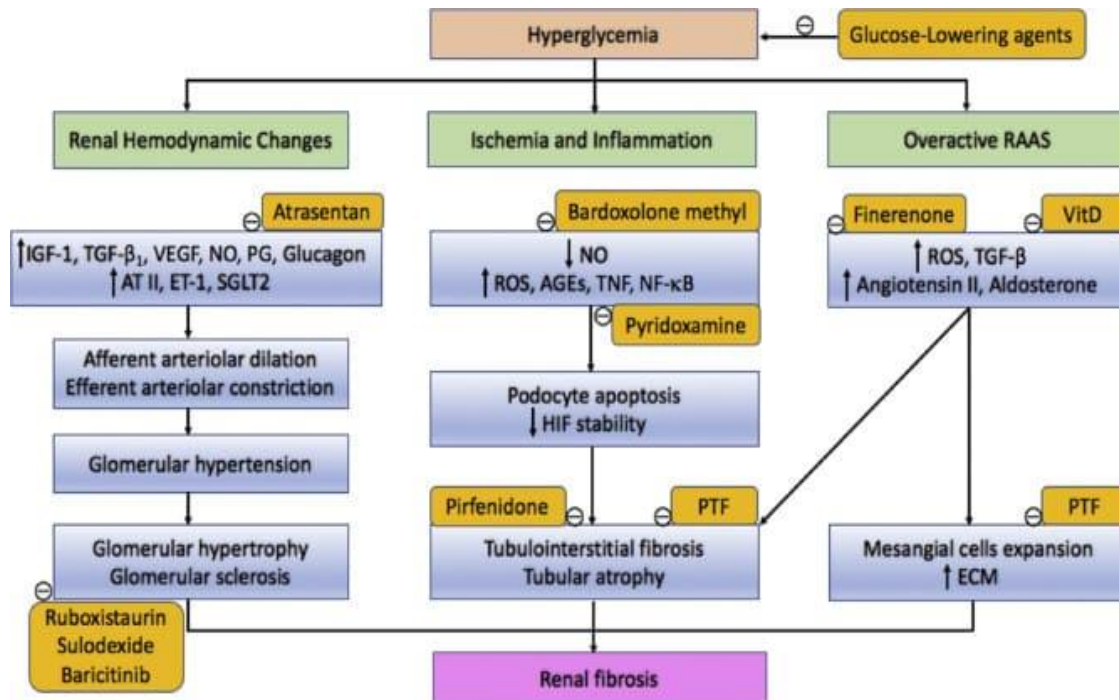


Table 4: the conventional pathogenesis of diabetic nephropathy

Conventional pathophysiology and novel medical treatment of diabetes kidney disease.

IGF-1, insulin-like growth factor 1; TGF- β_1 , transforming growth factor β_1 ; VEGF, vascular endothelial growth factor; NO, Nitric oxide; PG prostaglandin [AT II, angiotensin $_2$; ET-1, endothelin-1; SGLT2, sodium glucose co-transporters 2; ROS, reactive oxygen species; AGEs, advanced glycation end products; TNF, tumour necrosis factor; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; HIF, hypoxia-inducible factor; RAAS, renin-angiotensin-aldosterone system; ECM, extracellular matrix; PTF, pentoxifylline; VitD, vitamin D^[12]

Hemodynamic factors

There is an imbalance in afferent and efferent arteriolar resistance, resulting in increased glomerular hydrostatic pressure and hyperfiltration. Activation of the renin-angiotensin system (RAS) increases angiotensin II levels, leading to efferent arteriolar vasoconstriction and production of proinflammatory and profibrotic molecules through multiple mechanisms.^[13] High angiotensin converting enzyme (ACE) levels are associated with greater albuminuria and nephropathy in diabetic mice and humans. Increase level of endothelin-1 and urotensin II also

contribute to vasoconstriction. Various dysregulation of nitric oxide and nitric oxide synthase has been described in DN. Nitric oxide mediates endothelium-dependent vasodilatation, and is formed from L-arginine by endothelial nitric oxide synthase. Diabetic endothelial nitric oxide synthase knockout mice develop more severe glomerular lesions and proteinuria compared to wild-type mice.

Metabolic factors

Oxidative stress and generation of reactive oxygen species (ROS) damage DNA and protein, or function as signaling amplifiers to activate cellular stress pathways such as PKC, MAPK, and NF- κ B. Activation of the polyol pathway, with aldose reductase converting excess glucose to sorbitol, and subsequent conversion to fructose by sorbitol dehydrogenase contributes to oxidative stress by increasing the NADH/NAD⁺ ratio. recently described novel mechanism of injury also involves endogenous fructose production with activation of fructokinase in the proximal tubule. The formation of advanced glycation end-products (AGE) by nonenzymatic binding of glucose to proteins, lipids, and nucleic acids can lead to alteration of protein structure and function, oxidative stress, and expression of proinflammatory cytokines and growth factors.

Growth factors/cytokines:

Activation of TGF- β and its downstream cytokine, CTGF, induce extracellular matrix formation and fibrosis. In kidney biopsies, glomerular expression of TGF- β 1 and CTGF were higher in diabetics compared to controls, and correlated with albuminuria. PDGF expression is also increased in DN, which can modulate chemotaxis, vascular tone, and platelet aggregation. VEGF is crucial in angiogenesis but also mediates vasodilatation and leukocyte trafficking in DN.^[15]

Cell signaling and transcription factors

Increased renal gene transcription of PKC- β showed a strong relationship with glycemic control. PKC activation has wide ranging effects, including enhancing angiotensin II actions, nitric oxide dysregulation, endothelial dysfunction, and activation of MAPK and NF- κ B. MAPKs are intracellular kinases which integrate cell signaling into cellular responses. MAPKs activate a number of nuclear transcription factors, including NF- κ B, which then regulates the gene expression of various cytokines, chemokines, and adhesion molecules. The activation of p38 α isoform of the p38 MAPK pathway is most strongly associated with renal inflammation and DN. There may also be a role for toll-like receptors (TLR2, TLR4) and B7-1 costimulatory signaling in modulating inflammation and injury in DN. Finally, transcription factors bind to the promoter regions of genes and modulate transcription of messenger RNA. NF- κ B has been the best studied in DN. Activation of NF- κ B in both human peripheral blood mononuclear cells and kidney biopsies correlate with severity of proteinuria and glycemic control. A review of transcription factors in DN is provided by Sanchez and Sharma.^[16]

Inflammation

In DN, there is recruitment and activation of innate immune cells and elaboration of proinflammatory cytokines. Macrophages and T-lymphocytes are prominent in early diabetic glomeruli while an interstitial infiltrate develops later. Strategies impairing kidney leukocyte recruitment, proliferation, or activation have demonstrated that macrophages mediate DN. In humans, kidney macrophage accumulation is associated with the severity of glomerulosclerosis. Accumulation of interstitial macrophages correlated strongly with proteinuria, interstitial fibrosis.

Multifactorial risk factor reduction

The benefits of intensive multifactorial intervention in type 2 diabetics were shown in the Steno-2 trial of 160 patients with microalbuminuria. Intensive therapy included: reduced dietary fat, light/moderate exercise, smoking cessation, tight glycemic control (<6.5%), tight blood pressure control (<130/80), ACE inhibitors, and anti-lipid medications (cholesterol <4.5 mmol/L). After a mean follow-up of 7.8 years, patients receiving multifactorial intervention had significantly lower risk of overt nephropathy (hazard ratio 0.39; 95% confidence interval 0.17–0.87) than those receiving regular management.^[17]

Transplantation

Simultaneous pancreas/kidney transplantation is an effective treatment for type 1 diabetics with ESRD, with most achieving insulin independence and preventing recurrence of DN in the allograft. In patients with CKD after 10 years of pancreas transplantation alone, patients with sustained normoglycemia showed reductions in albuminuria and reversal of DN lesions on serial biopsy, including regression of glomerular basement membrane thickening and mesangial matrix deposition. Some of these benefits may be offset by interstitial fibrosis and arteriolar hyalinosis due to calcineurin inhibitor (example, cyclosporine) use. However, the same authors note that tubulointerstitial remodeling at 10 years had ameliorated some of the interstitial collagen deposition noted at 5 years, although vascular changes were not affected.

Novel agents

The diabetic milieu is a complex environment where a number of interventions may be utilized to target various pathological processes. As no single therapy completely ameliorates DN, novel strategies are needed to complement existing interventions.

Renin inhibitors

Renin catalyses the rate-limiting step in the production of angiotensin II. In diabetic rats, aliskiren reduced albuminuria and glomerulosclerosis, and was more effective than perindopril in reducing interstitial fibrosis. In type 2 diabetics after a 4-week washout of previous medications, aliskiren reduced blood pressure and albuminuria, with the effects on albuminuria persisting after withdrawal of medication. In the AVOID trial of 599 type 2 diabetics, the combination of aliskiren 300 mg and losartan 100 mg for 6 months reduced the urine ACR independent of blood pressure. However, the much larger ALTITUDE trial, which randomized 8,561 high-risk type 2 diabetics to aliskiren 300 mg or

placebo as adjunctive to RAS inhibition, found no significant difference in renal outcomes. It is noted that the trial was terminated prematurely due to excess hyperkalemia and hypotension in the aliskiren group. Due to the lack of good randomized controlled trial evidence supporting the use of aliskiren in combination with ACE inhibitors or ARBs, and the increased adverse effects, the combination is not recommended. From the US Food and Drug Administration perspective, the combination should be contraindicated in patients with diabetes. However, it could be considered as an alternative RAS blocker for blood pressure lowering and proteinuria reduction. More research is needed to demonstrate that aliskiren is as good as ACE inhibitors or ARBs.

Endothelin inhibitors

In diabetic rats, an ET_A receptor blockade with atrasentan or avosentan reduced albuminuria and renal fibrosis.^[18] The ASCEND trial of 1,392 type 2 diabetics with overt nephropathy examined the effect of avosentan on time to doubling of serum creatinine, ESRD, or death. Avosentan halved proteinuria but increased fluid retention, edema, and congestive heart failure, resulting in the trial being stopped early. Since ASCEND, two other randomized controlled trials have noted reduction in albuminuria at the cost of edema and congestive heart failure. The latter trial involving 1,392 type 2 diabetics was also stopped prematurely after a median follow-up of 4 months. In a randomized trial of 211 type 2 diabetics, atrasentan added to RAS inhibition for 12 weeks reduced albuminuria in association with lowering blood pressure. Fluid overload was reported as manageable, albeit more patients discontinued treatment on the higher dose of atrasentan. The SONAR trial with atrasentan is currently in progress to evaluate renal outcomes in type 2 diabetics.

Gene and cell-based therapy

Gene therapy involves introducing a gene into cells to increase the production of a protein of interest. A carrier or vector such as modified adenovirus is employed to deliver the gene to the nucleus where the protein coded by the gene is produced by the cellular machinery. Gene therapy targeting TGF- β /SMAD signaling has shown promise in reducing kidney injury in diabetic models. Ka et al studied Smad7 gene therapy in the db/db mouse model of type 2 diabetes. Treatment inhibited TGF- β /SMAD and NF- κ B activation, resulting in a reduction in proteinuria, macrophage infiltration, inflammation, podocyte injury, and renal fibrosis.⁴⁴ A similar finding was noted by Zhang et al by using gene therapy to

enhance decorin expression in the streptozotocin model of type 1 diabetes. The beneficial effects were attributed to downregulation of TGF- β /SMAD signaling as decorin is a natural inhibitor of TGF- β 1. HGF gene therapy has been shown in db/db mice to enhance renal expression of SDF-1, associated with increased numbers of bone marrow-derived monocyte/macrophages with a higher proportion of M2 markers (anti-inflammatory phenotype). This was associated with a reduction in proinflammatory cytokines, reduced histological injury, and preservation of podocytes. Kosugi et al examined soluble Flt-1 gene therapy in db/db mice. sFlt-1 is an endogenous inhibitor of VEGF and treated animals showed reduced VEGF expression in association with elevated sFlt-1 levels in the kidney. Although sFlt-1 gene therapy reduced podocyte injury and albuminuria, tubulointerstitial injury was enhanced, leading the authors to conclude that this approach would not be beneficial in DN. Thus, there are some potential risks with gene therapy, which may be related to the inserted gene itself or the viral vector utilized but this discussion is beyond the scope of this review.

Progenitor (stem) cells are multipotent cells capable of self-renewal and differentiation into specialized cells, and are broadly categorized into embryonic stem cells and adult stem cells. Adult stem cells can be derived from bone marrow, adipose tissue, or peripheral blood. Stem cells can also be harvested from umbilical cord blood at birth. The potential benefits of stem cell treatment in DN include-

- 1) replacing or regenerating damaged cells,
- 2) modulating inflammation,
- 3) reducing oxidative stress, and
- 4) improving glycemia

There have been several experimental studies of stem cell treatment in DN. Most studies have demonstrated a blood glucose lowering effect by improved pancreatic β -cell function and insulin levels, whilst some others have not. This may relate to the nature of the cells utilized or the method of delivery. Some of these studies suggest that a paracrine effect is more important as a protective mechanism, rather than regeneration or replacement of injured cells. This is based on observations of low level engraftment of mesenchymal stem cells in the kidney and the production of beneficial growth factors, antifibrotic factors, and factors which protect from oxidative stress.^[19]

Treatment:

The first step in treating diabetic nephropathy is to treat and control diabetes and high blood pressure. Treatment includes diet, lifestyle changes, exercise and prescription medicines. Controlling blood sugar and blood pressure might prevent or delay kidney issues and other complications.

Medications:

In the early stages of diabetic nephropathy, your treatment might include medicines to manage the following

Blood pressure

Medicines called angiotensin-converting enzyme (ACE) inhibitors and angiotensin 2 receptor blockers (ARBs) are used to treat high blood pressure.

Blood sugar

Medicines can help control high blood sugar in people with diabetic nephropathy. They include older diabetes medicines such as insulin. Newer drugs include Metformin (Fortamet, Glumetza, others), glucagon-like peptide 1 (GLP-1) receptor agonists and SGLT2 inhibitors.

High cholesterol

Cholesterol-lowering drugs called statins are used to treat high cholesterol and lower the amount of protein in urine.

Kidney scarring

Finerenone (Kerendia) might help reduce tissue scarring in diabetic nephropathy. Research has shown that the medicine might lower the risk of kidney failure. It also may lower the risk of dying from heart disease, having heart attacks and needing to go to a hospital to treat heart failure in adults with chronic

Kidney dialysis

This treatment removes waste products and extra fluid from the blood. dialysis filters blood outside the body using a machine that does the work of the kidneys. For hemodialysis, you might need to visit a dialysis center about three times a week. Or you might have dialysis done at home by a trained caregiver. Each session takes 3 to 5 hours. Peritoneal dialysis uses the inner lining of the abdomen, called the peritoneum, to filter waste. A cleansing fluid flows through a tube to the peritoneum.^[21] This treatment can be done at home or at work. But not everyone can use this method of dialysis.

Treatment / Management

Treatment of diabetic nephropathy targets four areas: cardiovascular risk reduction, glycemic control, control of blood pressure, and inhibition of the renin-angiotensin system (RAS). Risk-factor modification, including tobacco cessation and optimal lipid control strategies, are crucial for cardiovascular risk reduction. Studies have shown a significant reduction in the risk of developing proteinuria and microalbuminuria with intensive diabetes control in T1DM. These studies include DCCT (Diabetes Control and Complications Trial) and EDIC (Epidemiology of Diabetes Interventions and Complications study). The benefits of good glycemic control early in the onset of disease carried over even after a long time, despite glycemic control being similar in both groups on longer follow up. This effect is "metabolic memory," a term coined by DCCT/EDIC investigators.

In T2DM, UKPDS (United Kingdom Prospective Diabetes Study) showed that targeting an HbA1C of 7% led to a lower risk of microvascular complications, including nephropathy. However, blood pressure (BP) control also led to a decrease in cardiovascular mortality.

Studies have shown the benefit of ARBs (angiotensin receptor blockers) in delaying the progression of kidney disease.^[22] These include studies like RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study) and IDNT (Irbesartan Diabetes Nephropathy Trial), which also showed that the BP achieved, better-predicted kidney outcome rather than BP at entry, emphasizing the need for BP control. UKPDS showed the benefit of BP control on any DM-related complication such as death, adverse cardiovascular events, and the composite of microvascular events. However, aggressive control of systolic BP to less than 120 mm Hg, as opposed to standard therapy (less than 140 mm Hg systolic), found no difference in cardiovascular outcome or end-stage renal disease.

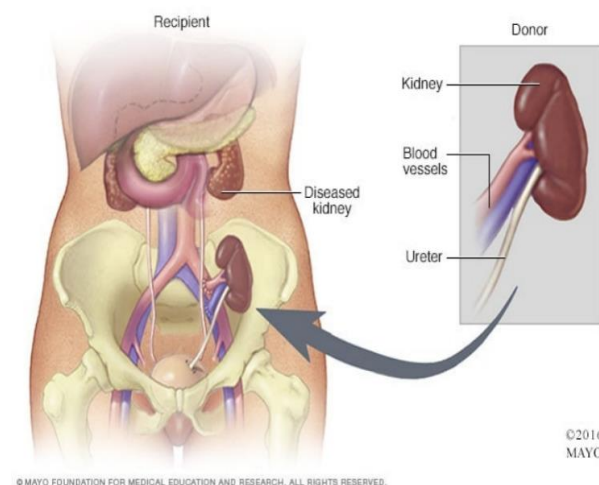


FIG 1: the overview of kidney scarring

Kidney transplant

For kidney failure, also called end-stage kidney disease, treatment focuses on either replacing the work of your kidneys or making you more comfortable. Options include:

The Eighth Joint National Committee (JNC 8) guidelines recommend a goal BP less than 140/90 mm Hg for most patients with T2DM and diabetic nephropathy, but with individualization. Recent diabetic society guidelines suggest goals of 130/80 for people with diabetes.

While RAS blockade is crucial to prevent the development of diabetic nephropathy, multiple studies show that early therapy in patients with T1DM is ineffective in preventing the development of microalbuminuria. However, studies, including ROADMAP (Randomized Olmesartan and Diabetes Microalbuminuria Prevention), have shown that RAS blockade can prevent the development of microalbuminuria in T2DM.

Studies like IRMA2 (Irbesartan in Microalbuminuria, Type 2 Diabetic Nephropathy Trial) have shown the benefit of ARB in preventing proteinuria in patients with microalbuminuria. Studies in patients with T1DM and overt proteinuria have also shown that ACE inhibitors slow the progress of diabetic nephropathy. The IDNT and RENAAL studies have shown similar benefits in T2DM patients. These studies provide clear evidence of the benefit of RAS-blocking medication on slowing progression of diabetic nephropathy, independent of their effect on BP. However, the use of more than one RAS-blocking agents resulted in multiple adverse outcomes, including acute renal failure, and has fallen out of favor.

Newer drugs like a third-generation mineralocorticoid receptor antagonist, finerenone, has shown albuminuria reduction in diabetic nephropathy at 90 days, on patients already on ARB.⁶⁴ The EMPAREG and CANVAS studies showed that SGLT2 (sodium-glucose co-transporter 2) inhibitors that prevent reabsorption of glucose via the renal tubules reduced cardiovascular mortality.^[23] In these cardiovascular outcome trials, the SGLT2 inhibitors had positive effects on kidney outcomes, namely albuminuria reduction and a reduction in the occurrence of a composite renal outcome. However, since these are secondary outcomes of trials designed to test cardiovascular benefit, many studies are now underway to test the actual potential of this group of drugs to prevent the progression of diabetic nephropathy.

Routine screening tests may include

Urinary albumin test. This test can detect a blood protein called albumin in urine. Albumin(or) creatinine ratio. Creatinine is a chemical waste product that healthy kidneys filter out of the blood. Glomerular filtration rate (GFR).

SCREENING FOR DIABETIC NEPHROPATHY

Diabetic patients with microalbuminuria are at high risk for the development of overt nephropathy and cardiovascular complications. The justification for screening is that identification of this cohort of patients allows aggressive intervention with a view to prevention.

Microalbuminuria

Several methods can be used for detection of microalbuminuria. The urinary albumin/creatinine ratio (ACR) can be determined from a random, or preferably early morning, urine sample. This is often the easiest test in the setting of primary care and provides a practical screening method less prone to patient error than timed collection. The albumin excretion rate (AER) is more precise and can be measured formally from any timed collection, most commonly overnight (8 hours)—which is technically easier for the patient than a 24-hour collection. Recently developed urine dipstick assays provide a useful initial screening test that can be performed in the surgery if assays for microalbuminuria are not readily available. However, they are subject to error from alterations in urine concentration and all positive tests should be confirmed by more specific methods.

Microalbuminuria should be diagnosed on the basis of three positive tests—ACR, AER or a combination of the two—over a 3-6 month period. Albumin excretion can vary by as much as 40% and physicians should be aware of potential confounding factors and non-diabetic causes of renal impairment and proteinuria.

Clinical assessment of diabetic nephropathy

clinically, DN is classically characterized by progressive increase in urinary albumin excretion, paralleled by an increase in blood pressure and cardiovascular risk. This is accompanied by a gradual decline in glomerular filtration rate and eventual progression to ESRD. Defects at the level of the GFB leads towards increased urinary protein known as albuminuria, one of the earliest signs of DN and systemic vascular dysfunction the degree of albuminuria and proteinuria correlates with and is also an important clinical predictor of the rate of kidney disease progression (at the macroproteinuria stage). Estimation of GFR is an important clinical investigation utilized to monitor renal function. annual surveillance is recommended for all diabetic patients to monitor the progression and rate of decline of renal function. Traditionally, DN has five identified stages based on UAE and GFR: glomerular

hyper filtration ,a silent stage, incipient nephropathy with microalbuminuria.^[25]

Complications

- Complications of diabetic nephropathy can come on slowly over months or years. They may include:
- Body fluid build-up, this could lead to swelling in the arms and legs, high blood pressure, or fluid in the lungs, called pulmonary.
- A rise in the levels of the mineral potassium in the blood, called hyperkalemia.
- Heart and blood vessel disease, also called cardiovascular disease. This could lead to a stroke.
- Fewer red blood cells to carry oxygen. This condition also is called anaemia.

APPLICATIONS OF A NEW HYPOGLYCEMIC

Early metformin and RAAS inhibitors, such as ACEI/ARB, are effective for preventing and treating DKD. Nevertheless, DKD progression is still unavoidable, so it is impending to find a new treatment. Nowadays, there are more and more studies on the pathological mechanism and molecular mechanism of DKD, and there are more and more new drugs based on them. Three kinds of new hypoglycemic drugs show sound renal protective effects, including, SGLT2 inhibitors), GLP-1 receptor agonist , and DPP-4 inhibitors.

Canagliflozin

It was reported that canagliflozin decreased the overall risk of heart failure (HF) events in T2DM patients and with high cardiovascular risk patients, and there was no apparent difference in the impact on HF preserved ejection fraction (HFPEF) and HF reduced ejection fraction (HFREF) events. This may bring some hope to people with diabetes and HFPEF. In the CANVAS (Canagliflozin Cardiovascular Assessment Study, NCT01032629) and CANVAS-R (NCT01989754) clinical trials, 10,142 participants with T2DM who were at high risk of cardiovascular events (with a baseline mean eGFR 76.5 mL/min per 1.73 m², median UACR 12.3 mg/g, and 80% of whom were receiving renin-angiotensin system blockade), radiometrically assigned to receive canagliflozin or placebo group. The composite outcome of sustained doubling of serum creatinine, ESRD, and death.

SGLT2

SGLT-2 inhibitors increase the excretion of glucose in urine by restraining SGLT-2 activity in proximal

convoluted tubules. In patients with poor blood glucose control, SGLT-2 inhibitors showed significant hypo glycemic effects because of increased excretion of glucose in urine and improvement of renal hyperfiltration state. In recent years, it has been found that the renal protective mechanisms of SGLT-2 inhibitors include reducing blood glucose, improving renal hyperfiltration, reducing proteinuria, improving renal hypoxia, losing weight, reducing blood pressure, reducing uric acid, reducing inflammation and OS, etc.The representative drugs of SGLT2 inhibitors include empagliflozin, canagliflozin, dapagliflozin, ertugliflozin.

Empagliflozin:

EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality, NCT01131676) test found that for T2DM patients with CVD, the increase of UACR was smaller than that of the placebo group after 12 weeks of short-term treatment. After 16 weeks of long-term therapy, the quantitative levels of UACR and urinary albumin in the placebo group were obviously slower than the placebo group, and the same results were found in the subgroup analysis of 1517 Asian patients. It was found that empagliflozin could delay the decline of eGFR, indicating short-term or long-term use of empagliflozin is good for the excretion of albuminuria.^[25]

Dapagliflozin

DECLARE (Dapagliflozin effect on cardiovascular events) is currently the largest clinical trial on improving cardiovascular prognosis by SGLT2 inhibitors. The main observation event is the death of CVD or the compound endpoint of hospitalization due to HF. The secondary observation event is the occurrence of renal endpoint events. The results showed that dapagliflozin could decrease the decline of cardiac and renal function; what's more, it is safe for patients.The DECLARE-TIMI(Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction trial showed that the incidence of renal endpoint events (eGFR decrease \geq 40%, ESRD or nephrogenic death) in T2DM patients treated with dapagliflozin was lower than placebo group. Moreover, the DAPA-CKD.^[26]

GLP-1 receptor agonist

GLP-1 receptor agonist are another kind of new therapeutic drug for DKP. GLP-1 is a hormone produced through the intestinal tract that binds to GLP-1 receptors in the pancreas, stimulating insulin production and inhibiting glucagon production in the glucose-dependent way GLP-1 binds to its receptor in

human glomerular arterioles, directly exerts vasodilation, counteracts the vasoconstriction caused by glomerular feedback, and maintains the average level of global GFR. It can also protect mesangial cells by reducing the expression of AGE receptors, thus protecting mesangial cells. The level of GLP-1 is reduced in T2DM patients, and GLP-1 receptor agonist can assist GLP-1 to play a role. GLP-1 receptor agonists include liraglutide, lixisenatide, dulaglutide.

Liraglutide

The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of CV Outcome Results) trial indicated that in T2DM patients with cardiovascular risk factors, the incidence of renal events with liraglutide was 22% lower than the placebo group (NCT01179048)^[27]. Another study reported that the therapeutic response to liraglutide was primarily individual; there was no significant cross-dependence in risk factors (body weight, systolic blood pressure, LDL-C, UACR, and eGFR) responses except for the link between body weight and reduced glycosylated haemoglobin.

Lixisenatide

Hanefeld et al. reported that the primary renal condition did not affect the efficacy of patients treated with lixisenatide or placebo. It was not necessary to change the dose of lixisenatide in T2DM patients who have mild or moderate renal damage. After using lixisenatide to treat 6068 T2DM patients with recent coronary events, the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial (NCT01147250) found that lixisenatide could slow down the progression of UACR in patients who have massive albuminuria, reduce the probability of producing massive albuminuria, and didn't raise the possibility of cardiovascular events. Approved by the US FDA in 2016, it is used to alleviate blood glucose levels in adult T2DM patients.^[27]

The inhibitors of DPP-4

The degradation agent of GLP-1 is another critical direction in the research and development of new drugs for DKD, and DPP-4 is the degradation agent of GLP-1.99 DPP-4 inhibitors can not only promote insulin secretion by increasing the level of endogenous GLP-1, but also protect renal function independent of GLP-1. DPP-4 inhibitors can reduce the level of TNF- α , inhibit the immune response of malondialdehyde, and play the role of anti-inflammation and anti-oxidation, thus delaying glomerulosclerosis. In the kidney, inhibition of DPP-4 leads to distal include linagliptin, saxagliptin, and sitagliptin, and so on.^[28]

diuresis, but usually does not significantly affect renal hemodynamics. DPP-4 inhibitors

In agliptin

In a summary analysis of phase 3 trials of T2DM and albuminuria in adults, contrasted to placebo, linagliptin reduced albuminuria by 28% after six months of treatment, regardless of changes in blood glucose or blood pressure. Besides, in a summary analysis that included 13 trials, about 16% decrease in predetermined compound renal harmful events was found. Another related study has shown that in the early period of DKD patients, using linagliptin can effectively improve blood glucose control, but cannot significantly reduce albuminuria, and there is no significant change in eGFR after placebo adjustment. Approved by the FDA in 2011, it is used to alleviate blood glucose levels in T2DM patients in combination with diet and exercise treatment.^[29]

Saxagliptin

In the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53) trial, 16,492 patients with T2DM were treated with salbutamol to improve UACR, but the decrease in eGFR was similar to the placebo group.^[30]

Sitagliptin

Hattori first found that sitagliptin has an inhibitory effect on proteinuria in patients with T2DM, and its mechanism of reducing proteinuria does not depend on the decrease of eGFR. The TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) trial also did not observe the protective effect of sitagliptin on eGFR.^[31] The study treated 14,671 other DM patients with CVD and observed that renal function is no apparent difference in the sitagliptin group and placebo group.^[32]

CONCLUSION:

Our review suggests the early diagnosis of microalbuminuria will help to identify patients with DN at the earliest. Poor blood sugar level control, longer duration of the DM, uncontrolled blood pressure, smoking, and physical inactivity are some of the risk factors for DN mentioned in the literature.^[34] Controlled diet, improved glycemic control, protein restriction coupled with sodium and potassium could help to manage the condition. Transplantation, stem cells, novel molecules for therapeutic, and treatments are warranted for DN control and treatments. Second-line antihypertensives include non-dihydropyridine CCBs and diuretics.^[35] Lipid management with a statin is prudent for cardiovascular disease even though a direct impact on renal disease has not been conclusively shown other than as part of the multifactorial risk intervention

similar to the Steno-2 study (which includes aspirin).^[36] No alternative medicines or supplements have been shown to slow GFR decline although effects on albuminuria are reported by some small studies. None can be routinely recommended currently and further studies on vitamin D are awaited.^[37] Further data on uric acid management with allopurinol are also awaited. Mild salt and protein restriction may also benefit some patients but strict monitoring and compliance can be problematic.^[38]

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