

A Review: Diabetics Leading To Ckd

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ABSTRACT

Chronic kidney disease is a common chronic consequence of diabetes mellitus that has a poor prognosis and can progress to end-stage renal disease if not managed. The multifaceted pathophysiology of Chronic kidney disease (CKD), which includes both hemodynamic & metabolic variables, makes it challenging to design effective therapeutic therapies. As the symptoms appear quite late, an early detection is the key to prevent further development. Several therapeutic and novel agents are developed that target specific pathophysiological pathways and interrupt the process. Some of the treatment agents are evaluated in clinical studies and some are under investigations to establish their safety and efficacy. In India, lack of education and poor diagnosis are important factors that increase the prevalence of DKD. The available diagnosis measures need to be adopted in clinical routine practice and awareness of the disease among the patients, especially the patients with prediabetes may be beneficial along with the current treatments available. Even though the characteristic clinical introduction of Chronic kidney disease (ckd is categorized by just a steady crawl from nephropathy to normal buminuria and therefore by endothelial dysfunction at the important developmental and progressive decline of renal function at the late stage, recent epidemiological studies have indicated that DKD people with the disease have quite a wide range of clinical presentations and rates of progression to ESRD. Some DKD patients exhibit overall reduction in glomerular filtration rate absent renal disease, however tubular histology represents a major microvascular as well as intervening degradation. Individuals with DKD are now more sensitive to acute nephrotoxicity, which may also result in interstitial fibrosis. A significant number of people with type 2 diabetes with renal disease may very well have underlying impaired glucose tolerance glomerular illness, necessitating a liver examination for evaluation of patients.

Keywords: DKD, filtration, glomerular, clinical presentation Diabetic kidney disease, diabetes, chronic kidney disease, albuminuria, glomerular filtration rate

INTRODUCTION

Given recent pharmaceutical improvements, diabetic kidney disease or also known as DKD remains a significant clinical concern with significant medical comorbidities. There has to be a greater emphasis on identifying people with diabetes category of type 2 that are at higher risk for CKD or also known as chronic kidney disease early, particularly in terms of genetics, biomarkers, as well as high-risk phenotypes. Quality treatment models are needed to decrease racial and socioeconomic inequities, which is another significant area of potential. Thankfully, new treatment prospects have now been found in the last several years, and it is being investigated to be used in enhancing diagnostic evidence. Since 2001, angiotensin receptor blockers seem to be the most significant advancement in the treatment of renal disease. The unexpected findings in cardiovascular effects studies of better renal & cardiovascular outcomes with SGLT2 or known as sodium-glucose co transporter 2 inhibitors as well as glucagon-like peptide 1 receptor were significant outcomes. All such findings were confirmed in 2 big nephrological protection experiments in volunteer patients with the disease of DKD. the CREDENCE trial, which used the SGLT2 inhibitor, as well as the Finerenone in Reduction of Renal Failure & Progression of Disease in Diabetic Kidney Disease study. As additional treatment choices become available, people need a better knowledge of such mechanics behind the development of diabetic vascular diseases as well as target organ failure as then new as well as conventional targeted therapies may be combined to achieve the best clinical results. People must assess the pharmacological activity of these medications and recognize the large volume of pharmacopeia consumed on a regular basis by diabetic patients & CKD. As a result, further information of the processes of cardiovascular as well as renal disease development in type 2 diabetes is needed to improve the accuracy of medication. Recent clinical study outcomes, as well as studies which are scheduled or are presently continuing, are yet another relevant topic for discussion. Participants in the recent drug trials already were receiving optimum medical treatment, which included enhanced management of blood pressure, the greatest tolerable dosages of lipid-lowering medication as well as reninangiotensin system blocker. Despite the substantial novel treatment choices accessible, researchers will eventually require more accuracy in directing pharmacotherapy. These compilations will give an improved chance to assess our success in attempts to enhance the long-term results of diabetic and CKD patients.

Diabetic renal disease affects nearly 20 percent of 400 million people around the world who have diabetic kidney disease (DKD). DKD is linked to an increased risk of cardiovascular as well as all illness & death, hence early recognition and diagnosis are essential. Yearly spotted urination creatinine/albumin ratio testing is an essential way to screen for initial symptoms DKD, as diagnosis is proven by recurring elevations in urinary albumin. Treatment of hypertension, hyperglycemia, hyperlipidemia, as well as smoke cessation are all components of treatment. Antihyperglycemic drugs such as glucagon-like peptide-1 receptor agonists, sodium-glucose

cotransporter-2 inhibitors, & dipeptidyl-peptidase-4 inhibitors could actually reduce DKD by reducing glucose in blood levels as well as providing intrinsic kidney preservation. To avoid microvascular alterations, pressure of blood should be checked at each and every clinic session & kept below 140/90 mm Hg. Angiotensin receptor blockers & Angiotensin-converting enzyme inhibitors stop DKD from progressing and might even lower albuminuria. Nicotine cessation reduces risk for Diabetic nephropathy, and statins medication must be explored for all individuals with the disease. Patients experiencing to stages disease or even beyond could profit by referrals to nephrology subspecialists due to the disease's complexities as well as the potential of bad results.

Hyperglycemia

Unregulated diabetes causes hyperglycemia, or high blood sugar, which causes widespread destruction to several of the body's functions, including the neurons and arteries, over time[6]. It is a predominant factor forming the ground for development of CKD. As per findings from the Global Burden of Disease Study 2016, overall, diabetes and hyperglycemia contributed to 28 million (DALYs) in 2016. Nearly 10 million (37.8% DALYs) of the 28 million resulted directly from sufferings caused by simple diabetes or direct diabetic microvascular complexity. Other factors included ischemic heart disease, CKD, stroke, tuberculosis, specific cancers, and diseases related to peripheral arteries as a result of intermediate hyperglycemia [7].

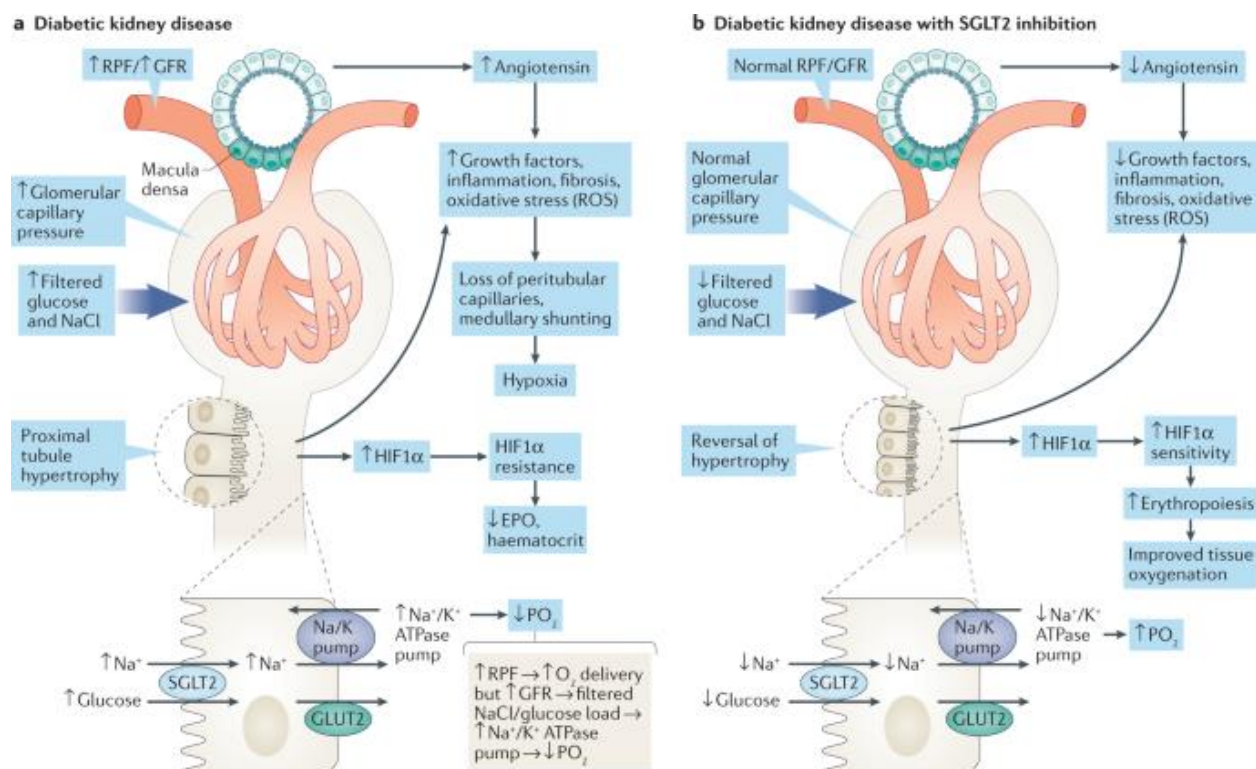


Figure 1 - Effect of Hyperglycemia on the Kidney

Source: [Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors | Nature Reviews Nephrology](#)

Prevalence of Diabetes in CKD in India

As per study conducted by a group, the prevalence of DKD in India was estimated to be approximately 34.4% [8]. A composite prevalence of diabetic-CKD was reported as approximately 62.3% in a multicenter study from India [9]. Indian Council of Medical Research, researched and the result was that the prevalence of diabetes in the Indian adults has risen to 7.1% and prevalence of hypertension in the adults is estimated approximately 17% [10]. In view of rising prevalence of these two most common diseases that form the base for CKD, the prevalence of this disease is expected to rise.

Global Burden of Disease Study shows that the renal failure death rates per 100,000 population from diabetes increased by 53% between 1990 and 2016. Approximately 2,883,185 patient's deaths were reported by CKD due to diabetes in India in 2016, further segregated as 63% among males and approximately 88% among elder patients more than 50 years of age [6].

Another Global Burden of Disease Study shows that for all ages, the burden of CKD due to diabetes per 100,000 population increased by 40% between 1990 and 2016 (156.5 in 1990 to 219 DALYs in 2016). The total number of DALYs caused by diabetes increased by 115% between 1990 and 2016 (1.35 million in 1990 to 2.9 million in 2016) [6].

DISCUSSION

Diabetic Kidney Disease – How Diabetes Causing CKD

DKD is estimated to be developed in 40% and 30% of patients with type 2 diabetes mellitus (T2DM) and type 1 diabetes, respectively, is a major cause of CKD and also for end-stage renal disease [13]. Along with, kidney disease is responsible for a high rate of mortality and estimated to increase the mortality risk by approximately 31% in diabetics and depends on severity, i.e, mortality risk increases with severity of disease [14,15]. The mortality rate is also high in patients with DKD and has a huge economic burden along with the humanistic and societal burden [16,17].

An elevation in blood glucose can damage the blood vessels in kidneys. When the blood vessels are damaged, they are not able to work properly and are unable to transport the blood. Many patients who have diabetes, also develop high blood pressure, which is also an important factor in damaging the kidneys.

Pathophysiology of DKD

The pathophysiology of DKD is considered multifactorial and the various processes are believed to be contributing to the progressive decline in GFR. These processes include structural, physiological, hemodynamic and inflammatory processes. As shown in the diagram, both behavioral and physiological anomalies are responsible for initiating a complicated network of pathogenic chain of events that led to DKD **Figure 2**.

Recent research has also shown that dysregulated autophagy has a crucial and necessary pathogenic role in DKD. In addition, the significance of epigenetic modifications in DKD has been recognized and has received attention in research [22]. Epigenetic changes impact gene expression despite modifying the fundamental Sequence of DNA, and they play a role in mediating gene-environment interaction. Diabetes causes a variety of epigenetic alterations, including DNA methylation, histone modification, chromatin structural changes, as well as modifications in non-coding RNA expression [23]. DNA methylation was found in the mice which had mesangial cells of type 2 diabetic, which contributed to the higher output of transformation of the growth factor-(TGF) [24]. Very critically, epigenetic alterations are thought to have a role in the long-term expression of phenotypic and diabetes-related genes produced by past hyperglycemia, even after glycemic management [23,25].

Figure 2 Pathogenesis of DKD

Source: Sugahara M, Pak WLW, Tanaka T, Tang SCW, Nangaku M. Update on diagnosis, pathophysiology, and management of diabetic kidney disease. *Nephrology (Carlton)*. 2021 Jun;26(6):491-500.

Diagnosis of DKD

Usually, a clinical diagnosis is required for DKD. First, a diagnosis of diabetes is required to be established and secondly, presence of kidney disease is demonstrated which further can be identified by albuminuria or decreased GFR. The most frequent test for albuminuria is a urine albumin-to-creatinine ratio (UACR). An increased spot UACR of >30 mg/g is regarded important, and that should be aware of at least two of the three samples during a duration of three to six months to minimize confounding by activity, fever, urinary tract infection, hematuria, and sudden cardiac arrest [26]. The CKD epidemiology collaboration (CKDEPI) equation is chosen for calculating GFR from serum creatinine levels. It is deemed noteworthy if the estimated GFR (eGFR) is consistently 60 mL/min/1.73 m² [27]. Kidney disease monitoring must be executed once a year for accurate identification, and it can begin as early as Five years following a patient's symptoms of type 1 diabetes as well as type 2 diabetes.

Although for typical DKD cases, renal biopsies are not necessary for diagnosis, it can be suggested for non-DKD cases [27]. The features for non-DKD include short diabetes duration, absence of diabetic retinopathy, decline in GFR, symptoms and signs linked with other types of kidney disease, such as abrupt onset nephrotic syndrome as well as quickly developing albuminuria [27].

Because quick diagnosis is critical in dealing with this life-threatening illness, creatinine & albuminuria are presently the only accessible indicators in clinical practice for detecting chronic disease [28]. Galectin-3, development differentiating GDF-15, , fibroblast growth factor-23 (FGF-23), platelet-derived growth factor (PDGF), neutrophil gelatinase-associated lipocalin as well as Kidney injury Molecule-1 (KIM-1) are the other newly found indications for Chronic kidney disease [28].

Preventive Measures for Diabetics to Prevent Kidney Disease

When an individual develops prediabetes, taking steps to avoid type 2 diabetes is critical for avoiding kidney damage. According to some research, overweight persons are more likely to acquire type 2 diabetes, and blood sugar can be avoided or postponed by decreasing 5% to 7% of total body weight. Weight loss can be achieved by consuming healthy food and dedicating time each week to physical activity. The National Diabetes Prevention Program lifestyle modification initiative of the Centers for Disease Control and Prevention (CDC) can assist in developing the good lifestyle behaviors required to avoid type 2 diabetes[29].

People can keep their renal system healthy by maintaining their sugar in blood, blood pressure, and levels of fats. Managing these is also a very important strategy to maintain the blood vessels and heart and other systems. All these factors (blood pressure, high blood sugar, and different types of fat's levels) are contributory risk factors for stroke and diseases regarding heart and other body systems. There are various recommendations to track the health indicators for DKD prevention. These include keeping blood sugar levels in target range, have HbA1C test at least twice a year, checking regularly the BP or blood pressure and maintain it below 140/90 mm/Hg, staying in target cholesterol range, consumption of feed lower in sodium, having more fruits and vegetables, and taking the medicines as directed [29].

Medications

There are certain recent and future strategies for the treatment and management of DKD and are described below:

Mineralocorticoid receptor & RAAS inhibitors:

Hyperglycemia & blood pressure management are handled by RAAS inhibitors in the treatment of DKD, and the advantages of using RAAS inhibitors have been proven in multiple trials. Renoprotection by RAAS inhibitor is mediated by a decrease in glomerular hyperfiltration & intraglomerular [30,31]. Angiotensin II-induced inflammation, oxidative stress, as well as fibrosis were also reduced by RAAS inhibitors [32]. The advantages of inhibiting RAAS with a mixture of ACE inhibitors & ARBs are also investigated [18].

GLP-1 receptor & SGLT2 inhibitors agonists: Glucose-lowering effects aren't the only benefit:

Inhibitors of the sodium-glucose cotransporter 2 (SGLT2) have been proven to increase glucosuria while reducing blood sugar levels. When empagliflozin was administered to type 2 diabetic patients, it resulted in a significant reduction in increased morbidity and mortality, as well as a decreased risk of developing or aggravating nephropathy [33,34]. GLP-1 receptor agonists are anti-diabetic drugs that enhance insulin production in response to meal consumption and have the ability to prevent DKD [18]. In clinical studies (SUSTAIN-6 & LEADER trials), its equivalents (liraglutide and semaglutide) showed a decreased risk of serious cardiovascular events or mortality.

Bardoxolone methyl:

Certain medications are developed that trigger the antioxidants pathways in the cell include nuclear factor-erythroid 2-related factor 2 (Nrf2). Nrf2 is involved in regulation of expression of various antioxidant and cytoprotective genes. Bardoxolone methyl acts by inducing the change of Keap1, acts as both NF- κ B inhibitor & Nrf2 inducer [37]. In the 2nd phase of the study, bardoxolone methyl demonstrated elevation in eGFR in patients with type 2 diabetes and stage 3b-4 CKD, however, Phase 3 study was terminated due to high cardiovascular events [38,39]. The results were re-evaluated and a 2nd phase of the study was conducted in Japan that showed positive results (increased GFR without any serious adverse events) and subsequent Phase 3 was also conducted [40,41].

ET-1 receptor A antagonists:

The level of ET-1 increased in diabetic patients that contribute to the development of DKD [42,43]. In a preclinical study of streptozotocin-induced diabetic rats, ET-A receptor antagonist lowered albuminuria and improved glomerulosclerosis [44]. Avosentan in conjunction with normal RAAS blocking improved albuminuria in CKD patients in a short-term clinical investigation [45]. Lower dosages of extremely selective ET-A receptor antagonists (atrasentan) have been shown in investigations to have favorable benefits without major side effects [46]. To determine the effectiveness of ET-1 receptor antagonists as a new therapeutic, more research is needed.

ASK-1 inhibitor:

Sustained oxidative stress leads to activation of apoptosis signal-regulating kinase (ASK)-1 that induces apoptosis, inflammation, and fibrosis [47]. Studies are conducted to evaluate the efficacy of selective ASK-1 inhibitors in CKD patients.

Anti-inflammatory agents:

Anti-inflammatory drug therapies might be an unique approach, as inflammatory response is a major cause of DKD. Pentoxifylline (a generic phosphodiesterase inhibitor with anti-inflammatory characteristics) and baricitinib (a specialized JAK-2 & JAK-2 inhibitor) are being investigated as potential DKD therapeutics [18].

Harmful Socio - economic and demographic Status and DKD: A Background Of the study

The key psychosocial factors (SDOH) comprise societal resources including such schooling, income, accommodation, medical coverage, accessibility to good meals, access to medical services, and other resources that occur in the environment in which individuals are born, wise up, stay, labor, as well as retire. Lack of investment in very many traditionally underrepresented neighborhoods adds to inequalities in DKD diagnosis, advancement, as well as sought clarification in the allocation of these structural and resources of the system. This aggregate particle of wealth was introduced in the United States by previous oppressive laws, regulations, as well as activities explicitly intended to divert funds in racial / ethnic minorities groups, and is alluded to as "systematic racism."

Key Determinants of Health Values and Socio - economic and demographic Status

The World Health Organization's Board on the Environment And development discovered that limited humans' impoverished health are closely associated to the socioeconomic spectrum in nutrition inside including across regions of the world, that is resulted by redistribution of power, revenue, merchandise, and facilities, respectively globally as well as nationally [55].

Significantly, the authority has said that discriminatory as well as unjust social policies, poor economic systems, & terrible governance all contribute to much of the country's disparities in access. For very many years, it has been shown in infectious sickness morbidity and death, and even more subsequently in chronically diseases like heart disease, hyperglycemia, as well as DKD.

Nutrients

Minimal as well as minority populations suffer inequalities in access to quality food products of what would be typically called to as "access to healthy food." There seem to be more groceries and even more independent retailers as well as small hardware retailers, who provide few fresh food or nutrition meals but instead just specialize on greater, elevated, and power generation items. Bad nutrition would have a negative impact on glycaemic control and indeed the development of DKD.

Proximity to Green Space

Limited and minority populations suffer from the lack of verdant locations as well as a lack of supervision in and use such spots for activity, which would be a critical feature of Chronic kidney disease (ckd) therapy. Individuals who are exposed to more green areas, specifically out of their own community, have just a greater chance of strength training and a decreased incidence of obesity rates and diabetes.[54].

Education

The degree of academic attainment has been linked to hurdles to healthcare in persons experiencing Chronic kidney disease (ckd). A number of studies have shown that academic ability is associated with the regulation of DKD potential confounders and even the advancement with Chronic kidney disease (ckd). Even though academic attainment is just not shared evenly across ethnic minorities, the bad effects of inadequate knowledge on dibetic renal disease development and progress disproportionately hurt traditionally underrepresented populations [57].

SES

SES has also been linked to health-care obstacles for patients with dibetic renal disease . Many researchers have found that having a higher income level is associated with better control of dibetic renal disease risk variables and a slower development of DKD. But since Socio - economic status is not evenly distributed across racial groups, low Income seems to have a bigger influence on Chronic kidney disease (ckd) in racial minority populations.

Knowledge in Medical Services

Medical insurance literature is typically defined as a mental ability expected to perform properly in such a clinical setting. Healthcare insurance knowledge is closely relevant to, but it does not consistently follow, a patient's degree of education. In general, poorer health literacy is related with some more hospitals and readmission rates, decreased adoption of protective treatments, and much worse common manifestation rates [56].

Future agents:

Because fibrosis is a fundamental & ultimate path way in all renal disease, therapeutic medicines targeting fibrosis appear to have the ability to slow DKD development. Pirfenidone treatment to cure idiopathic pulmonary fibrosis decreased TGF-β expression in diabetic mice [48]. In a trial, 77 DKD patients demonstrated slight increase in eGFR after administration of pirfenidone 1200 mg/day [49]. However, further studies are required to establish if pirfenidone may be used to cure DKD. Second possible system was demonstrated by administration of cobalt chloride, in streptozotocin-induced diabetic rats [50]. The cobalt chloride is used to activate hypoxia-inducible factor (HIF) and reduce proteinuria. Recently various HIF have been developed to treat anemia in CKD [51,52]. Because epigenetics plays a pathogenic role of DKD, studies were conducted in CKD patients and diabetic mice's kidneys, which revealed upregulation of the histone demethylase UTX (ubiquitously transcribed tetratricopeptide repetition on chromosome X, commonly recognised as KDM6A [lysine demethylase 6A]) [18]. GSK-J4, a histone demethylase inhibitor, was given to an experimental animal of type 2 diabetes, and it reduced albuminuria while also improving tubulointerstitial damage & glomerular expansion [53].

RELATED STUDIES

Williams.ME	A progress report of CKD statistics due to diabetics of 2010
Zelnick, CR	Diabetes in India and Nephrology
Anders, HJ	Difference in between diabetic and nondiabetic kidneys.
Ekundayo	Chronic Kidney Diseases
Duncan	The burden of diabetes on Kidney

CONCLUSION

Diabetic kidney disease is a disease with high prevalence and multifactorial pathophysiology. Poor diagnosis and lack of novel biomarkers make it difficult to detect the disease in the early stage. An early detection of the disease is of utmost importance to prevent it from developing further. Certain

plasma and urinary biomarkers have shown promising results for the early diagnosis, however, there is a need to translate these into routine clinical practice. The key definitive measure for the prevention of DKD can be achieved by maintaining HbA1c <6.5% (upper limit of the prediabetic range) and ideally within the normal range (<5.7%). When the symptoms appear and clinical and histological evidence are more prominent then to slow down kidney failure, different pathophysiological disruptions are targeted. The multifactorial actions by different classes of drugs help in breakdown of the different pathophysiological pathways and prevent progression of DKD. Further research for different novel therapeutic approaches is required to assess the long-term effects of the newly developed medications.

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