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Diabetic kidney disease: Risk factors, challenges and opportunities in the era of precision medicine

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Abstract

DKD is now recognized as the primary cause of chronic and end-stage-renal disease worldwide. The disease is characterized by changes in renal function and structure, followed by a gradual decline in kidney function, leading to ESRD. Risk factors for DKD include age, sex, race/ethnicity, family history of hyperglycemia and AKI. Recent studies have shown that certain medication classes, such as SGLT-2 inhibitors, can protect the kidneys independent of diabetes control. However, there are still gaps in our understanding of DKD, and its diagnosis is subjective due to the lack of a noninvasive biomarker. This makes it challenging to design clinical trials to identify effective treatments for the disease. Our review article aims to provide information on basic mechanisms of DKD, various treatment strategies and challenges by using personalized approaches to diagnosis and prevention.

Keywords: Precision medicine; Diabetic kidney disease; Personalized medicine; Heterogeneity; Diagnosis; Treatment; Prevention; Research

1. Introduction

In both type 1 diabetes (DM1) and type 2 diabetes, diabetic nephropathy (DN), now more frequently known as diabetic kidney disease (DKD), continues to be a major source of morbidity and mortality (DM2). DKD is now the most common cause of end-stage renal disease, accounting for more than 50% of patients in some regions of the world who need dialysis and/or transplantation. [1]. The changes in renal structure and function are used to define DKD. Mesangial expansion, glomerular and tubular basement membrane thickening, and glomerular sclerosis are three significant structural alterations of the kidney in DKD. Clinical symptoms of DKD typically include persistent albuminuria, elevated blood pressure, sustained decline in glomerular filtration rate (GFR), increased cardiovascular events, and mortality linked to cardiovascular events. Almost 380 million people worldwide, or 8.3% of the population, had diabetes in 2014, according to figures from the International Diabetes Foundation. DM accounted for 30e47% of the global causes of ESRD. About 54.4% of type 1 diabetes patients in the United States will eventually require renal replacement therapy (RRT).[2] The most common cause of end-stage renal disease (ESRD) and CKD worldwide is DKD. [3] and are the single most reliable predictors of mortality in diabetic patients. In the United States, 50,000 new patients begin dialysis each year, and 200,000 people with DKD undergo ESRD therapy. [3]. If it weren't for the fact that DKD raises the likelihood of patients dying from cardiovascular disease before developing ESRD, the incident dialysis rate might even be greater. An annual death rate of 20% is experienced by DKD patients with ESRD, which is higher than the rate for many solid malignancies (including prostate, breast, or even renal cell cancer). Danish doctors, especially Mogensen et al.,

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thoroughly detailed the natural history of DKD in the 1970s. [4, 5] Although DKD has traditionally been thought to result from the combination of hemodynamic and metabolic variables, new research shows that its pathophysiology is multifaceted, with the immune response and inflammation playing a significant role. [6, 7]. Promising therapeutic targets and developing novel indicators are pro-inflammatory signalling pathways and their downstream byproducts. [8]. Initially, Mogensen described DKD [7]. microalbuminuria, also known as occult or incipient nephropathy, was first recognised in the 1980s as a progressive condition that started with the loss of small amounts of albumin into the urine (30–300 mg per day). The phrases macro-albuminuria or overt nephropathy were used as progressively greater levels of albumin were lost in the urine and albuminuria became detectable by the then-standard dipstick urinalysis (>300 mg per day). Following this presentation, kidney function steadily declined, leading to renal impairment and eventually end-stage renal disease (ESRD). In clinical investigations, this paradigm has been beneficial for locating cohorts that are more likely to experience negative health outcomes, particularly in type 1 diabetes. The artificial nature of any stage border and the link between urine albumin excretion and poor health [9]. Angiotensin II (ANG II), in particular, is known to be activated by the renin-angiotensin system (RAS), which has been linked to the promotion of diabetic nephropathy for more than two decades. [10]. According to published guidelines, DKD patients with hypertension should take ACEIs or ARBs as their first line of treatment to lower their risk of cardiovascular disease, renal failure, and mortality. [11]. There is mounting evidence that certain drug types protect the kidneys without affecting diabetes management. The most intriguing class consists of sodium-glucose cotransporter 2 (SGLT-2) inhibitors. The principal mechanism for the tubular reclamation of glucose is thought to be SGLT-2, which is virtually entirely expressed in the proximal kidney tubule 1368 Clinical Journal of the American Society of Nephrology. By the suppression of tubular glucose absorption, SGLT-2 inhibition decreases HbA1c and lowers blood pressure. At lower levels of the GFR, the positive benefits of SGLT-2 inhibitors may be muted since their actions need filtration via the glomerulus. It has been demonstrated that SGLT-2 inhibitors affect kidney health and function. For instance, they momentarily reduce GFR [12]

2. Risk factors of diabetic kidney disease

Age, sex, race/ethnicity, and family history are some examples of DKD risk variables that can be theoretically divided into susceptibility, initiation, and progression categories (e.g., hypertension, dietary factors, and obesity) **(Table 1)** [13]. Two of the most prominent established risk factors are hyperglycemia and hypertension.

Risk Factor	Susceptibility	Initiation	Progression
Demographic			
Older age	+		
Sex (men)	+		
Race/ethnicity (black, American Indian, Hispanic, Asian/Pacific Islanders)	+		+
Hereditary			
Family history of DKD	+		
Genetic kidney disease		+	
Systemic conditions			
Hyperglycemia	+	+	+
Obesity	+	+	+
Hypertension	+		+
Kidney injuries			
AKI		+	+
Toxins		+	+
Smoking	+		+
Dietary factors	+		+
High protein intake	+		+

Table 1 Risk Factor of Diabetic Kidney Disease

2.1. Hyperglycemia

In individuals with type 1 diabetes who do not have proteinuria, poor glycemic control is an independent predictor of progression to proteinuria and/or ESRD [14]. Two important studies with early-stage type 1 or type 2 diabetes patients have shown that early, intensive blood glucose control has a long-lasting positive effect on the risk of developing DKD. This effect, also known as "metabolic memory," suggests that early and strict glycemic control can prevent irreversible damage caused by high blood glucose levels, such as changes to the epigenome [15-17]. An aggressive glucose management program targeting a HbA1C level of 7% reduced the risk of developing microalbuminuria and macroalbuminuria by 34% and 56%, respectively, over a nine-year period when compared to standard care. Similarly, in patients with newly diagnosed type 2 diabetes, 10 years of intensive glycemic control aimed at a HbA1C of 7%

resulted in a 24% reduction in the development of microvascular complications, including DKD [18]. After 12 years, intensive glycemic control significantly reduced the risk of developing microproteinuria or clinical grade proteinuria by 33%, and the proportion of patients with a doubled blood creatinine level was also lower compared to those on conventional therapy [19,20].

2.2. Hypertension

A significant 37% risk reduction of microvascular complications was observed in newly diagnosed DM2 patients who were treated to a goal blood pressure of 150/85 mmHg over a median of 15 years. This was in contrast to patients who were treated to a target blood pressure of 180/105 mmHg. As mean systolic blood pressure increased by 10 mmHg, the risk of developing micro- and macroalbuminuria as well as impaired kidney function, which is measured by an eGFR of 60 ml/min per 1.73 m2 or a doubling of blood creatinine, increased by 15%. [21]. Broadly, a baseline systolic BP.140mmHg in patients with DM2 has been associated with a higher risk of ESRD and death [22,23].

3. Pathophysiology of diabetic kidney disease

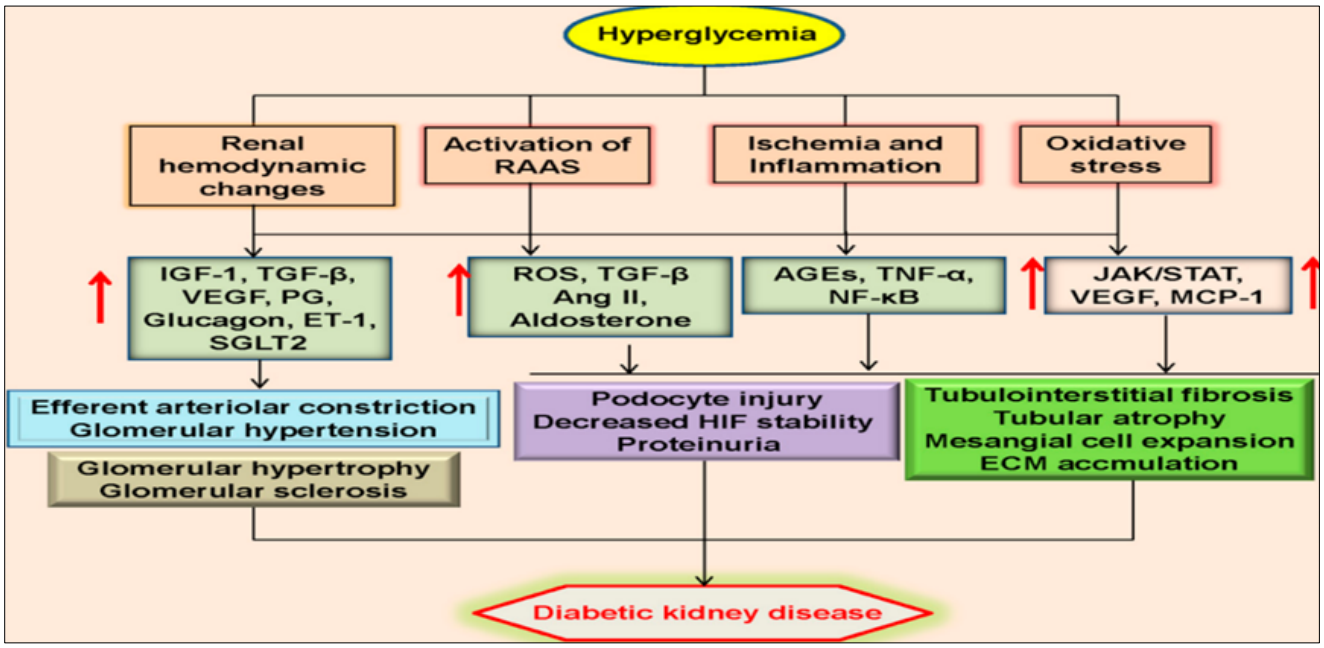

Figure 2 Pathogenesis of Diabetic Kidney Disease

Early diabetes causes significant metabolic alterations, including hyperaminoacidemia, which encourages glomerular hyperfiltration and hyperperfusion, and hyperglycemia, that affect kidney hemodynamics and encourage inflammation and fibrosis. [24–25]. By mechanisms including highly transmitted systemic BP and glomerular hypertrophy, systemic hypertension and obesity in DM2 also contribute to glomerular hyperfiltration [26]. A well-known side effect of early diabetes is glomerular hyperfiltration. Generally, 10%–40%, or up to 75%, of patients with DM1 and up to 40% of those with DM2 experience it. [27]. We don't fully understand the mechanisms causing glomerular hyperfiltration in diabetes. [27]; However, one possible explanation is that sodium-glucose cotransporter 2 is involved in enhanced proximal tubular reabsorption of glucose, which reduces the distal supply of solutes, particularly sodium chloride, to the macula densa. [28,29]. While concurrently high local angiotensin II production at the efferent arteriole causes vasoconstriction, the consequent decrease in tubuloglomerular feedback may widen the afferent arteriole to promote glomerular perfusion. High intraglomerular pressure and glomerular hyperfiltration are the overall effects. [26,28].

3.1. Structural Changes in Nephrons

Many structural changes to numerous kidney compartments are linked to the onset of DKD. The thickening of the glomerular basement membrane, which becomes noticeable after 1.5–2 years following DM1 diagnosis, is the earliest consistent alteration. Capillary and tubular basement membrane thickening are parallel to it. [30-33]. Loss of endothelial fenestrations, (**Figure.2**) mesangial matrix enlargement, and loss of podocytes with effacement of foot processes are other glomerular alterations. With DM1 diagnosis, mesangial volume increase can be seen within the first 5-7 years. [30,32,34,35]. Segmental mesangiolysis is seen as diabetes progresses and is believed to be linked to the

formation of Kimmelstiel-Wilson nodules and microaneurysms, which frequently co-exist. [36,37]. Exudative lesions arise in minor artery branches, arterioles, glomerular capillaries, and microaneurysms as a result of subendothelial plasma protein deposits that create periodic acid-Schiff-positive and electron-dense deposits. These deposits may damage the luminal integrity (e.g., hyaline arteriosclerosis). The proximal renal tubules and Bowman's capsule (capsular drop lesion) both exhibit comparable subepithelial deposits. Interstitial alterations and glomerulopathy combine to form segmental and global sclerosis in the latter stages of diabetes. [38]. In patients with DM1, GFR, albuminuria, and hypertension are strongly correlated with mesangial expansion and somewhat less strongly associated with glomerular basement membrane width [38]. (Figure 3. Shows Electron microscope images of structural changes in diabetic kidney disease. Structural changes in diabetic glomerulopathy found with electron microscopy. A indicates marked expansion of the mesangium. B indicates marked diffuse thickening of capillary basementmembranes (to three times the normal thickness in this case). C indicates segmental effacement of the visceral epithelial foot processes).

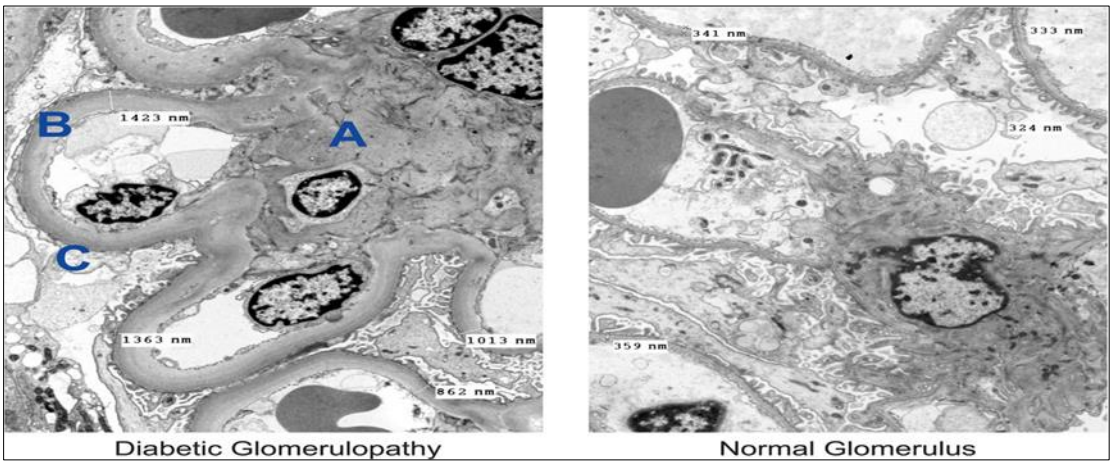

Figure 3 Electron microscope images of structural changes in diabetic kidney disease

While DM2 patients' renal structural changes are similar to those reported in DM1, they are more diverse and less consistently correlated with clinical manifestations. [39]. Due to selection bias patients with diabetes who had biopsies tended to have unusual presentations of DKD early renal pathology investigations on individuals with DM2 showed a high frequency of nondiabetic glomerular disease. Recent biopsy studies have reached more cautious conclusions, suggesting a 10% frequency of non-DKD in people with diabetes and albuminuria. [31]. The uncertain timing of DM2 onset compared to DM1, with probable extended exposure to hyperglycemia before diagnosis; an older patient group; and a larger load of atherosclerosis are possible explanations for the distinct presentation of DKD in DM2. In addition, many DM2 patients get renin-angiotensin system inhibitors prior to receiving a diabetes diagnosis. To address the variety of DKD presentation, an international consensus working group has developed a pathologic classification system that includes scoring of glomerular, interstitial, and vascular lesions. [40].

3.2. Mechanisms of Diabetic Kidney Disease

As was already indicated, better outcomes for those who are affected are anticipated to result from a better knowledge of the common and unique mechanisms causing DKD and NDKD in individuals with DM. In the sections that follow, we analyse the mechanisms that cause CKD to advance in these individuals in order to offer a conceptual framework for selecting appropriate pharmacological targets. Up to 50% of all occurrences of ESRD in Western populations are caused by DKD, a serious microvascular complication of DM. [42, 43]. As mentioned above, DKD is an important risk factor for cardiovascular mortality in patients, particularly when accompanied by hypertension. The earliest detectable clinical manifestation of DKD is microalbuminuria, and in the absence of early intervention, approximately 50% of patients with established microalbuminuria will progress to macroalbuminuria, which is associated with a tenfold higher risk of progression to ESRD than that of patients with normoalbuminuria [44, 45]. It should be noted that traditional cardiovascular risk factors, such as high urinary albumin: creatinine ratio, older age, high haemoglobin A1C (HbA1c), elevated blood glucose, and hypertension, but not hemodynamic risk factors, such as estimated GFR (eGFR), are associated with the development of microalbuminuria in patients with DM2 [46]. Over 30% of DM1 patients experience microalbuminuria, which is mostly dependent on medication adherence and blood glucose management. [47]. Around 30% of patients with DM2 have microalbuminuria, however this condition is typically accompanied by hypertension [48,49]. In both situations, albuminuria cannot develop in the absence of hyperglycemia, and the key factor influencing the development of overt DKD is glucose management. [41, 50]. The ability of lowering HbA1c in DM1 patients with

proteinuria (for instance, from 9.3% to 8.7%) to stop the progression of ESRD highlights the significance of hyperglycemia in the development of DKD. [51]. Also, after 10 years of normoglycemia, pancreas transplantation in individuals with DM1 can totally repair diabetic glomerulosclerosis in native kidneys. [52]. Morbid obesity, low birth weight, and genetic susceptibility factors are additional risk factors for DKD beyond glycemic management, which may help to explain why some but not all DM patients go on to develop DKD. [53,54]. DKD can be caused by a variety of pathomechanisms, some of which are detailed below; however, as was already indicated, not all individuals with CKD and DM will also have DKD. Understanding the early versus late effects of hyperglycemia on the kidney is crucial to analysing differences in the pathogenic processes of DKD and NDKD.

3.3. Metabolic Memory of Diabetes

DKD can be caused by a variety of pathomechanisms, some of which are detailed below; however, as was already indicated, not all individuals with CKD and DM will also have DKD. Understanding the early versus late effects of hyperglycemia on the kidney is crucial to analysing differences in the pathogenic processes of DKD and NDKD. Many different pathomechanisms, some of which are described below, can lead to DKD; however, as was already mentioned, not everyone with CKD and DM will also have DKD. Analyzing the variations in the pathogenic processes of DKD and NDKD requires an understanding of the early vs late effects of hyperglycemia on the kidney. [55]. Unlike genetic risk factors, metabolic memory is unquestionably a consequence of DKD-related hyperglycemia. In DM2 patients, a 10-year follow-up study indicated that strict glycemic management continued to reduce micro- and macrovascular risks as well as mortality. [56, 57]. This "legacy impact," which involves the consolidation of metabolic clues and transcriptional changes through historical pathways and epigenetic modifications, has been backed by growing experimental and clinical evidence over time. [58,59]. As a change in phenotype happened without a change in genotype, epigenetics is the study of heritable variations in gene expression without changing the underlying DNA sequence. Epigenetics involves at least three different mechanisms, including RNA interference, histone modification, and DNA methylation. [60]. In DKD, The effects of epigenetic changes on the extracellular matrix, the transforming growth factor-signaling pathway, the activation of the RAAS system, and other genes are well recognised. Particularly, the interaction of non-enzymatic protein glycation, oxidative stress, chronic inflammation, hypoxia, and dietary and environmental alterations is linked to the aetiology of DKD. The epigenetic patterns in the metabolic memory of DKD are likewise modified by these pathologic variables. DNA methylation is the epigenetic change that has received the most research because it was the first to be described decades ago. It is the process of giving the DNA molecule additional methyl groups. Two of the four DNA bases cytosine and adenine can be methylated. The most recent reported clinical research examined the levels of cytosine methylation in DM2. [61]. The findings showed that eGFR reduction in blood leukocytes of DKD patients was substantially correlated with methylation levels at 77 locations. Renal fibrosis was linked to DNA methylation, altered gene expression, and five out of 77 areas. [61]. The results demonstrated a significant correlation between eGFR decline in blood leukocytes of DKD patients and methylation levels at 77 sites. DNA methylation, changed gene expression, and five out of 77 regions were associated with renal fibrosis. [61, 62].

3.4. Diabetic Kidney Disease originates from metabolic dysregulation

DKD is brought on by the dysregulated metabolic environment, which includes hyperglycemia, hyperlipidemia, and insulin resistance. Moreover, the groundbreaking DCCT (Diabetes Complications and Treatment) experiment showed that DM1 patients with tight glucose control (HbA1c levels of 7% vs. 9%) have a more than 50% lower risk of developing DKD. [64, 65]. Interestingly, recent big clinical trials (ACCORD, VADT, ADVANCE) did not provide a statistically significant effect for lowering HbA1c to less than 7% in individuals with type 2 diabetes [66–68]. These results are unexpected and show that while hyperglycemia is important for DKD initiation, more research is needed to determine how it affects progression. One issue with interpretation may be that individuals with DM2 may have had years of metabolic changes prior to being given a diagnosis of diabetes, which may have contributed to DKD even before they were given the DM2 diagnosis. [63].

4. Current treatment strategies

4.1. BP Control

According to the clinical practise guidelines for Kidney Disease Improving Global Outcomes, patients with DKD should reach systolic and diastolic objectives of 135 and 80 mmHg, respectively, for those who excrete urine albumin. 30 mg/24 h (grade 2D) (grade 2D). A lower BP is inversely correlated with albuminuria, and this recommendation was made only on the basis of observational data, which shows that urine albumin levels are predictive of worse cardiovascular and kidney outcomes. [69,70]. The ACCORD Study (Action to Reduce Cardiovascular Risk in Diabetes) [71] compared tight to conventional systolic BP (mean achieved, 119 versus 134 mmHg) in 4733 patients with DM2 who had been following them for an average of 11 years on average and had hypertension. Microalbuminuria was dramatically reduced by

aggressive BP management by 16%, but not macroalbuminuria or renal failure, as shown by a high blood creatinine. Dialysis, kidney transplantation, or 3.3 mg/dl. In conclusion, neither the optimum BP goal for individuals with pre-existing DKD nor solid clinical trial results exist to support tight BP management for kidney protection in patients with DM2. Hence, individual clinical discretion is advised with the understanding that, despite the possibility of further significant advantages from reducing BP in these patients, too stringent BP management may be harmful. [72]. preferred hypertensive medications High-quality randomised controlled trials throughout the spectrum of DM2 and DKD support the use of RAAS blockers as first-line BP-lowering medications in patients with DKD. [73–76]. In a study of patients with early DKD [74]. In 590 patients with DM2, hypertension, normal mean creatinine clearance, and microalbuminuria, the ARB irbesartan was contrasted with a placebo. Irbesartan significantly and dose-dependently decreased the risk of developing macroalbuminuria or a rise in microalbuminuria by 30% over a median of 2 years (44% reduction with 150 mg/d and 68% reduction with 300 mg/d, after adjusting for baseline albuminuria level and BP). Patients with more advanced DKD have also been investigated when RAAS inhibition is used. The Angiotensin II Antagonist Losartan Study: Endpoint Reduction in NIDDM [75] 1513 people with type 2 diabetes and proteinuric DKD (serum creatinine, 1.3–3.0 mg/dl; urine albumin-to-creatinine ratio [UACR].300 mg/g creatinine or proteinuria.500 mg/g creatinine) were randomly assigned to receive losartan or a placebo for a mean of 3.4 years. The primary composite end point of mortality, ESRD, or doubling of serum creatinine was decreased by 16% as a result of losartan medication, with the individual risks of ESRD or doubling of serum creatinine falling by 25% and 28%, respectively. The median rate of eGFR reduction was slowed by losartan by 0.8 ml/min per 1.73 m2 each year. [76] A mean of 2.6 years was spent monitoring 1715 patients with DKD and hypertension who were randomly assigned to receive irbesartan, amlodipine, or a placebo. Irbesartan treatment was linked with a 20% and 23% decreased risk of developing the primary composite outcome, which included doubling baseline blood creatinine, ESRD, or mortality, respectively, compared to placebo or amlodipine. Irbesartan reduced the chance of doubling serum creatinine by 33% and 37%, respectively, and the risk of ESRD by 23%, albeit these reductions were statistically borderline significant. In the irbesartan, amlodipine, and placebo groups, the rate of eGFR reduction was 5.5, 6.8, and 6.5 ml/min per 1.73m2 per year, respectively. It should be noted that despite the fact that the evidence for the use of angiotensin-converting enzyme inhibitors (ACEIs) is not as strong as the evidence for ARBs, these drugs do exist. Clinical characteristics separating type 2 DKD from other kidney diseases Clinical Aspect DKD Non-DKD beginning of proteinuria Rapid Progressive Development of CKD Diabetes Rapid Progressive Duration, 5 to 10 years Urinalysis dynamic sediment (hematuria, pyuria, casts) dull sediment Retinopathy Absent In published guidelines and everyday clinical practise, present classes have been interchanged. The ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Study examined combination ACEI/ARB therapy as a predetermined secondary outcome.[77], which randomly assigned 25,620 patients with atherosclerotic vascular disease, diabetes, and end-organ damage to ramipril, telmisartan, or both and monitored them over a median of 56 months. Combined therapy was linked to noticeably lower results (a greater number of events in the primary and secondary renal composite outcomes, which included doubling of serum creatinine, dialysis, or death). Losartan alone or in combination with lisinopril was given to 1448 patients with DM2, a baseline Egfr between 30 and 89.9 ml/min per 1.73 m2, and UACR of $300 mg/g in the Veterans Affairs Nephropathy in Diabetes Study. [78]. Although trends indicating benefits were seen for the secondary endpoint (first occurrence of decline in eGFR) (hazard ratio [HR], 0.78; 95% confidence interval [95% CI], 0.58 to 1.05; P50.10) and development of ESRD (HR, 0.66; 95% CI, 0.41 to 1.07; P50.07), combination therapy did not improve cardiovascular or mortality outcomes. The trial was prematurely terminated due to safety concerns including a greater incidence of hyperkalemia (6.3 versus 2.6 events per 100 person-years with monotherapy; P,0.001) and AKI (12.2 compared 6.7 events per 100 person-years; P,0.001) in the combination therapy arm. Intriguingly, a secondary analysis of this trial revealed that individuals in the dual therapy arm who developed AKI had lower 30-day mortality (4.7% versus 15.0%; P,0.01), lower risk for the first occurrence of reduction in eGFR (HR, 0.60; 95% CI, 0.37 to 0.98), and a higher rate of kidney function recovery (75.9% versus 66.3%; P50.04) during follow-up than those in the monotherapy arm. [79] Two trials have looked at direct renin inhibition as an adjunctive therapy to ACEI/ARB therapy. The Trial of Aliskiren in the Assessment of Proteinuria in Diabetes [80] aliskiren or a placebo was given to 599 individuals with DM2, hypertension, and DKD (defined as UACR.300 mg/g or.200 mg/g if on RAAS blockers). Aliskiren reduced the primary outcome of UACR by 20% over the course of a 6-month research, while a minor impact on blood pressure was also observed. The considerably bigger Aliskiren Study in Type 2 Diabetes Utilizing Cardio-Renal Endpoints, however (ALTITUDE) [81] 8561 individuals with DM2 and nephropathy (UACR.200 mg/g, eGFR$30 ml/min per 1.73 m2, or eGFR#60 ml/min per 1.73 m2 with 20 mg/g $UACR.200 mg/g or cardiovascular disease) were compared with aliskiren and a placebo. A lack of impact on kidney-related outcomes and a greater risk of hyperkalemia in the add-on arm led to the early termination of ALTITUDE.

4.2. Glycemic Control

Numerous significant research have concentrated on the alleged advantage of glycemic control for DKD. The UKPDS Study that was referenced earlier [82] compared the haemoglobin A1c (HbA1c) levels of 3867 newly diagnosed DM2 patients who were randomly assigned to intensive versus conventional glycemic control (median achieved HbA1c, 7.0%

versus 7.9%), tracked them for up to 15 years, and looked at a number of clinical outcomes. The most consistent kidney-related finding was a decrease in the occurrence of microalbuminuria in the intensive glycemic control group. However, macroalbuminuria and a doubling of serum creatinine were also significantly lower at 9 and 12 (but not 15) years of follow-up in that group, despite the rarity of events in these two categories. Another trial, the Veterans Affairs Diabetes Trial, examined the impact of strict glycemic control on kidney outcomes. [83] which compared intensive (achieved mean HbA1c of 6.9%) to standard (achieved mean HbA1c of 8.4%) glucose control in 1791 veterans with a mean duration of DM2 of 11.5 years, meanHbA1c of 9.4%, and serum creatinine #1.6 mg/dl. The secondary outcome of nephropathy was evaluated throughout the course of a 5-7 year follow-up period. There was no difference between the groups in terms of GFR decline, but the intensive control group had a considerably lower rate of progression to micro- and macroalbuminuria and any rise in albuminuria. Glycemic control was investigated in two very sizable trials in populations that comprised patients with mild to moderate DKD. Preterax and Diamicron MR Controlled Assessment Study for Action in Diabetes and Vascular Disease [84] followed 11,140 type 2 diabetes patients for a median of five years who had been randomly assigned to intensive versus routine glycemic control (mean achieved HbA1c, 6.5% versus 7.3%). At baseline, 31% of patients had microalbuminuria or more, and a total of 19% had an eGFR of 60 ml/min per 1.73 m2. Improvements in a number of kidney outcomes, including a 9% decrease in new microalbuminuria, a 30% decrease in new macroalbuminuria, and a 65% decrease in ESRD, were linked to intensive glycemic management (with relatively few of these events). In the ACCORD Trial, which randomly assigned 10,251 individuals with type 2 diabetes and high cardiovascular risk to intensive versus routine glycemic management (median HbA1c, 6.4% versus 7.5%), and then followed them for an average of 3.5 years, conflicting results were observed. At that time, 33% of patients had microalbuminuria or more, and the median eGFR was 90 ml/min per 1.73 m2. Although increased mortality rates in the intensive glucose control arm caused the trial to stop early, kidney-related outcomes were assessed as predetermined secondary objectives. [85]. Intensive glycemic management had no influence on the onset of ESRD but was substantially linked with a 21% and 31% lower incidence of micro- and macroalbuminuria, respectively, a 7% greater rate of serum creatinine doubling, or a.20 ml/min per 1.73 m2 drop in eGFR. In conclusion, there is inconsistent evidence regarding whether or not stringent glycemic control long-term protects kidney health, yet it appears to benefit micro- or macroalbuminuria. Another clear cause for concern is the greater mortality risk linked to stricter glycemic control that was revealed in the ACCORD Trial.

4.3. Preferred Diabetes Regimen

There is mounting evidence that certain drug types protect the kidneys without affecting diabetes management. The most intriguing class consists of sodium-glucose cotransporter 2 (SGLT-2) inhibitors. The proximal renal tubule is almost entirely where SGLT-2 is expressed, and this is thought to be the primary mechanism for the tubular reclamation of glucose. By preventing tubular glucose uptake, SGLT-2 inhibitors reduce HbA1c and cause weight reduction and lower blood pressure. At lower levels of GFR, the positive effects of SGLT-2 inhibitors might be less pronounced because their actions need filtering via the glomerulus. It has been demonstrated that SGLT-2 inhibitors affect kidney health and function. For instance, they momentarily reduce GFR [86] diminish albuminuria, likely by enhancing the tubuloglomerular feedback pathway. [87]. The Empagliflozin, Cardiovascular Outcomes, and Mortality in DM2 (EMPA-REG OUTCOME) Study, which randomised 7020 individuals with type 2 diabetes and cardiovascular disease to the SGLT-2 receptor empagliflozin at two doses versus placebo, provides the most compelling evidence for renoprotection. [88]. At baseline, 40% of patients had micro- or macroalbuminuria and 26% had an eGFR of 60 ml/min per 1.73 m2. Empagliflozin use was associated with fewer cardiovascular and mortality events and better kidney-related outcomes after a median of 3.1 years of follow-up. In particular, although the latter endpoints were sparse in number, it was linked to a statistically significant decreased rate of incident macroalbuminuria (38%), doubling of serum creatinine and eGFR#45 ml/min per 1.73m2 (44%), and beginning of RRT (55%). These results held true across the spectrum of baseline eGFR and empagliflozin dose. Although the preliminary data for SGLT-2 inhibition seem encouraging, it is yet unknown if these findings will hold true in a number of ongoing clinical trials with primary kidney-related outcomes. The US Food and Drug Administration also recently issued a warning regarding the possibility of AKI when using SGLT-2 inhibitors. [89]. The frequency of AKI will need to be determined by postmarketing surveillance even though the EMPA-REG OUTCOME Trial did not report higher rates of the condition. DPP-4 inhibitors are a different family of diabetes medications that may have kidney-protective benefits. DPP-4 inhibitors increase the amount of insulin secreted from the pancreas by preventing the breakdown of compounds like glucagon-like peptide-1. Using the DPP-4 inhibitor linagliptin for 24 weeks reduced albuminuria by 32%, regardless of blood pressure or haemoglobin A1c levels, in a post hoc examination of 217 individuals with DM2 and micro- or macroalbuminuria who were taking RAAS blockers. [90]. A post hoc analysis of the Trial Evaluating Cardiovascular Outcomes with Sitagliptin, which included 14,735 patients with DM2 and cardiovascular disease and was randomised to the DPP-4 inhibitor sitagliptin versus placebo as add-on therapy, was published more recently. It found that over the course of the study's 4-year follow-up period, the sitagliptin group had a marginally lower median UACR (20.18 mg/g) and lower mean e [91].

4.4. Weight Reduction and Diet

It is appropriate to think about strategies focusing on these aspects in the management of DKD given the substantial correlation between dietary practises and excess adiposity and the development of DM2. Despite the lack of dietary guidelines specifically for DKD patients, the Action for Health in Diabetes Trial [92] examined the impact of a rigorous lifestyle intervention—increasing physical activity and reducing calorie intake—versus conventional diabetes support and education on the predetermined secondary outcome of DKD. 5145 overweight or obese patients with DM2 and baseline median albuminuria and serum creatinine values within the normal range comprised the participant group. In comparison to the group receiving conventional care, the intensive lifestyle group's weight decreased by 4 kg throughout a 10-year period of follow-up. Moreover, their cumulative incidence of having very high-risk CKD was 31% lower, which is statistically significant. [93These preliminary results imply that diet and weight can alter the onset and progression of DKD. Several thorough reviews have examined whether bariatric surgery, the most successful and long-lasting weight loss method, is useful in treating DKD. [94]. This subject was also investigated in a more recent case-control study with 985 bariatric surgery patients and matched controls. [95]. Bariatric surgery was linked to a 58% reduced risk of a $30% fall in eGFR and a 57% lower risk of doubling serum creatinine or ESRD after a median follow-up of 4 years. In the roughly 40% of those with DM2 who were included in the trial, similar results were observed. Given the significant impact that significant weight loss has on serum creatinine (and eGFR) due to the loss of muscle mass and the very small number of people who met the clinical criteria, the results should be regarded with caution. Nonetheless, given the promising outcomes and continuous developments in surgical weight loss methods, bariatric surgery may prove to be a valuable addition to the treatment toolbox for DKD.

5. Emerging therapies for diabetic kidney disease

This section examines a number of cutting-edge treatments for DKD that are presently undergoing phase 31 clinical trials. Antagonists of the endothelin-1 receptor A receptor for endothelin-1 Increased oxidative stress, podocyte damage, vasoconstriction, fibrosis, and inflammation are brought on by A activation within the kidney. [96]. Atrasentan, a selective endothelin-1 receptor A antagonist, decreased albuminuria and blood pressure in DKD patients, according to results of a phase 2 clinical trial titled "Reducing Residual Albuminuria in Patients with Diabetes and Nephropathy with Atrasentan Trial." [97]. The Study of Diabetic Nephropathy with Atrasentan was founded on a post hoc study that demonstrated reduced renal risk when using atrasentan (SONAR) [98]. 4148 DKD patients are anticipated to join in SONAR, which has a composite endpoint of mortality, ESRD, or a doubling of serum creatinine. Late 2018 is the anticipated completion date.

5.1. Mineralocorticoid Receptor Antagonists

The protective function of substances that impede the RAAS cascade downstream is becoming more and more popular. Due to hyperkalemia and other side effects, steroidal mineralocorticoid receptor (MR) antagonists like spironolactone and eplerenone have a limited role to play as an adjunct therapy to ACEI/ARBs. This is likely to be partially due to inadequate antagonism and variability in the cell-specific actions of steroidal MR antagonists. Ongoing research aims to identify nonsteroidal MR antagonists with predictable antagonistic responses and more manageable side effects. One such agent being looked into is finerenone. According to the Mineralocorticoid Receptor Antagonist Tolerability Study-DN Study, adding finerenone to ACEIs/ARBs improved UACR. [99]. The renal outcomes are secondary goals of the Efficacy and Safety of Finerenone in Subjects with DM2 and the Clinical Diagnosis of DKD Study, which is anticipated to be completed in early 2019. The kidney objective is the major endpoint of the Efficacy and Safety of Finerenone in Individuals with Type 2 Diabetes Mellitus and DKD Study, which is anticipated to be completed in the middle of 2019. The study is expected to enrol 4800 patients.

5.2. TGF-b Inhibitors

Fibrosis is a hallmark of DKD and TGF-b1 is a potent profibrotic molecule. Pirfenidone interferes with the secretion, expression, and action of TGF-b1 by an unknown mechanism. It is currently being evaluated in a phase 3 trial with planned recruitment of 62 patients with type 2 diabetes and with changes in albuminuria and GFR as primary endpoints. It is expected to end in early 2018. Given its modest size, this trial should be expected to be more hypothesis-generating than definitive in nature.

5.3. Phosphodiesterase Inhibitors

In numerous short investigations, the nonselective phosphodiesterase inhibitor pentoxifylline showed anti-inflammatory, antifibrotic, and antiproteinuric properties. A prospective clinical investigation comparing it to CKD

stages 3 and 4 in non-patients with diabetes and 350 patients with advanced DKD is now evaluating it. The trial is anticipated to be finished in December 2018 and has a primary kidney outcome.

5.4. 5-Hydroxytryptamine 2a Receptor Antagonists

Sarpogrelate hydrochloride, a selective 5-hydroxytryptamine 2a receptor antagonist, has been demonstrated to have renoprotective benefits in a number of diabetic animal investigations. The Sarpogrelate on the Nephropathy in DM2 Study, which included 166 patients with type 2 diabetes and albuminuria or overt proteinuria, was created to assess the efficacy and safety of sarpogrelate hydrochloride. The study's main kidney result is. Due to the fact that Clinicaltrials.gov's most recent update was in July 2014, the study's status is still uncertain.

6. Conclusion

Possibly the most significant site of microvascular damage in diabetes is the kidney. Due to their condition and/or additional co-morbidities including hypertension and nephron loss brought on by ageing, a significant portion of people with diabetes will acquire kidney disease. The prevalence and severity of CKD can be used to identify those who are more likely to experience unfavourable health outcomes and die young. As a result, one of the main goals of patients' overall management is now to prevent and control CKD in patients with diabetes. Controlling blood sugar levels, blood pressure, and renin-angiotensin-aldosterone system blockage are all part of intensive therapy of diabetic patients; these measures will lower the incidence of diabetic kidney disease and halt its progression. Yet, there are still significant gaps in our knowledge about DKD. Due to the lack of a noninvasive biomarker, the diagnosis of DKD is still based on subjective evaluation. Because of this restriction, it is more challenging to plan clinical studies to find DKD treatments that work.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors declare that they have no conflict of interest.

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