kidney and dialysis

MDPI

Review

The Epidemiology of Diabetic Kidney Disease

Ellen K. Hoogeveen [1,2]

[1] Department of Clinical Epidemiology, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands; e.k.hoogeveen@lumc.nl
[2] Department of Nephrology, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands

Abstract: Globally, the incidence and prevalence of diabetes mellitus has risen dramatically, owing mainly to the increase in type 2 diabetes mellitus (T2DM). In 2021, 537 million people worldwide (11% of the global population) had diabetes, and this number is expected to increase to 783 million (12%) by 2045. The growing burden of T2DM is secondary to the pandemic of obesity, which in turn has been attributed to increased intake of processed food, reduced physical activity, and increased sedentary behaviour. This so-called western lifestyle is related with the global increase in urbanization and technological development. One of the most frequent and severe long-term complications of diabetes is diabetic kidney disease (DKD), defined as chronic kidney disease in a person with diabetes. Approximately 20–50% of patients with T2DM will ultimately develop DKD. Worldwide, DKD is the leading cause of chronic kidney disease and end-stage kidney disease, accounting for 50% of cases. In addition, DKD results in high cardiovascular morbidity and mortality, and decreases patients' health-related quality of life. In this review we provide an update of the diagnosis, epidemiology, and causes of DKD.

Keywords: chronic kidney disease; diabetes mellitus; epidemiology; end-stage kidney disease

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1. Introduction

Diabetic kidney disease (DKD) is a frequent long-term complication of diabetes. Globally, DKD is the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD), accounting for 50% of cases [1]. Typically, DKD is defined by the presence of chronic kidney disease (CKD) characterized by persistently (at least 3 months) elevated urinary albumin excretion (albumin-to-creatine ratio [ACR] $\geq$ 30 mg/g) and/or low estimated glomerular filtration rate (eGFR < 60 mL/min/1.73 m^2) in a person with diabetes [2]. The risk of adverse outcomes, including death and ESKD, increases with decreasing GFR and increasing albuminuria. Individuals with a GFR below 30 mL/min/1.73 m^2 (i.e., CKD stage 4–5) are at especially high risk across all albuminuria categories [2].

In developed as well as in developing countries, diabetes is a major public health challenge [3,4]. Type 2 diabetes mellitus (T2DM) accounts for about 90% of the global burden of diabetes [4–6]. The number of people with diabetes worldwide has more than doubled in the past 20 years, secondary to the obesity epidemic that has resulted in nearly a tripling in obesity since 1975 [7–9]. During this period, obesity prevalence in children, adolescents, and adults has increased in every country [9]. Obesity results from a long-term energy imbalance, with more calories consumed than expended, typically with increased intake of processed food, reduced physical activity, and increased sedentary behaviour. This so-called western lifestyle has accompanied the global trend toward urbanization and technological development. The rising prevalence of T2DM is also related to the aging of the world population, as well as the decreasing mortality of diabetics due to improved health care [4]. Presently, more than one in three people are expected to develop diabetes in their lifetimes. These people will have a nearly twofold higher mortality risk from any cause compared with people without diabetes, and a life expectancy that is about six to seven years shorter than the remainder of the population [10].

In 2021, the estimated global prevalence of diabetes among people 20–79 years of age was 11%, which is expected to increase to 12% by 2045 [4]. The prevalence of diabetes in 2021 was similar in men and women, steadily increasing with age, higher in urban (12%) than rural (8%) areas, and greater in high-income (11%) and middle-income (11%) compared with low-income countries (6%). Of note, about 6% of people older than 20 years of age live in a low-income country. The highest rates of T2DM are reported in specific ethnic groups, particularly indigenous populations in the US, Australia, and New Zealand [4]. More than 80% of people with diabetes live in low- or middle-income countries (Table 1). China now has more people with diabetes than any other nation, with 92 million people affected, being almost 1 in 10 adults. The greatest relative increase in prevalence from 2021 to 2045 is expected in middle-income countries, especially in Africa. Finally, the global epidemiology of T2DM is changing from a chronic disease in middle aged and older people, into one that is increasingly common at younger ages, including in young adults, adolescents, and children [6,11].

Table 1. Number of adults (20–79 y) in 2021 and 2045 with diabetes around the world.

	2021 (Millions)	Proportion People with Diabetes	Predicted in 2045 (Millions)
Africa	24	9%	55
Europe	61	9%	69
Middle-East and North Africa	73	17%	136
North America and Caribbean	51	14%	63
South and Central America	32	9%	49
South-East Asia	90	9%	151
West Pacific	206	13%	260

Source: International Diabetes Federation Diabetes Atlas.

The kidney is an important target of microvascular damage in diabetes. Diabetic patients have twice the risk of CKD as those without diabetes. Although diabetes management has improved and lowered the risk for people with diabetes of developing CKD, improved life expectancy combined with the rising incidence of both T2DM and T1DM has led to an increasing prevalence of CKD globally [12,13]. Excess mortality associated with T1DM and T2DM is largely confined to those with CKD [14,15]. Consequently, the prevention and timely diagnosis of CKD in patients with diabetes is key.

2. Epidemiology of Diabetic Kidney Disease

Diabetic kidney disease develops in nearly half of patients with T2DM and one-third of those with T1DM during their lifetime. It is one of the most frequent, burdensome, and expensive long-term complications of diabetes [4]. About 20% of adults with T2DM will develop an eGFR < 60 mL/min/1.73 m^2, and between 30–50% will have elevated urinary albumin excretion. The UK Prospective Diabetes Study showed that after a median follow-up of 15 years, 28% had an eGFR < 60 mL/min/1.73 m^2, and 28% had albuminuria [16]. If T2DM develops between the ages of 15–24 years, the lifetime risk of moderate albuminuria is almost 100% [17]. Generally, the annual incidence of albuminuria is about 8% in T2DM and approximately 2% to 3% in T1DM. The incidence of low eGFR is approximately 2% to 4% per year regardless of type of diabetes [8].

The percentage of patients who have CKD caused by diabetes is not precisely known, since people with diabetes may have other causes of CKD in addition to diabetes, and a kidney biopsy is rarely performed to establish the precise diagnosis. Particularly in people with T2DM, other causes of CKD are often present, such as hypertension, dyslipidemia, obesity, intra-renal vascular disease, acute kidney injury (AKI), glomerular atherosclerosis, or age-related kidney loss. The lower incidence of CKD in T1DM is likely due to the fact that these patients are younger, healthier at diagnosis, and have fewer co-morbidities than

patients with T2DM. Most likely, CKD in T1DM patients better reflects DKD than the mixed etiology of CKD in T2DM [18].

3. Burden of Diabetic Kidney Disease across Continents

About 700 million people, or 9% of the world's population, have CKD, of whom nearly four million patients require kidney replacement therapy (KRT) [19]. The prevalence of CKD, especially the earlier stages, is higher in women, but men are more likely to progress to ESKD for which KRT is needed [20]. Access to KRT for treatment of ESKD is as low as 16% in some countries. In 2010, more than 2.3 million deaths were attributed to lack of access to KRT worldwide [21]. The largest treatment gaps were noted in low-income countries, particularly in Asia and Africa, where 1.9 and 0.4 million people were needing, but not receiving KRT. Worldwide, the prevalence of KRT is projected to more than double to 5.4 million people by 2030, with the most growth in Asia (1 million to a projected 2 million) [21].

In patients with T2DM the prevalence of CKD varies in countries across the world, ranging from 27% in China to 84% in Tanzania [14,22–25]. A systematic review including data from more than 30 countries in Europe, North America, Asia, and Australia showed an annual incidence of albuminuria of about 8% in T2DM and 2–3% in T1DM, and a low eGFR < 60 mL/min/1.73 m^2 of about 2–4% in both T2DM and T1DM [18,26]. Worldwide, the number of individuals with DKD is expected to rise, mirroring the increasing prevalence of T2DM.

In the United States (US), the National Health and Nutrition Examination Survey (NHANES) showed that the proportion of diabetes in people with CKD stage 3–4 increased from 20% in 1999–2004 to 25% in 2011–2014 [27,28]. In 2017, the age-standardized prevalence of CKD in patients with diabetes was approximately 25 per 1000 in the US and globally 15 per 1000 [27,28]. Currently, one in seven US adults $\geq$ 20 years has CKD, with one in three of these individuals having diabetes. A cohort study showed that the incidence rates of CKD stage 3–5 in people with diabetes after 9 years of follow-up was 19 per 1000 person-years [29]. Although, incidence rates of ESKD owing to DKD stabilized in recent years in the US, high-risk sub-groups, such as African Americans, Native Americans, and Hispanics have increasing rates owing to an increased prevalence of hypertension, obesity, and DMT2 [30,31]. In Europe, the prevalence of CKD is 2–5 times higher in those with compared with those without T2DM [32]. In Sub-Saharan Africa, CKD is estimated to affect between 10–13% of the population [33]. Low-income countries, such as Uganda bear a large burden of advanced CKD because of a lack of preventive care. There is no national healthcare coverage, and most of the costs for the medical care of chronic disease are too expensive for patients. In Uganda, the prevalence of CKD ranges from 2–7% in the general population. Of all patients admitted with CKD, 16% have DM, whereas 90% have hypertension. The case fatality rate is 21% among patients admitted with CKD, while it is 51% for those with ESKD.

4. Diagnosis DKD versus Diabetic Nephropathy

As proposed by the international organization Kidney Disease Improving Global Outcomes (KDIGO), DKD is used to describe a clinical diagnosis defined by the presence of CKD in a patients with diabetes, whereas the term diabetic nephropathy (DN) is exclusively reserved for the histologic diagnosis of glomerular changes observed on biopsy [3]. Typical histological changes in DN include glomerular basement membrane thickening, mesangial expansion with and without nodular sclerosis (referred to as a Kimmelstiel–Wilson lesion), podocyte loss, and endothelial disruption, ultimately leading to nephron loss. In diabetic patients, disturbance of apoptosis and autophagy, essential for cellular housekeeping, causes DN. Experimental models of nephritis showed that necroptosis of neutrophils cause destruction of the glomerular filtration barrier and loss of kidney function [34]. Furthermore, protein loss in the primary urine and massive protein load in the proximal tubule can cause loss of kidney tubules. The considerable variability in pathologic features of DN can be

explained by the heterogeneous clinical presentation and disease progression [19]. Routine kidney biopsies are not performed in diabetic patients, because treatment options are limited. Therefore, in the absence of a diagnostic biopsy, registries assign the diagnosis DKD in the presence of both CKD and diabetes.

The course of DKD is heterogeneous, owing to its different underlying causes [19]. Patients with diabetes may have CKD that is unrelated to diabetes, superimposed on diabetic nephropathy (DN), or a specific kidney disease, as for example glomerulonephritis, minimal change disease, or primary or secondary forms of focal segmental glomerulosclerosis.

5. Pathophysiological Mechanism of DKD

Chronic hyperglycemia and glomerular hyperfiltration are the main causal factors of DKD in people with T1DM. In contrast, the pathophysiology of DKD in people with T2DM is more complex, since a cluster of cardiovascular risk factors, such as obesity, hypertension, and dyslipidemia, may also contribute to the development of microvascular damage. Hyperfiltration is thought to be a manifestation of increased intraglomerular capillary pressure and plays an important role in the development and progression of DKD [35]. Glomerular hyperfiltration, or supraphysiologic elevation in GFR, is defined as a GFR from 120 to 180 mL/min/173 m^2, or an absolute increase in GFR of more than two standard deviations above the mean GFR in age-matched healthy people. Glomerular hyperfiltration occurs within 1 to 5 years of T1DM and is present in 70% of those with T1DM and 50% of those with T2DM. Glomerular hyperfiltration classically has been hypothesized to predispose towards irreversible nephron damage, thereby contributing to the initiation and progression of kidney disease in diabetes [36,37]. However, recent data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study have called into question the importance of hyperfiltration in the progression of DKD [38].

6. Development of DKD

Many patients with T1DM and most with T2DM do not follow the classic course of DKD, which involves progressive hyperfiltration, starting with albuminuria, followed by proteinuria and progressive kidney function decline, eventually leading to ESKD [35]. In the past decade this concept has been challenged as evidence suggests that DKD in the current era presents more heterogeneously, owing to an increasingly routine use of renin–angiotensin–aldosterone system (RAAS) blockers. Many patients with diabetes present with CKD without albuminuria [39,40]. Furthermore, regression of albuminuria has been observed in diabetes, indicating that elevated urinary albumin excretion does not imply inexorably progressive nephropathy [16,40]. The UKPDS showed that after 15 years of follow-up, of the 28% who developed an eGFR below 60 mL/min/1.73 m^2, 51% did not have preceding albuminuria [16]. The Diabetes Interventions and Complications Study Group showed that 11% of T1DM patients developed an eGFR below 60 mL/min/1.73 m^2 after 14 years of follow-up, of whom 24% had no prior albuminuria [41]. These findings are in line with a study in the US showing a decline of the prevalence of albuminuria in T2DM from 21% in 1988–1994 to 16% in 2009–2014, despite an increasing prevalence of CKD stage 3–5 [42].

7. Kidney Biopsy: Differentiating DN from Non-DN

Retrospective cohort studies of T2DM patients in whom kidney biopsies were performed showed that it is possible to clinically differentiate DN from non-DN. In patients with DN, the onset of proteinuria and progression of kidney function decline was more often gradual, with a duration of DM > 10 years, and urinalysis showed a bland sediment and retinopathy. In contrast, the onset or proteinuria and progression of CKD in non-DN was more often rapid, with a duration of DM < 5 years, urinalysis showed an active sediment, and retinopathy was absent [8].

Although burdensome, a kidney biopsy provides a more specific and better risk stratification of DKD than the recommended routine laboratory measurements of urine ACR and eGFR. A meta-analysis of 48 kidney biopsy studies including almost 5000 patients with T1DM or T2DM from countries in Asia, Europe, North America, and Africa showed a wide range of different kidney diseases [22]. The prevalence in all patients of DN varied across studies from 7–94%, non-DN 3–83%, and mixed lesions were present in about 4–6%, mainly with IgA nephropathy.

Additionally, DN in T2DM is likely when diabetes is present longer than 10 years, and there is proliferative retinopathy and progressive CKD shown by increased albuminuria with declining eGFR. Of these patients, about 17–33% may also have non-DN lesions [43]. In patients with T1DM particularly, proliferative retinopathy and diabetes duration > 5 years may point to DN, whereas albuminuria is not always present [44].

8. Screening and Risk Factors for DKD

Annually screening for DKD is recommended from the time of diagnosis of T2DM and 5 years after the onset of T1DM [45]. Identifying risk factors for CKD in patients with diabetes is important for targeted prevention or to slow the progression of CKD. There are non-modifiable and modifiable risk factors of DKD. Non-modifiable risk factors are as follows: genetic factors, male sex, older age, onset of diabetes between 5–15 years, family history of DMT2 or DKD, insulin resistance, and ethnicity (e.g., Black, Hispanic, American Indian, Asian). Modifiable risk factors include the following: obesity, metabolic syndrome, poor glycemic control, hypertension, AKI, smoking of cigarettes, dyslipidemia, a sedentary lifestyle, high salt intake, and low birth weight [18,22,30,31,35,46–48].

In the US, the prevalence of patients who are aware they have CKD, among those who actually have CKD, varies between 6% in Hispanics, 8% in white to 12% in Black individuals. The percentage of patients with diabetes who are aware that they have CKD increases with worsening kidney function, from 3% for those with an eGFR > 90 mL/min/1.73 m^2 to 53% for an eGFR 15–29 mL/min/1.73 m^2 [49]. Awareness of CKD in patients with diabetes is important to improve clinical outcomes. For example, the population-based approach in American Indians and Alaskan Natives, known to have a high prevalence of diabetes, showed a 53% reduction in ESKD between 2000 and 2016 by means of targeted CKD management for patients with diabetes in primary care [50]. Therefore, screening and diagnosis of DKD are important to initiate therapy and prevent or postpone complications.

9. Treatment of DKD

Consistent with the multifactorial etiology of DKD, clinical guidelines recommend targeting multiple risk factors simultaneously to improve kidney outcome in T2DM. These strategies include lifestyle interventions, such as a healthy diet and physical exercise to achieve weight loss, smoking cessation, and pharmacological management of glucose, blood pressure, and lipids [51–53]. With respect to blood pressure control, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are specifically advised, since these RAAS inhibitors have demonstrated renoprotective effects beyond their ability to lower blood pressure. Recent clinical trials with new-generation glucose-lowering drug classes, the sodium-glucose cotransporter-2 (sGLT2) inhibitors, and agents that target the incretin pathway have been shown to improve kidney outcomes in patients with T2DM [54]. Combined with this, therapeutic advances have lowered the average yearly kidney function decline in patients with DKD by about 65% since 1980 [55].

Evidently, the remaining risk of DKD progression and cardiovascular morbidity remains high. Treatment with steroidal mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, reduces albuminuria, slows kidney function decline, and has anti-inflammatory and anti-fibrotic effects in DKD [56]. However, the risk of hyperkalemia and the hormonal side effects related to these drugs has limited their use. Non-steroidal MRAs are a new class of drugs developed to address the medical need for more effective treatment to protect the kidney and the heart in patients with DKD, with

a safer profile and lower risk of hyperkalemia. The tissue distribution of non-steroidal MRAs is balanced between the kidney and the heart, whereas steroidal MRAs more prominently accumulate in the kidney. The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial showed that patients with DKD treated with finerenone, a non-steroidal MRA, had a lower risk of CKD progression and cardiovascular events compared with patients on placebo, when added to an optimal treatment with RAAS inhibitors. The incidence of hyperkalemia was low [57]. Whether combining non-steroidal MRAs with sGLT2 inhibitors may provide additive cardio-renal protective effects remains to be studied.

10. COVID-19 Pandemic and DKD

Unfortunately, the COVID-19 lockdown measures had a negative impact on lifestyle behaviors [58]. In most countries, lockdown measures of varying duration and stringency included working at home, the closing of schools and sports clubs, and social distancing measures. Population-based studies across the world showed a decrease in physical activity and an increase in screen time and sedentary behaviour [58,59]. In addition, food choices changed, with an increased intake of unhealthy food categories [58]. People with obesity or T2DM are thought to be at even larger risk for lifestyle changes and weight gain due to lockdown measures [58].

In patients with COVID-19, those with obesity or T2DM had a 2- to 3-fold increased risk of hospitalization, ICU admission, and death [60,61]. Obesity and T2DM are associated with low-grade systemic inflammation, likely hampering an optimal and timely response by the local and systemic immune system to an infection, such as COVID-19 [62]. Another potential mechanism through which obesity and T2DM may lead to a worse COVID-19 outcome is the high ACE2 receptor expression, the functional receptor for SARS-CoV-2. The ACE2 receptor is upregulated in adipocytes of patients with obesity and diabetes, which turns adipose tissue into a potential target and viral reservoir [63,64]. Finally, COVID-19 infection may induce a prothrombotic state, as reflected by a significant increase in fibrinogen and D-dimer levels, and high rates of severe pulmonary embolism that forecast a poor prognosis [65]. The latter could provide another link between obesity and worse outcome in COVID-19, since obesity and T2DM are independently associated with both arterial and venous thrombotic events [66].

Because of the high ACE2 receptor expression on kidney tubular epithelial cells, SARS-CoV2 can infect these cells and replicate [60,61]. The viral protein expression on the surface of the kidney tubular epithelial cells (e.g., the spike) is recognized by T-cells, resulting in cell death, especially in a hyperglycemic condition, such as diabetes [67]. A recent meta-analysis showed that among hospitalized COVID-19 patients, the prevalence of AKI was 28%, and 9% needed KRT. Among those admitted to the ICU, 46% had AKI and 19% needed KRT [61]. In a post-mortem analysis of a cohort of 85 patients who died from COVID-19, of whom 51% had a history of diabetes, 85% had AKI, and 27% had diabetic nephropathy [68].

Fortunately, the three COVID-19 vaccines approved in 2021 by the European Medical Association and US Food and Drug Administration have shown high efficacy in reducing the occurrence of severe COVID-19 disease [69–71].

11. Future Perspectives

Because DKD is a multifactorial, heterogenous disease, not all patients will benefit from the same treatment. Variation between patients regarding the underlying pathophysiology results in a wide diversity of individual treatment responses. Future studies will combine new therapies to continue to slow the progression of DKD.

The development and progression of DKD is influenced by both genetic and environmental factors, including nutritional factors. Ideally, there should be a multi-directional approach that includes individual lifestyle-based prevention, regulatory changes for the

food industry by the government, and urban planning that takes into account a more healthful environment.

Unfortunately, many diabetic patients suffer from severe complications following blood glucose normalization. This phenomenon is called 'metabolic memory'. It is hypothesized that the prior glucose exposure in target cells leads to persistent detrimental effects long after glycemic control has been established [72]. Additionally, exposure to hyperglycemia early in life, especially in utero, increases the risk of T2DM in adults. There is growing evidence that persistent hyperglycemia causes a 'metabolic memory' through epigenetic modifications in DKD, changing the expression of genes [73]. Genetic interventions, including CRISPR–Cas editing, might lead to the development of new therapeutic options for DKD, erasing the 'metabolic memory'.

12. Conclusions

In summary, DKD has emerged as a major consequence of the global diabetes pandemic, largely driven by obesity. Therefore, diabetes and obesity prevention are the cornerstones of reducing the burden of DKD. Identification of DKD depends on screening for increased albuminuria and low kidney function.

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