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"Kidney Disease and Diabetic Patients"

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ABSTRACT

Diabetes mellitus has become an epidemic on a global scale. One major cause of this is the increasing prevalence of type 2 diabetic mellitus (T2DM). As of 2021, 537 million individuals, or 11% of the global population, were diabetic. A projected 783 million, or 12% of the total population, will fall into that category by the year 2045. The obesity pandemic, which is driven by increased consumption of processed foods, decreased physical activity, and prolonged sitting, is directly responsible for the increasing number of individuals diagnosed with type 2 diabetes. With the rise of urban centres and advanced technologies, the so-called "Western lifestyle" is associated. Diabetic kidney disease (DKD) refers to patients who have diabetes and have chronic renal disease. As a result of diabetes, it is one of the major complications that might develop over time. In the long run, DKD will affect 20–50% of patients with T2DM. Around the world, DKD accounts for half of all cases of chronic kidney disease and end-stage kidney disease. Also, DKD reduces quality of life and is associated with an increased risk of cardiovascular disease and mortality. Get up-to-date details on DKD's prevalence, causes, and diagnostic criteria from this study.

KEYWORDS: chronic kidney disease; diabetes mellitus; epidemiology; end-stage kidney disease.

المستخلص:

لقد أصبح داء السكري وباءً على نطاق عالمي. أحد الأسباب الرئيسية لذلك هو الانتشار المتزايد لمرض السكري من النوع 2 (T2DM). اعتبارًا من عام 2021، كان هناك 537 مليون فرد، أو 11% من سكان العالم، مصابين بالسكري. ومن المتوقع أن يندرج 783 مليون نسمة، أو 12% من إجمالي السكان، تحت هذه الفئة بحلول عام 2045. ويعد جائحة السمنة، الناجم عن زيادة استهلاك الأطعمة المصنعة، وانخفاض النشاط البدني، والجلوس لفترات طويلة، مسؤولا بشكل مباشر عن تفاقم المشكلة. عدد متزايد من الأفراد الذين تم تشخيص إصابتهم بمرض السكري من النوع 2. ومع ظهور المراكز الحضرية والتقنيات المتقدمة، يرتبط ما يسمى بـ "نمط الحياة الغربي". يشير مرض الكلى السكري (DKD) إلى المرضى الذين يعانون من مرض السكري والذين يعانون من مرض كلوي مزمن. نتيجة لمرض السكري، فهو أحد المضاعفات الرئيسية التي قد تتطور مع مرور الوقت. على المدى الطويل، سوف يؤثر DKD على 20–50٪ من مرضى T2DM. في جميع أنحاء العالم، يمثل مرض الكلى المزمن (DKD) نصف حالات أمراض الكلى المزمنة وأمراض الكلى في المرحلة النهائية. كما أن DKD يقلل من جودة الحياة ويرتبط بزيادة خطر الإصابة بأمراض القلب والأوعية الدموية والوفيات. احصل على تفاصيل محدثة حول انتشار DKD وأسبابه ومعايير التشخيص من هذه الدراسة.

1. INTRODUCTION:

Diabetes often leads to kidney disease (DKD), which lasts for a long time. DKD is the main cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) around the world, making up half of all cases (Kianmehr, H., et al.2022). A person with diabetes is usually said to have DKD if they have chronic kidney disease (CKD) and their albumin-to-creatine ratio (ACR) is at least 30 mg/g or their estimated glomerular filtration rate (eGFR) is less than 60 mL/min/1.73 m2 for at least three months (Hovind, P., et al.2003). When GFR goes down and albuminuria goes up, the risk of bad events like death and ESKD goes up. People with a GFR of less than 30 mL/min/1.73 m2 (stages 4–5) of CKD are at the highest risk for all types of albuminuria (Hovind, P., et al.2003). Diabetes is a big problem for public health and not just in poor countries (Afkarian, M., et al.2013; Groop, P. H. et al.2009). About 90% of people with diabetes around the world have type 2 diabetes mellitus (T2DM) (Groop, P. H., et al.2009; Zimmet, P. Z., et al.2014). In the last 20 years, the number of people with diabetes has more than doubled. This is because of the obesity problem, which has caused the number of obese people to almost triple since 1975 (Thomas, M. C., et al.2015; Carrero, J. J., et al.2018). Every country has seen a rise in the number of overweight or obese children, teens, and adults during this time (Carrero, J. J., et al.2018). Long-term energy imbalance, where more calories are eaten than are burned, leads to obesity. This usually happens when people eat more processed foods, do less physical exercise, and stay in bed more often. This so-called "Western way of life" has grown along with the world's move toward cities and better technology. T2DM is becoming more common because the world's population is getting older and because better health care is lowering the death rate of diabetics (Groop, P. H., et al.2009). At this point, more than one-third of people will get diabetes at some point in their lives. People with diabetes will have a nearly twofold higher chance of death from any cause than people who don't have diabetes, and they will also live about six to seven years less than the rest of the population (Liyanage, T. et al.2015).

It is thought that 11% of people aged 20 to 79 around the world had diabetes in 2021. This number will rise to 12% by 2045 (Groop, P. H., et.al.2009). In 2021, the rate of diabetes was the same for both men and women. It slowly rose with age and was higher in cities (12%) than in rural areas (8%). It was also higher in high-income (11%) and middle-income (11%) countries than in low-income countries (6%). It is interesting to note that about 6% of people over 20 live in a country with a low income. People of certain ethnicities, especially native people in the US, Australia, and New Zealand, have the highest rates of T2DM (Groop, P. H., et al.2009). Table 1 shows that more than 80% of people with diabetes live in countries with low or middle income. China has 92 million people with diabetes, which is almost 10% of all adults. This is more than any other country. From 2021 to 2045, the relative rise in frequency is most likely to happen in middle-income countries, especially in Africa. Last but not least, T2DM is changing from a disease that mostly affects middle-aged and older people to one that is becoming more common in younger people, such as teens, kids, and young adults [Zimmet, P. Z., et al.2014; Fiorentino, M., et al.2017).

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.

Diabetes can damage small blood vessels, which can lead to damage in the kidneys. People with diabetes are twice as likely to get CKD as people who don't have diabetes. People with diabetes are less likely to get CKD now that they are better managed, but the number of people with CKD is still rising around the world because people are living longer and more people are getting both T2DM and T1DM (Parving, H. H. et al.2006; Thomas, M. C., et al.2006). Most of the extra deaths linked to T1DM and T2DM are in people with CKD (de Boer, I. H. et al.2011; Thomas, M. C., et al.2016). As a result, it is very important to keep people with diabetes from getting CKD and to find them early if they do.

Problem statement:

One of the most significant complications associated with diabetes is diabetic kidney disease (DKD), a chronic renal condition that affects a substantial proportion of diabetic patients over time. DKD poses a considerable burden on healthcare systems globally, accounting for a significant portion of cases of chronic kidney disease and end-stage kidney disease. Moreover, DKD significantly diminishes patients' quality of life and escalates the risk of cardiovascular complications and mortality. Despite its profound impact on public health, DKD remains inadequately addressed, with limited awareness, prevention, and management strategies in place. Therefore, there is an urgent need for comprehensive research and interventions targeting the prevention, early detection, and management of DKD among diabetic patients. By addressing this pressing issue, healthcare providers can mitigate the adverse outcomes associated with DKD and improve the overall well-being of diabetic individuals.

Research objectives:

- To determine the prevalence of diabetic kidney disease (DKD) among patients diagnosed with type 2 diabetes mellitus (T2DM) globally.
- To review and analyze the diagnostic criteria utilized for identifying DKD in diabetic patients.
- To propose preventive strategies aimed at reducing the incidence or delaying the onset of DKD in diabetic patients.

Epidemiology of Diabetic Kidney Disease

Nearly half of people with T2DM and one-third of people with T1DM get diabetic kidney disease at some point in their lives. This is one of the most common, annoying, and pricey long-term effects of diabetes (Groop, P. H., et al.2009**)**. About 20% of people with T2DM will have an eGFR of less than 60 mL/min/1.73 m2, and another 30% to 50% will have high albumin levels in their urine. After a mean of 15 years of follow-up, the UK Prospective Diabetes Study found that 28% of people had an eGFR of less than 60 mL/min/1.73 m2 and 28% had albuminuria (Thomas, B. 2019). If you get T2DM between the ages of 15 and 24, you have a nearly 100% chance of having mild albuminuria throughout your life (Vart, P., et al.2020). About 8% of people with T2DM get albuminuria every year, while only 2% to 3% of people with T1DM do. It happens to about 2% to 4% of people with diabetes every year, no matter what kind of diabetes they have (Bikbov, B., et al.2020).

It is not possible to say for sure what number of patients have CKD caused by diabetes because people with diabetes may also have other causes of CKD and a kidney biopsy is not usually done to make the exact diagnosis.

Other conditions can lead to CKD, especially in people with T2DM. These include high blood pressure, cholesterol, obesity, intrarenal vascular disease, acute kidney injury (AKI), glomerular atherosclerosis, or kidney loss that comes with getting older. Most likely, the lower rate of CKD in people with T1DM is because they are younger, healthy, and have fewer other health problems than people with T2DM. Most likely, CKD in people with T1DM is a better reflection of DKD than CKD with a mixed cause in people with T2DM (Bash, L. D., et al.2009).

Burden of Diabetic Kidney Disease across Continents

About 9% of the world's population, or 700 million people, have CKD, and about 4 million of them need kidney replacement therapy (KRT) (Saran, R., et al.2018). Women are more likely than men to have CKD, especially in its early stages. However, men are more likely to get ESKD, which needs KRT (McCullough, K. P., et al.2019). In

some countries, only 16% of people with ESKD can get KRT to help their condition. More than 2.3 million deaths around the world in 2010 were linked to not having access to KRT (Brück, K., et al.2016). Most of the treatment gaps were found in low-income countries, especially in Asia and Africa, where 1.9 and 0.4 million people needed KRT but were not getting it. The number of people with KRT is expected to more than double to 5.4 million by 2030. Most of the growth will happen in Asia, where the number will rise from 1 million to 2 million (Brück, K., et al.2016).

Different countries around the world have different rates of CKD in people with T2DM. In China, only 27% of people have CKD, while in Tanzania, 84% do (de Boer, I., et al.2011; Stanifer, J. W., et al.2014; Mogensen, C. E. 1994). More than 30 countries in Europe, North America, Asia, and Australia were used in a systematic review. The results showed that about 8% of people with T2DM and 2–3% of people with T1DM had albuminuria every year, and about 2–4% of people with both types of diabetes had an eGFR of less than 60 mL/min/1.73 m2 (Bash, L. D., et al.2009; Brenner, B. M., et al.1996). Like the number of people with T2DM, the number of people with DKD is projected to rise around the world.
From 1999 to 2004, 25% of people with CKD stage 3 or 4 in the US had diabetes. From 2011 to 2014, that number rose to 25%, according to the National Health and Nutrition Examination Survey (NHANES) (Molitch, M. E. et al.2019; Thomas, M. C., et al.2009). In 2017, about 25 out of every 1000 people with diabetes in the US and 15 out of every 1000 people around the world had CKD based on their age (Molitch, M. E. et al.2019; Thomas, M. C., et al.2009). One in seven US adults aged 20 and up has CKD right now, and one in three of these people also has diabetes. 19 out of every 1000 person-years in a group study with diabetes showed that they had CKD stage 3 or 5 after 9 years of follow-up (Perkins, B. A. et al.2003). In the US, the number of cases of ESKD caused by DKD has stayed the same over the past few years, but rates are going up for high-risk groups like African Americans, Native Americans, and Hispanics because they are more likely to have high blood pressure, obesity, and DMT2 (Molitch, M. E., et al.2010; Afkarian, M., et al.2016). In Europe, people with T2DM are 2–5 times more likely to have CKD than people without T2DM (Lamacchia, O., et al.2018). About 10 to 13 percent of people in Sub-Saharan Africa are thought to have CKD (Kidney Disease Outcomes Quality Initiative. 2007). The lack of preventive care in low-income countries like Uganda makes them home to a lot of people with severe CKD. There is no state health insurance, and most of the costs of treating long-term illnesses are too high for patients to afford. There are between 2 and 7 percent of people in Uganda who have CKD. Out of all the people who are admitted with CKD, 16% have diabetes and 90% have high blood pressure. The case death rate for people with CKD is 21%, but it's 51% for people with ESKD.

Diagnosis DKD versus Diabetic Nephropathy

The international group Kidney Disease Improving Global Outcomes (KDIGO) says that DKD is a clinical diagnosis that means a person with diabetes has CKD, while DN is only used for the histologic diagnosis of changes seen in the glomeruli on biopsy (Afkarian, M., et al.2013). In DN, the glomerular basement membrane gets thicker, the mesangial expands with or without nodular sclerosis (known as a Kimmelstiel–Wilson lesion), podocytes die, and endothelial breakdown happens, which leads to the loss of nephrons. DN happens when apoptosis and autophagy, two processes needed for cell cleaning, don't work right in people with diabetes. In experiments with nephritis models, it was shown that neutrophils dying causes the glomerular filtration barrier to break down, which leads to kidney failure (Harjutsalo, V., & Groop, P. H. 2014). Loss of kidney tubules can also be caused by protein loss in the main urine and a large protein load in the proximal tubule. The wide range of pathologic traits of DN is due to the fact that the disease shows up in different ways and progresses in different ways (Saran, R., et al.2018). People with diabetes don't usually get kidney biopsies because they don't have many treatment choices. Because of this, databases give the diagnosis of DKD when both CKD and diabetes are present without a diagnostic biopsy.

The way DKD progresses is different because it has different causes (Saran, R., et al.2018). These people with diabetes might also have CKD that isn't linked to their diabetes, on top of diabetic nephropathy (DN) or a specific kidney disease, like glomerulonephritis, minimal change disease, or primary or secondary forms of focal segmental glomerulosclerosis.

Pathophysiological Mechanism of DKD

People who have T1DM are most likely to get DKD because of chronic hyperglycemia and renal hyperfiltration. On the other hand, DKD in people with T2DM is more complicated because a group of cardiovascular risk factors, including obesity, high blood pressure, and cholesterol, may also play a role in the development of microvascular damage. People think that hyperfiltration is a sign of higher intraglomerular capillary pressure, and it plays a big part in how DKD starts and gets worse (Esmeijer, K., et al.2018). Glomerular hyperfiltration, also known as supraphysiologic rise in GFR, is when GFR goes from 120 to 180 mL/min/173 m2 or when it goes up by more than two standard deviations above the mean GFR in healthy people the same age. It happens between one and five years after T1DM and is found in 70% of people with T1DM and 50% of people with T2DM. It has long been thought that glomerular hyperfiltration makes nephrons more likely to get damaged in a way that can't be fixed, which in turn helps kidney disease start and get worse in people with diabetes (Esmeijer, K., et al.2019; Hoogeveen, E. K., et al.2017). The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study shows new information that makes people wonder how important hyperfiltration is in the progression of DKD (Burrows, N. R. et al.2020).

2. DEVELOPMENT OF DKD

A lot of people with T1DM and most people with T2DM don't get DKD the way it usually does, which is progressive hyperfiltration that starts with albuminuria and then proteinuria and a gradual loss of kidney function that ends in ESKD (Esmeijer, K., et al.2018). In the last ten years, this idea has been questioned because more and more people are using renin– angiotensin–aldosterone system (RAAS) blockers, which shows that DKD looks different these days. A lot of people with diabetes have CKD without having albuminuria (Doshi, S. M., & Friedman, A. N. 2017; Stevens, P. E., et al.2013). Also, albuminuria has gone down in people with diabetes, showing that high albumin levels in the urine do not always mean that nephropathy will get worse (Thomas, B. 2019; Stevens, P. E., et al.2013). Following people for 15 years, the UKPDS found that 51% of the 28% who got an eGFR below 60 mL/min/1.73 m2 did not have albuminuria before (Thomas, B. 2019). A study by the Diabetes Interventions and Complications Study Group found that after 14 years of follow-up, 11% of T1DM patients had an eGFR below 60 mL/min/1.73 m2, and 24% of those patients had never had albuminuria before (Eckardt, K. U., et al.2018). These results are similar to those of a study done in the US that found the number of people with T2DM who had albuminuria dropped from 21% in 1988–1994 to 16% in 2009–2014, even though the number of people with CKD stage 3–5 rose (Bilo, H., et al.2015).

Kidney Biopsy: Differentiating DN from Non-DN

It is possible to tell the difference between DN and non- DN based on clinical signs in groups of T2DM patients who had kidney biopsies. Protein in the urine and worsening kidney function usually happened slowly in people with DN who had had the disease for more than 10 years. A urinalysis showed bland sediment and blindness. On the other hand, proteinuria and CKD development were more common in people who did not have DN. They usually had DM for less than 5 years, urinalysis showed active sediment, and retinopathy was not present (Bikbov, B., et al.2020).

A kidney biopsy is more accurate and useful for figuring out the risk of DKD than the usual urine ACR and eGFR measures, even though they are more time-consuming. A big study that looked at 48 kidney tissue studies with almost 5,000 people with T1DM or T2DM from Asia, Europe, North America, and Africa found a lot of different kidney diseases (Stanifer, J. W., et al.2014). Different studies found that between 7 and 94% of all patients with DN had non-DN lesions and between 3 and 83% had mixed lesions, mostly with IgA nephropathy.

There is also a high chance of DN in T2DM if the person has had it for more than 10 years, along with proliferative retinopathy and worsening CKD, which is shown by higher albuminuria and falling eGFR. About 17 to 33% of these people may also have lesions that aren't DN (Muskiet, M. H., et al.2019). Proliferative retinopathy and having had diabetes for more than 5 years may be signs of DN in people with T1DM, but albuminuria is not always present (Barrera-Chimal, J.et al.2022).

Screening and Risk Factors for DKD

When someone is diagnosed with T2DM or 5 years after they were first diagnosed with T1DM, they should get a DKD test once a year (Agarwal, R., et al.2021). Finding out what makes people with diabetes more likely to get CKD is important for preventing it or slowing its development. There are risk factors for DKD that can't be changed and risk factors that can. Genetics, being male, being older, getting diabetes between the ages of 5 and 15, having a family history of DMT2 or DKD, insulin resistance, and race (e.g., Black, Hispanic, American Indian, Asian). Some risk factors that can be changed are being overweight, having metabolic syndrome, not being able to control blood sugar well, having high blood pressure, AKI, smoking cigarettes, having cholesterol, not being active, eating a lot of salt, and having a low birth weight (Bash, L. D. et al.2009; Stanifer, J. W., et al.2014; Molitch, M. E.,et al.2010; Afkarian, M., et al.2016; Esmeijer, K. et al.2018; Bakris, G. L.,et al.2020; Hoogeveen, M. J.,et al.2022).
In the US, only 6% of people with CKD are aware they have it, compared to 8% of white people and 12% of black people. The number of diabetics who know they have CKD goes up as their kidney function gets worse. It goes from 3% for people whose eGFR is >90 mL/min/1.73 m2 to 53% for people whose eGFR is 15–29 mL/min/1.73 m2 (Morrow, A. J., et al.2022). To improve clinical results, it is important to know that people with diabetes can develop CKD. For instance, the population- based approach found that between 2000 and 2016, ESKD dropped by 53% among American Indians and Alaskan Natives, who have a high rate of diabetes. This was achieved by managing diabetes patients with CKD more effectively in primary care (Silver, S. A., et al.2021). So, screening for and diagnosing DKD are necessary to start treatment and stop or put off consequences.

Treatment of DKD

Because DKD is caused by a lot of different things, clinical standards say that to improve kidney outcomes in T2DM, you should target a lot of different risk factors at the same time. Some of these tactics are changing your lifestyle by eating well and exercising to lose weight, giving up smoking, and taking medicine to control your glucose, blood pressure, and lipids (Lengton, R., et al.2022; Braun, F., et al.2020). Angiotensin- converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are especially recommended for controlling blood pressure because they have been shown to protect the kidneys in addition to lowering blood pressure. In recent clinical studies, new types of drugs that lower glucose levels, including sGLT2 inhibitors and drugs that target the incretin pathway, have been shown to improve the kidney health of people with T2DM (Martens, E. S., et al.2022). On top of that, improvements in treatments have cut the average yearly loss of kidney function in people with DKD by about 65% since 1980 (Bergner, D. W., & Goldberger, J. J. 2010).
It's clear that the chance of DKD getting worse and heart disease still remains high. Using steroidal mineralocorticoid receptor antagonists (MRAs), like eplerenone and spironolactone, lowers albuminuria, slows down the loss of kidney function, and fights inflammation and scar tissue in people with DKD (Maremonti, F., et al.2022). But these drugs aren't used as much as they could be because they can cause hyperkalemia and hormonal side effects. Non- steroidal MRAs are a new group of drugs that were created to meet the medical need for better ways to protect the kidneys and heart in people with DKD, while also being safer and having a lower risk of hyperkalemia. Steroid MRAs tend to build up in the kidney more than any other organ. Non-steroidal MRAs are evenly distributed between the heart and the kidney. Patients with diabetic kidney disease who were given finerenone, a non-steroidal MRA, had a lower risk of CKD progression and cardiovascular events compared to patients who were given a placebo. This was seen in the FIDELIO-DKD trial, which was part of the best treatment with RAAS inhibitors. Hyperkalemia didn't happen very often (Rivero, J., et al.2021). It needs to be studied if adding non-steroidal MRAs to sGLT2 inhibitors might make the benefits of heart and kidney protection even stronger.

COVID-19 Pandemic and DKD

Unfortunately, the COVID-19 lockdown steps made people change the way they lived (Polack, F. P., et al.2020). In most countries, lockdown measures that ranged in length and severity included working from home, stopping schools and sports clubs, and keeping people from talking to each other. Population-based studies from around the world found that people were less active and more likely to spend time in front of a screen or do nothing (Polack, F. P., et al.2020; Baden, L. R., et al.2021). In addition, people's food choices changed, and they ate more bad foods (Polack, F. P., et al.2020). With lockdown steps in place, people who are already overweight or have T2DM may be even more likely to change their lifestyle and gain weight (Polack, F. P., et al.2020).

More than twice as many people with COVID-19 who were overweight or had T2DM ended up in the hospital, the intensive care unit, or died (Sadoff, J., et al.2021; Nathan, D. M., & DCCT/Edic Research Group. 2014). Obesity and T2DM are linked to low-grade systemic inflammation, which may make it harder for the immune system to respond properly and quickly to an infection like COVID-19 (Kato, M., & Natarajan, R. 2019). A high level of ACE2 receptor expression, which is the functional receptor for SARS-CoV-2, is another way that fat and T2DM may make COVID-19 outcomes worse. People who are overweight or have diabetes have higher levels of the ACE2 receptor in adipocytes. This makes adipose tissue a possible target and viral repository (Polack, F. P., et al.2020; Baden, L. R., et al.2021). Lastly, COVID-19 infection may cause a prothrombotic state, which is shown by a large rise in fibrinogen and D-dimer levels, as well as a high risk of severe pulmonary embolisms that indicate a poor outlook (Kato, M., & Natarajan, R. 2019). This could be another link between being overweight and having a worse result in COVID-19, since both overweight and T2DM are linked to both arterial and venous thrombotic events. SARS-CoV2 can attack and multiply in kidney tubular epithelial cells because they have a lot of ACE2 receptors (Sadoff, J., et al.2021; Nathan, D. M., & DCCT/Edic Research Group. 2014). T-cells spot the spike-shaped viral protein on the surface of kidney tubular epithelial cells and kill the cells, especially in people with high blood sugar, like those with diabetes. A new meta-analysis found that 28% of COVID-19 patients who were hospitalized had AKI and 9% needed KRT. Out of the people who were taken to the ICU, 46% had AKI and 19% needed KRT (Nathan, D. M., & DCCT/Edic Research Group. 2014). A study of 85 people who died from COVID-19 after they had died showed that 51% had a history of diabetes, 85% had AKI, and 27% had diabetic nephropathy (Polack, F. P., et al.2020).
Luckily, the three COVID-19 vaccines that were approved by the European Medical Association and the US Food and Drug Administration in 2021 have worked very well to lower the number of people who get serious COVID-19 disease.

Future Perspectives

Different treatments will not work for all people with DKD because it is a complex disease with many causes. Different people have different underlying pathophysiologies, which means that their treatment responses are also very different. In the future, researchers will mix new therapies to find ways to slow the progression of DKD even more.

Both genetic and environmental factors, such as food factors, can affect how DKD develops and gets worse. In an ideal world, there would be a multifaceted approach that includes people changing their lifestyles to avoid getting sick, the government making changes to the rules for the food business, and urban planning that takes a healthier environment into account.
Unfortunately, many diabetics have serious problems after their blood sugar levels return to normal. "Metabolic memory" is the name for this effect. It is thought that exposing target cells to glucose before glycemic control is set up has harmful effects that last for a long time. Also, people are more likely to get T2DM if they were exposed to high blood sugar early in life, especially while they were still in the womb. More and more data shows that long-term hyperglycemia creates a "metabolic memory" in DKD by changing the expression of genes through epigenetic changes (Rivero, J., et al.2021). By erasing the "metabolic memory," genetic methods like CRISPR–Cas editing could lead to the creation of new treatments for DKD.

CONCLUSIONS

To summarise, diabetes mellitus has emerged as a significant consequence of the worldwide diabetes epidemic, which is primarily brought on by being overweight. Therefore, the most significant things that can be done to reduce the burden of diabetes and cardiovascular disease are to prevent diabetes and obesity. When diagnosing diabetic kidney disease (DKD), it is necessary to search for excessive protein levels in the urine as well as poor kidney function.

REFERENCES

1. Kianmehr, H., Zhang, P., Luo, J., Guo, J., Pavkov, M. E., Bullard, K. M., ... & Shao, H. (2022). Potential gains in life expectancy associated with achieving treatment goals in US adults with type 2 diabetes. *JAMA Network Open*, *5*(4), e227705-e227705.
2. Hovind, P., Tarnow, L., Rossing, K., Rossing, P., Eising, S., Larsen, N., ... & Parving, H. H. (2003). Decreasing incidence of severe diabetic microangiopathy in type 1 diabetes. Diabetes care, 26(4), 1258-1264.
3. Afkarian, M., Sachs, M. C., Kestenbaum, B., Hirsch, I. B., Tuttle, K. R., Himmelfarb, J., & de Boer, I. H. (2013). Kidney disease and increased mortality risk in type 2 diabetes. Journal of the American Society of Nephrology: JASN, 24(2), 302.
4. Groop, P. H., Thomas, M. C., Moran, J. L., Waden, J., Thorn, L. M., Mäkinen, V. P., ... & Forsblom, C. (2009). The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. Diabetes, 58(7), 1651-1658.
5. Retnakaran, R., Cull, C. A., Thorne, K. I., Adler, A. I., Holman, R. R., & UKPDS Study Group. (2006). Risk factors for renal dysfunction in type 2 diabetes: UK Prospective Diabetes Study 74. diabetes, 55(6), 1832-1839.
6. Zimmet, P. Z., Magliano, D. J., Herman, W. H., & Shaw, J. E. (2014). Diabetes: a 21st century challenge. The lancet Diabetes & endocrinology, 2(1), 56-64.
7. Thomas, M. C., Brownlee, M., Susztak, K., Sharma, K., Jandeleit-Dahm, K. A., Zoungas, S., ... & Cooper, M. E. (2015). Diabetic kidney disease. Nature reviews Disease primers, 1(1), 1-20.
8. Bikbov, B., Purcell, C. A., Levey, A. S., Smith, M., Abdoli, A., Abebe, M., ... & Owolabi, M. O. (2020). Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The lancet, 395(10225), 709-733.
9. Carrero, J. J., Hecking, M., Chesnaye, N. C., & Jager, K. J. (2018). Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. Nature Reviews Nephrology, 14(3), 151-164.
10. Liyanage, T., Ninomiya, T., Jha, V., Neal, B., Patrice, H. M., Okpechi, I., ... & Perkovic, V. (2015). Worldwide access to treatment for end-stage kidney disease: a systematic review. The Lancet, 385(9981), 1975-1982.
11. Fiorentino, M., Bolignano, D., Tesar, V., Pisano, A., Biesen, W. V., Tripepi, G., ... & ERA-EDTA Immunonephrology Working Group. (2017). Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies. Nephrology Dialysis Transplantation, 32(1), 97-110.
12. Parving, H. H., Lewis, J. B., Ravid, M., Remuzzi, G., & Hunsicker, L. G. (2006). Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. Kidney international, 69(11), 2057-2063.
13. Thomas, M. C., Weekes, A. J., Broadley, O. J., Cooper, M. E., & Mathew, T. H. (2006). The burden of chronic kidney disease in Australian patients with type 2 diabetes (the NEFRON study). Medical journal of Australia, 185(3), 140-144.
14. de Boer, I. H., Rue, T. C., Hall, Y. N., Heagerty, P. J., Weiss, N. S., & Himmelfarb, J. (2011). Temporal trends in the prevalence of diabetic kidney disease in the United States. Jama, 305(24), 2532-2539.
15. Thomas, M. C., Cooper, M. E., & Zimmet, P. (2016). Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nature Reviews Nephrology, 12(2), 73-81.
16. Thomas, B. (2019). The global burden of diabetic kidney disease: time trends and gender gaps. Current diabetes reports, 19, 1-7.
17. Vart, P., Powe, N. R., & McCulloch, C. E. (2020). Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. National trends in the prevalence of chronic kidney disease among racial/ethnic and socioeconomic status groups, 1988-2016 (vol 3, e207932, 2020). JAMA NETWORK OPEN, 3(8).

18. Bash, L. D., Coresh, J., Köttgen, A., Parekh, R. S., Fulop, T., Wang, Y., & Astor, B. C. (2009). Defining incident chronic kidney disease in the research setting: The ARIC Study. American journal of epidemiology, 170(4), 414-424.

19. Saran, R., Robinson, B., Abbott, K. C., Agodoa, L. Y., Bhave, N., Bragg-Gresham, J., ... & Shahinian, V. (2018). US renal data system 2017 annual data report: epidemiology of kidney disease in the United States. American Journal of Kidney Diseases, 71(3), A7.

20. McCullough, K. P., Morgenstern, H., Saran, R., Herman, W. H., & Robinson, B. M. (2019). Projecting ESRD incidence and prevalence in the United States through 2030. Journal of the American Society of Nephrology: JASN, 30(1), 127.

21. Brück, K., Stel, V. S., Gambaro, G., Hallan, S., Völzke, H., Ärnlöv, J., ... & European CKD Burden Consortium. (2016). CKD prevalence varies across the European general population. Journal of the American Society of Nephrology, 27(7), 2135-2147.

22. Stanifer, J. W., Jing, B., Tolan, S., Helmke, N., Mukerjee, R., Naicker, S., & Patel, U. (2014). The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. The Lancet Global Health, 2(3), e174-e181.

23. Lin, T. A., Wu, V. C. C., & Wang, C. Y. (2019). Autophagy in chronic kidney diseases. Cells, 8(1), 61.

24. Tonneijck, L., Muskiet, M. H., Smits, M. M., Van Bommel, E. J., Heerspink, H. J., Van Raalte, D. H., & Joles, J. A. (2017). Glomerular hyperfiltration in diabetes: mechanisms, clinical significance, and treatment. Journal of the American Society of Nephrology: JASN, 28(4), 1023.

25. Mogensen, C. E. (1994). Glomerular hyperfiltration in human diabetes. Diabetes Care, 17(7), 770-775.

26. Brenner, B. M., Lawler, E. V., & Mackenzie, H. S. (1996). The hyperfiltration theory: a paradigm shift in nephrology. Kidney international, 49(6), 1774-1777.

27. Molitch, M. E., Gao, X., Bebu, I., de Boer, I. H., Lachin, J., Paterson, A., ... & Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. (2019). Early glomerular hyperfiltration and long-term kidney outcomes in type 1 diabetes: the DCCT/EDIC experience. Clinical journal of the American Society of Nephrology: CJASN, 14(6), 854.

28. Thomas, M. C., MacIsaac, R. J., Jerums, G., Weekes, A., Moran, J., Shaw, J. E., & Atkins, R. C. (2009). Nonalbuminuric renal impairment in type 2 diabetic patients and in the general population (national evaluation of the frequency of renal impairment cO-existing with NIDDM [NEFRON] 11). Diabetes care, 32(8), 1497-1502.

29. Perkins, B. A., Ficociello, L. H., Silva, K. H., Finkelstein, D. M., Warram, J. H., & Krolewski, A. S. (2003). Regression of microalbuminuria in type 1 diabetes. New England Journal of Medicine, 348(23), 2285-2293.

30. Molitch, M. E., Steffes, M., Sun, W., Rutledge, B., Cleary, P., De Boer, I. H., ... & Epidemiology of Diabetes Interventions and Complications (EDIC) Study Group. (2010). Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. Diabetes care, 33(7), 1536-1543.

31. Afkarian, M., Zelnick, L. R., Hall, Y. N., Heagerty, P. J., Tuttle, K., Weiss, N. S., & de Boer, I. H. (2016). Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. Jama, 316(6), 602-610.

32. Lamacchia, O., Viazzi, F., Fioretto, P., Mirijello, A., Giorda, C., Ceriello, A., ... & De Cosmo, S. (2018). Normoalbuminuric kidney impairment in patients with T1DM: insights from annals initiative. diabetology & metabolic syndrome, 10, 1-8.

33. Kidney Disease Outcomes Quality Initiative. (2007). KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. American Journal of Kidney Diseases, 49(2), S12-S154.

34. Harjutsalo, V., & Groop, P. H. (2014). Epidemiology and risk factors for diabetic kidney disease. Advances in chronic kidney disease, 21(3), 260-266.

35. Esmeijer, K., Geleijnse, J. M., Giltay, E. J., Stijnen, T., Dekker, F. W., de Fijter, J. W., ... & Hoogeveen, E. K. (2018). Body-fat indicators and kidney function decline in older post-myocardial infarction patients: The Alpha Omega Cohort Study. European journal of preventive cardiology, 25(1), 90-99.

36. Esmeijer, K., de Vries, A. P., Mook-Kanamori, D. O., de Fijter, J. W., Rosendaal, F. R., Rabelink, T. J., ... & Hoogeveen, E. K. (2019). Low birth weight and kidney function in middle-aged men and women: the Netherlands epidemiology of obesity study. American Journal of Kidney Diseases, 74(6), 751-760.

37. Hoogeveen, E. K., Rothman, K. J., Voskamp, P. W., de Mutsert, R., Halbesma, N., Dekker, F. W., & PREPARE-2 Study Group. (2017). Obesity and risk of death or dialysis in younger and older patients on specialized pre-dialysis care. PLoS One, 12(9), e0184007.

38. Burrows, N. R., Zhang, Y., Hora, I., Pavkov, M. E., Sheff, K., Imperatore, G., ... & Albright, A. L. (2020). Sustained lower incidence of diabetes-related end-stage kidney disease among American Indians and Alaska Natives, Blacks, and Hispanics in the US, 2000–2016. Diabetes care, 43(9), 2090-2097.

39. Doshi, S. M., & Friedman, A. N. (2017). Diagnosis and management of type 2 diabetic kidney disease. Clinical journal of the American Society of Nephrology: CJASN, 12(8), 1366.

40. Stevens, P. E., Levin, A., & Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members*. (2013). Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Annals of internal medicine, 158(11), 825-830.

41. Eckardt, K. U., Bansal, N., Coresh, J., Evans, M., Grams, M. E., Herzog, C. A., ... & Williams, A. W. (2018). Improving the prognosis of patients with severely decreased glomerular filtration rate (CKD G4+): conclusions from a kidney disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney international, 93(6), 1281-1292.

42. Guideline Development Group, Bilo, H., Coentrão, L., Couchoud, C., Covic, A., De Sutter, J., ... & Van Biesen, W. (2015). Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR< 45 mL/min). Nephrology Dialysis Transplantation, 30(suppl_2), ii1-ii142.

43. Muskiet, M. H., Wheeler, D. C., & Heerspink, H. J. (2019). New pharmacological strategies for protecting kidney function in type 2 diabetes. The Lancet Diabetes & Endocrinology, 7(5), 397-412.

44. Barrera-Chimal, J., Lima-Posada, I., Bakris, G. L., & Jaisser, F. (2022). Mineralocorticoid receptor antagonists in diabetic kidney disease—Mechanistic and therapeutic effects. Nature Reviews Nephrology, 18(1), 56-70.

45. Agarwal, R., Kolkhof, P., Bakris, G., Bauersachs, J., Haller, H., Wada, T., & Zannad, F. (2021). Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. European heart journal, 42(2), 152-161.

46. Bakris, G. L., Agarwal, R., Anker, S. D., Pitt, B., Ruilope, L. M., Rossing, P., ... & Filippatos, G. (2020). Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. New England Journal of Medicine, 383(23), 2219-2229.

47. Welling, M. S., Abawi, O., van den Eynde, E., van Rossum, E. F., Halberstadt, J., Brandsma, A. E., ... & van der Voorn, B. (2022). Impact of the COVID-19 pandemic and related lockdown measures on lifestyle behaviors and well-being in children and adolescents with severe obesity. Obesity Facts, 15(2), 186-196.

48. Hoogeveen, M. J., Kroes, A. C., & Hoogeveen, E. K. (2022). Environmental factors and mobility predict COVID-19 seasonality in the Netherlands. Environmental Research, 211, 113030.

49. Morrow, A. J., Sykes, R., McIntosh, A., Kamdar, A., Bagot, C., Bayes, H. K., ... & Berry, C. (2022). A multisystem, cardio-renal investigation of post-COVID-19 illness. Nature medicine, 28(6), 1303-1313.

50. Silver, S. A., Beaubien-Souligny, W., Shah, P. S., Harel, S., Blum, D., Kishibe, T., ... & Harel, Z. (2021). The prevalence of acute kidney injury in patients hospitalized with COVID-19 infection: a systematic review and meta-analysis. Kidney medicine, 3(1), 83-98.

51. Lengton, R., Iyer, A. M., van der Valk, E. S., Hoogeveen, E. K., Meijer, O. C., van der Voorn, B., & van Rossum, E. F. (2022). Variation in glucocorticoid sensitivity and the relation with obesity. Obesity reviews, 23(3), e13401.

52. Braun, F., Huber, T. B., & Puelles, V. G. (2020). Proximal tubular dysfunction in patients with COVID-19: what have we learnt so far? Kidney international, 98(5), 1092-1094.

53. Braun, F., Lütgehetmann, M., Pfefferle, S., Wong, M. N., Carsten, A., Lindenmeyer, M. T., ... & Huber, T. B. (2020). SARS-CoV-2 renal tropism associates with acute kidney injury. The Lancet, 396(10251), 597-598.

54. Martens, E. S., Huisman, M. V., & Klok, F. A. (2022). Diagnostic management of acute pulmonary embolism in COVID-19 and other special patient populations. Diagnostics, 12(6), 1350.

55. Bergner, D. W., & Goldberger, J. J. (2010). Diabetes mellitus and sudden cardiac death: what are the data? Cardiology journal, 17(2), 117-129.

56. Maremonti, F., Locke, S., Tonnus, W., Beer, K., Brucker, A., Gonzalez, N. Z., ... & Linkermann, A. (2022). COVID-19 and diabetic nephropathy. Hormone and Metabolic Research.

57. Rivero, J., Merino-López, M., Olmedo, R., Garrido-Roldan, R., Moguel, B., Rojas, G., ... & Vazquez-Rangel, A. (2021). Association between postmortem kidney biopsy findings and acute kidney injury from patients with SARS-CoV-2 (COVID-19). Clinical journal of the American Society of Nephrology: CJASN, 16(5), 685.

58. Polack, F. P., Thomas, S. J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., ... & Gruber, W. C. (2020). Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. New England journal of medicine, 383(27), 2603-2615.

59. Baden, L. R., El Sahly, H. M., Essink, B., Kotloff, K., Frey, S., Novak, R., ... & Zaks, T. (2021). Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. New England journal of medicine, 384(5), 403-416.

60. Sadoff, J., Gray, G., Vandebosch, A., Cárdenas, V., Shukarev, G., Grinsztejn, B., ... & Douoguih, M. (2021). Safety and efficacy of single-dose Ad26. COV2. S vaccine against Covid-19. New England Journal of Medicine, 384(23), 2187-2201.

61. Nathan, D. M., & DCCT/Edic Research Group. (2014). The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes care, 37(1), 9-16.

62. Kato, M., & Natarajan, R. (2019). Epigenetics and epigenomics in diabetic kidney disease and metabolic memory. Nature Reviews Nephrology, 15(6), 327-345.