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Diabetes Mellitus Control and Chronic Kidney Disease

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ABSTRACT

Chronic kidney disease (CKD) is the rampant onset of diabetes and related complications; chronic kidney disorders and end-stage renal disease are progressing in more than 10% of the world population and mostly affect the elderly, women, minorities and patients with diabetes and hypersensitivity. The early stages of CKD are typically quiet; thus, many people are unaware they have the condition. Data for this review was gathered from Google Scholar, Scopus, PubMed, Elsevier, Cochrane, Sage, Medline, and Web of Science. Studies were selected from 2018-2023, using keywords such as Diabetes mellitus management, chronic kidney disease, microalbuminuria, target time in range, impaired fasting glucose, management ways, lifestyle modification, medication treatment, and diet control. Although blood glucose levels are too unpredictable to provide a reliable evaluation, measures reflecting long-term glycemic load are used instead. The results gathered after the review suggests that optimal glycemic control along with lifestyle medication and diet control contributes to better outcomes in individuals with DM, particularly for microvascular damage. While, HbA1c is the most well-known glycemic biomarker of long-term glycemic management. This suggests that effective treatments are progressing on progression.This review has discussed different CKD management parameters; the authors have discussed the disease's treatment criteria and protocols, such as pharmacological therapies, lifestyle modifications, physical activities and insulin therapy and concluded that to avoid CKD, it's critical to concentrate on underlying problems including hyperglycemia, hypertension, microalbuminuria, sedentary behaviour, and smoking. The occurrence of CKD can be reduced with changes in lifestyle, such as increased physical activity, nutritious food, and water consumption.

INTRODUCTION

Diabetes Mellitus is the most common and prevalent disease worldwide, affecting approximately 29.2% of people per year in the United States; while 537 million people around the world are reported to have diabetes, this number is expected to grow by half a billion by the year 2040 (Association, 2022; IDF, 2021; Prevention, 2020). Diabetes mellitus is a progressive metabolic disease that is implanted by the constant condition of hyperglycemia. Diabetes is prompted by the action of insulin that decreases insulin production, insulin resistance, or both (Goyal & Jialal, 2018). Hyperglycemia is a recognised marker for the onset and development of both DPN and CKD. This lethal disease causes more lethal macrovascular comorbidities such as cardiovascular diseases, diabetic peripheral neuropathy, Diabetic retinopathy and CKD, leading to increased mortality rates and decreased quality of life (Cole & Florez, 2020). During the 1st century AD, diabetes was considered a urinary tract disease or a kidney disease due to its high urine flow. Diabetes affects the kidneys primarily due to a deficiency in their retentive properties. Diabetes-related urine has a sweet flavour because it contains nutrients and water that have been ingested but not broken down (Eknoyan & Nagy, 2005). The sweetness of diabetic urine was the initial indicator used by Thomas Willis in 1674 to distinguish diabetes from other types of polyuria, and he proposed that the sweet flavour initially manifests in the blood(Sutherland & Gruessner, 2020). A century later, Matthew Dobson demonstrated that the sweet flavour of urine was caused by sugar and that blood sugar had both paved and followed it. Although diabetes was later linked to higher blood sugar levels, sugar in the urine was still accredited to the kidneys' reduced ability for retentive functioning (Porta, 2020).

Diabetic kidney disease or CKD happened by diabetes or diabetic nephropathy is the most typical onset of diabetes mellitus and also the major reason of end-stage renal disorder (ERSD). Diabetic kidney disease (DN) is characterised by hyperfiltration and albuminuria, followed by a loss of renal function. It can show in various ways, particularly in individuals with T2DM who may also have peripheral vascular and other glomerular/tubular diseases (Sagoo & Gnudi, 2020). CKD is reported to affect approximately 8 to 16 % population globally, and around 30-50 % of cases of end-stage renal disorder are considered to be preceded by diabetic kidney disease (Chen *et al.*, 2019; Copur *et al.*, 2020). The incidence of classic diabetic nephropathy in Type 1 diabetes has decreased from 25% to 10-15% with blood pressure management and more use of an angiotensin converter. The overall incidence of diabetes will rise from 6% to 10% of adults in the coming years, leading to more cases of Type 2 diabetes and kidney disease (Winocour, 2018). CKD is recognised by a biomarker called micro-albumin, which is present in urine. The higher levels of micro-

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albumin in urine indicate the presence of a disorder. At the same time, albuminuria is a condition of having too much protein in the urine, resulting in kidney damage (Raja *et al.*, 2021). Diabetes and CKD together increase the probability of amputations of the lower limbs by two to six times compared to diabetes alone in patients with CKD (Rodrigues *et al.*, 2022).

LITERATURE REVIEW

Progression of Micro and Macro- Albuminuria

Microalbuminuria is caused by a malfunction of the glomerular basement membrane (GBM). This enzyme is inhibited by insufficient blood sugar management, which lowers the negative charge on GBM and causes extra albumin to leak out. It is linked to type 1 and type 2 diabetic individuals (Prasad & Tikaria, 2022). In those with type 1 diabetes, microalbuminuria is 6% prevalent after three years but 41% common after five. Type 2 diabetes affects 20% to 25% of diabetic paeople (Prasad & Tikaria, 2022). A decreased glomerular filtration rate, increased microalbuminuria, or both characterise diabetic nephropathy or DKD. Laboratory tests are used to diagnose CKD, most frequently by estimating glomerular filtration rate (GFR) using a filtration marker like serum creatinine or cystatin C. The albumin or protein in the urine can be determined using several formulas or other methods (Kovesdy, 2022). Microalbuminuria, defined by urine albumin excretion of 30-300 mg/day, is thought to be a predictor of DKD. It is regarded as an adjustable problem for the progression of renal disease to its terminal stages (Hussain *et al.*, 2020). The progression of microalbuminuria can vary depending on the underlying cause and individual factors such as age, blood pressure, and blood sugar control (Oshima *et al.*, 2021). However, in general, the progression of microalbuminuria can be divided into three stages:

1. Early stage: In the early stages of microalbuminuria, the albumin in the urine is slightly elevated but still within a normal range. This stage may not cause symptoms, and kidney function may still be normal (Parving *et al.*, 2015).

2. Moderate stage: As microalbuminuria progresses, the albumin in the urine elevates, and kidney function may decline. This stage is often characterised by hypertension, an elevation in albuminuria, and a decline in the glomerular filtration rate (GFR) (Webster *et al.*, 2017).

3. Severe stage: In the severe stage of microalbuminuria, there is a significant elevation in the amount of albumin in the urine, and kidney function is severely impaired. At this stage, patients may experience fatigue, weakness, leg swelling, and difficulty concentrating (Romagnani *et al.*, 2017).

It is essential to diagnose and treat microalbuminuria in the early stages to prevent the progression of kidney disease. Treatment may involve medication to control blood pressure and blood sugar, lifestyle changes such as a healthy diet and exercise, and regular monitoring of kidney function. If left untreated, microalbuminuria can progress to macroalbuminuria, which is the presence of large amounts of albumin in the urine (Persson & Rossing, 2018). Macro albuminuria is a more advanced stage of kidney disease and is usually acknowledged with a degradation in kidney function and an increased risk of cardiovascular disease (Persson & Rossing, 2018).

Target Time in Range and Hba1c

The A1C test, blood glucose monitoring (BGM), and continuous glucose monitoring (CGM) are all used to examine glycemic control. The A1C is the commonly used biomarker for assessing blood glucose control in diabetics, as it decreases both long-term and short-term macrovascular disease and long-term microvascular consequences (Wright *et al.*, 2020). Whereas time in range (TIR) refers to the amount of time that a person with diabetes spends within a target range of blood glucose levels (Advani, 2020). For diabetic people, maintaining blood glucose levels within a target range is important for preventing complications such as nerve damage, kidney disease, and cardiovascular disease (Advani, 2020). TIR is useful for monitoring blood glucose levels and assessing how well diabetes management strategies work (Mayeda *et al.*, 2020). The target range for TIR can vary depending on the individual, but a common target range is between 70 and 180 mg/dL (Beck *et al.*, 2019). TIR can be measured using continuous glucose monitoring (CGM) devices, which provide real-time glucose readings throughout the day and night (Gabbay *et al.*, 2020). HbA1C and TIR are two essential diabetes management metrics. However, they serve different functions (Lu *et al.*, 2020). TIR is used to monitor short-term changes in blood glucose levels and evaluate the efficacy of diabetes management techniques, while HbA1C is used to examine long-term glycemic control and assist with treatment options (Yoo & Kim, 2020). However, a correlation exists between HbA1C and TIR due to the same variables impacting blood sugar levels, such as food, exercise, and medication use (Vigersky & McMahon, 2019). A lower HbA1C indicates better long-term glycemic management and is more common in patients with higher TIR levels. Generally, a higher TIR is associated with better diabetes management and lower risk of complications (Shah *et al.*, 2021). Through TIR and HbA1C metrics, diabetes can be managed, preventing the chances of CKD and other diabetes-related complications.

Prevention at the Level of Impaired Fasting Glucose and Prediabetes

Prevention of CKD and diabetes can only be done by managing the disease at impaired fasting glucose (IFG) and prediabetes levels. Impaired fasting blood sugar (IFG) is a pre-diabetic condition linked to a relatively elevated probability of developing diabetes2 (Yu *et al.*, 2020). Early identification of prediabetes and individualised therapy are required to effectively manage this steadily increasing diabetic population. IFG is a significant indicator of diabetes and its comorbidities (Yu *et al.*, 2020). Consistently high blood sugar levels can cause heart problems, diabetic nephropathy, retinopathy, neuropathy, and increased

mortality (Tong & Adler, 2018). Impaired fasting glucose (IFG) and prediabetes are conditions that can highten the probability of developing CKD and other issues, such as cardiovascular disease (Kim *et al*., 2020). Management of these conditions typically involves lifestyle modifications and medication, as appropriate, to improve glucose control and reduce the risk of complications.

1. Lifestyle modifications: A nutritious diet, frequent exercise, and weight management are examples of lifestyle changes. Frequent exercises, like brisk walking or cycling, can also improve glucose control and lower the risk of comorbidities (Beulens *et al*., 2020).

2. Medication: Sometimes, medication may be prescribed to improve glucose control. Metformin is commonly used to treat prediabetes and IFG (Beulens *et al*., 2020).

3. Blood pressure management: High blood pressure increases CKD risk and can accelerate the development of IFG and prediabetes. Periodic blood pressure assessments are recommended, and medication for hypertension can also be provided when necessary. (Ohishi, 2018)

4. Regular monitoring: Regular blood tests can help to monitor glycemic control and kidney function. This may include a blood test called the estimated glomerular filtration rate (eGFR) to assess kidney function (Miller & Jones, 2018). Overall, early identification and management of prediabetes and IFG are important to prevent the development or progression of CKD and other complications.

METHODOLOGY

To indicate the development of CKD into end-stage renal failure by managing diabetes mellitus, several recent studies, review articles, prospective studies, cross-sectional studies, and literature reviews, all published and peer-reviewed articles, were searched and considered. The area of search was based on how effective the management of debates mellitus is in preventing chronic kidney disease, microalbuminuria and other comorbidities. Data was gathered from different search engines and databases such as; Google Scholar, Scopus, PubMed, Elsevier, Cochrane, Sage, Medline, and Web of Science, Elsevier.

Numerous studies were selected from 2018-2023, using the keywords Diabetes mellitus management, chronic kidney disease, microalbuminuria, target time in range, Impaired fasting glucose, management ways lifestyle modification, and medication treatment, Diet Control. The full texts of the retrieved articles were made accessible.

This article is a review. Thus not all information on the prevention of CKD by management of diabetes mellitus has been provided are contained in this. We have included observational studies and all significant, pertinent big trials to highlight the overall conclusions. Although we tried to incorporate the largest and most pertinent research, it is important to remember that the tiny, hopeful observational studies were likely chosen due to publication bias.

DISCUSSION

Occurrence of CKD in T2DM

For populations with type 2 diabetes or a mix of diabetes types, the yearly rate of albuminuria is typically around 8%, while for groups with type 1 diabetes, it ranges from 2% to 3%. Regardless of the type of diabetes, low eGFR occurs between 2% and 4% of the time. However, due to significant demographic estimate variability, combined CKD incidence rates are impractical (Koye *et al*., 2018). Microalbuminuria and albuminuria occur about 2-3% of the time in Type 1 diabetes and about 8% in Type 2 diabetes or mixed diabetes types. The yearly occurrence of eGFR 60 ml/min/1.73 m2 is between 2 and 4 per cent. There was a relatively slight difference in prevalence rates within a single category of kidney illness, despite the considerable variation in methodologies and research design (Koye *et al*., 2017). Various studies have determined that an elevation in the occurrence rates of diabetes and hypertension increases the probability of CKD. However, according to a population-based cohort study, it was reported that diabetes and high blood pressure do not have an alliance when it comes to the incidence of chronic kidney disease (Erfanpoor *et al*., 2021). Prevalence of CKD in all phases varies globally, with 1.7% in China, 3.1% in Canada, 6.7% in the US and 5.8% in Australia. In Europe, 2.3% in Germany, 8.2% in Finland, 9.2% in Spain and 5.2% in England (Romagnani *et al*., 2017).

Risk Factors

CKD is a progressive problem of diabetes, particularly in people with poorly controlled blood glucose levels. Several Indisputable risk factors are crucial for diagnosing, treating and managing CKD in diabetes (Kazancioğlu, 2013). The risk factors for CKD in diabetes can be categorised as modifiable and non-modifiable. To stop or slow the start and advancement of CKD in patients with diabetes, early detection and management of these risk factors are crucial (Hannan *et al*., 2021). This may include regular monitoring of blood glucose and blood pressure levels, lifestyle modifications such as healthy eating and regular physical activity, and medication as appropriate. Non-modifiable factors may include Genetics, Male, age,

Table 1: Modifiable and un-modifiable risk factors of CKD

Non- Modifiable Risk Factors	Modifiable Risk Factors
Genetics factor	Hypertension
Male Sex	Poor Glycemic control
Age at onset of diabetes	Lipid abnormalities
Duration of diabetes	Smoking
Family History	Obesity
	Metabolic syndrome
	Vitamin D deficiency and Salt Intake
	Gestational Diabetes

family history, the onset of diabetes etc., while modifiable factors contain hypertension, poor glycemic control, insulin resistance, smoking, metabolic syndrome, vitamin D deficiency etc. (Hannan *et al*., 2021; Koye *et al*., 2018; Kurzhagen *et al*., 2020).

Elevated blood glucose levels can damage the kidney's small blood vessels, leading to CKD. Hypertension or high blood pressure also damages the blood vessels and contributes to the risk of causing CKD (Kurzhagen *et al*., 2020). CKD also depends upon the duration of diabetes onset; according to the reported studies that a longer duration of diabetes can increase the risk of developing CKD in patients (Hannan *et al*., 2021). Smoking is injurious on many levels; it damages the lungs and kidneys and worsens glucose control in diabetic people (Kazancioğlu, 2013).

Prevention of CKD

CKD can be prevented or delayed by taking measures to maintain healthy kidneys. Maintaining underlying conditions, quitting smoking, eating healthy foods, exercising regularly and drinking enough water can help stabilise CKD and diabetes. Other than these preventions, insulin therapies play a vital role in managing CKD, while some medications are widely used to prevent mortality. Some interventions to manage and prevent CKD are explained in this review.

Lifestyle Modification

Healthy dietary intake and weight are vital in reducing most chronic diseases, including renal end-stage diseases. Dietary and lifestyle modifications have been shown to help treat diabetes and improve glycemic control. When a patient's eGFR drops below 60 mL/min/1.73 m2, it is recommended that they seek the advice of a nutritionist to optimise their diet to improve hyperglycemia and ensure they are getting enough protein, potassium, and phosphorus to prevent the condition from worsening (Williams, 2017). Nutrition is essential for people with diabetic kidney disease to maintain an equilibrium of salt, potassium, phosphorus, protein, carbohydrate, and unhealthy fat intake. Patients who are overweight or obese should reduce their weight and improve their exercise, as cardiac stress testing is necessary (Hahr & Molitch, 2015). According to the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation, following a low-protein diet (LPD) can help CKD patients live better lives and decrease the progression of ESRD (Alkhatib *et al*., 2023). It has been proven that diets high in fruits and vegetables and low in saturated fat can effectively lower blood pressure. These diets also limit salt intake (Bello *et al*., 2005). Moreover, Cessation of smoking also helps in maintaining healthy kidney

Pharmacological Management

Intense care of glycemic control decreases the risk of microalbuminuria and macroalbuminuria. According to a report, every increase in systolic blood pressure in the general population above 115 mm Hg has been said to double the risk of cardiovascular disease (CVD). Management of hypertension is essential to prevent albuminuria/proteinuria and the ensuing development of CKD in both diabetic and non-diabetic individuals. Pre-hypertensive conditions, lower blood pressure levels in the general population, and more active blood pressure lowering in patients with hypertension and underlying CKD are essential (Bello *et al*., 2005). Standardising a distinct ratio for every patient is crucial for blood glucose management and CKD prevention. Maintaining a blood pressure (BP) less than 130/80 in DKD patients is the typical aim advised by the National Kidney Foundation; nevertheless, there is considerable debate around this recommendation (Williams, 2017). Due to their ability to preserve the kidneys, ACE inhibitors and ARBs are typically regarded as first-line treatments for hypertension in diabetic people. Patients with diabetes mellitus have been shown to benefit from ACE inhibitors in terms of kidney, heart, and, to a lesser extent, eye and peripheral nerve function. These positive outcomes result from angiotensin II's hemodynamic and tissular actions being inhibited (Williams, 2017).

Medications

Some treatments suggested by healthcare professionals are first-line care for the prevention of CKD, such as metformin (Betônico *et al*., 2016; Beulens *et al*., 2020). This medication has been advised to patients for years. The mechanism of this drug is to decrease the production of hepatic glucose, improve insulin tolerance, lowering impaired fasting glucose and plasma glucose. Although metformin is the most common drug to prevent and manage CKD, it still is contradictory to its nature because metformin excretes through the renal system and the emergence of lactic acidosis, which is one of its most serious drawbacks but only occurs in about 5 cases per 100,000 patient-years of patients on average. Metformin can be used to treat type 2 diabetes (T2DM) up to a GFR of 30 mL/min/1.73 m2, with a lower dose indicated at 45 mL/min/1.73 m2 (current UK guidelines) (Betônico *et al*., 2016).

Sulfonylureas (SUs) encourage pancreatic b cells to secrete endogenous insulin, leading to hypoglycemia, alcohol abuse, hepatic dysfunction, heart failure, malnutrition, advanced age, and interactions with other medications that displace SUs from their plasma protein-binding sites (Seino *et al*., 2016). This is due to accumulating one or more of these medications' metabolites, increasing the risk of hypoglycemia. Other medications help decrease the incidence of CKD in diabetes, such as glinides, Alpha-glucosidase inhibitors, glitazones, and dipeptidyl peptidase 4 inhibitors (Seino *et al*., 2016).

Insulin Therapy

The kidney is crucial in removing insulin from the bloodstream through two different mechanisms. In the initial stage, insulin is filtered by the glomerulus and then taken up by proximal tubular cells via endocytosis

(Peruchetti *et al*., 2021). The second process includes insulin attaching to the contra luminal tubular membrane of cells and diffusing through peritubular capillaries. Lysosomes transport insulin, broken down into amino acids and diffused into the peritubular arteries. Insulin clearance declines when renal failure worsens, necessitating a dosage reduction to prevent hypoglycemia (Peruchetti *et al*., 2021). This decrease in insulin clearance is initially offset by a rise in proximal tubular cells' insulin absorption, and it is also linked to an increase in insulin resistance. Muscle tissue is the predominant source of IR in CKD, occurring mostly at the extremities. In individuals with ESRD, hepatic glucose production is not elevated and repressed in response to insulin, and IR may not result in a proportional rise in insulin secretion (Gburek *et al*., 2021).

Lipid Metabolism

Dysregulation of lipid metabolism leads to higher levels of triglycerides, oxidised lipoproteins, and lower levels of HDL cholesterol in chronic renal disease and ESRD. Advanced CKD or ESRD patients have a distinctive lipid pattern that includes hypertriglyceridemia, low HDL cholesterol, and normal LDL cholesterol levels (Dincer *et al*., 2019). In the general population, there is a clear correlation between LDL cholesterol and atherosclerotic events, but in patients with ESRD, LDL cholesterol has a flat or weakly positive correlation with mortality at levels above the average and a negative correlation with these outcomes at levels below the average. Reducing LDL cholesterol helps prevent serious atherosclerotic events in people with CKD and kidney transplants but not for people who need dialysis (Ferro *et al*., 2018).

Limitations and Strengths

1. The management and treatments discussed in this review do not guarantee the reversal of the disease.
2. Several participants were not tested in this review; the review is based on factual data.
3. The most coherent risk factor of mortality due to CKD is increasing age, which has not been extensively discussed.
4. The biggest strength of this review is that very generalised terms have been used in searching strategies to combat vast unrelated data.
5. This review is based on scientifically proven facts.

CONCLUSION

In conclusion of this review, Diabetes mellitus is the most common and biggest risk factor for the occurrence of CKD and ESRD. It is advised to maintain and focus on the underlying conditions that result in CKD over time to prevent the disease. These conditions include hyperglycemia, hypertension, microalbuminuria, sedentary lifestyle, smoking, etc. These underlying conditions may turn into symptoms and eventually convert into morbidity. Changes in lifestyle, such as healthy eating, regular physical activity, and intake of advised ml of water in addition to some medications and therapies, can altogether increase improvement rates of CKD incidence. Further future studies need to be done to combat the disease better.

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