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Review Article

Interplay Between Antidiabetic Drugs And Kidney Health: Understanding The Risks And Optimizing Therapeutic Outcomes

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ABSTRACT

This comprehensive review explores the intricate relationship between antidiabetic drugs and kidney health, focusing on the significant risk diabetes mellitus poses to kidney function, particularly in cases of uncontrolled diabetes. The paper delves into the potential effects of various antidiabetic drug classes on renal health, considering factors such as pre-existing kidney conditions, nephrotoxicity, dehydration, cardiovascular disease, and age-related considerations. A detailed flowchart illustrates the pathophysiological impact of these drugs on kidney disease, covering aspects like glucose control, inflammation, fibrosis, and albuminuria. Clinical practice recommendations are provided for using antidiabetic drugs in patients with renal impairment, considering estimated glomerular filtration rates and the necessity for dialysis. The review also discusses the current treatment landscape for diabetic kidney disease, emphasizing multidisciplinary approaches and highlighting challenges and potential future treatments, ultimately emphasizing the importance of personalized approaches and regular monitoring in managing diabetes to optimize therapeutic outcomes while minimizing adverse effects on kidney function.

INTRODUCTION

Diabetes can significantly impact kidney health. Diabetes, particularly uncontrolled or poorly managed diabetes, increases the risk of chronic kidney disease (CKD). High blood glucose levels over an extended period can damage the small blood vessels in the kidneys, leading to diabetic nephropathy. Managing diabetes effectively through lifestyle changes and medication can help reduce this risk. Regular monitoring and early intervention are crucial to protecting kidney health in individuals with diabetes.

Importance of understanding the interplay between antidiabetics drug and kidney disease:

Understanding the interplay between antidiabetic drugs and kidney disease is crucial because the

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kidneys play a key role in drug metabolism and elimination. In individuals with kidney disease, drug clearance may be impaired, leading to potential toxicity or reduced efficacy. Moreover, some antidiabetic medications can impact kidney function directly. Tailoring drug regimens to a patient's renal status helps optimize diabetes management while minimizing the risk of adverse effects on kidney function.

Regular monitoring and adjustment of medications are essential in individuals with diabetes and kidney disease to achieve optimal therapeutic outcomes.

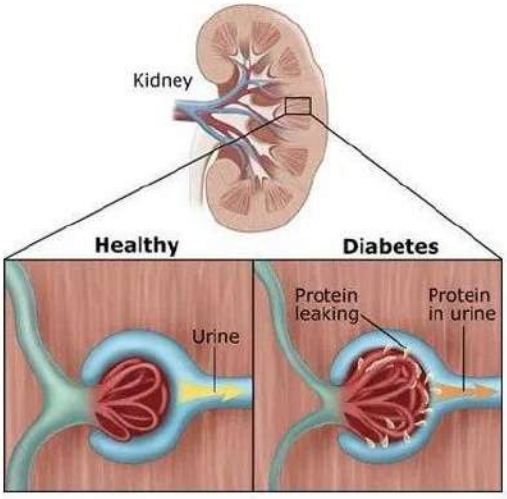

Fig. 1 Diabetic nephropathy (Diabetic and kidney disease)

Prolonged high blood sugar levels can lead to various complications, one of which is an increased risk of chronic kidney disease (CKD). Here's some information about this connection:

1. Damage to Kidneys: Over time, high blood glucose levels can harm the small blood vessels and filters in the kidneys. This damage impairs the kidneys' ability to filter waste and excess fluids from the blood effectively.
2. Progression of CKD: Individuals with diabetes are at a higher risk of developing CKD compared to those without diabetes. CKD is a progressive condition where the kidneys lose their function over time.
3. Diabetic Nephropathy: The specific kidney condition associated with diabetes is called diabetic nephropathy. It's a leading cause of CKD and can eventually lead to end-stage renal disease (ESRD), where dialysis or a kidney transplant may be necessary.
4. Diabetic Control and Regular monitoring: Managing diabetes through proper blood sugar control, a balanced diet, regular exercise, and medications as prescribed by a healthcare provider is crucial in reducing the risk of CKD. People with diabetes should have their kidney function regularly monitored, typically through tests like serum creatinine and estimated glomerular filtration rate (eGFR). Detecting kidney problems early allows timely action to be taken.

Blood Pressure Control and Lifestyle Changes: High blood pressure is often associated with both diabetes and CKD. Controlling blood pressure is essential in managing kidney health for individuals with diabetes. Lifestyle modifications, such as quitting smoking and limiting alcohol intake, can also help reduce the risk of kidney complications in people with diabetes [1, 2].

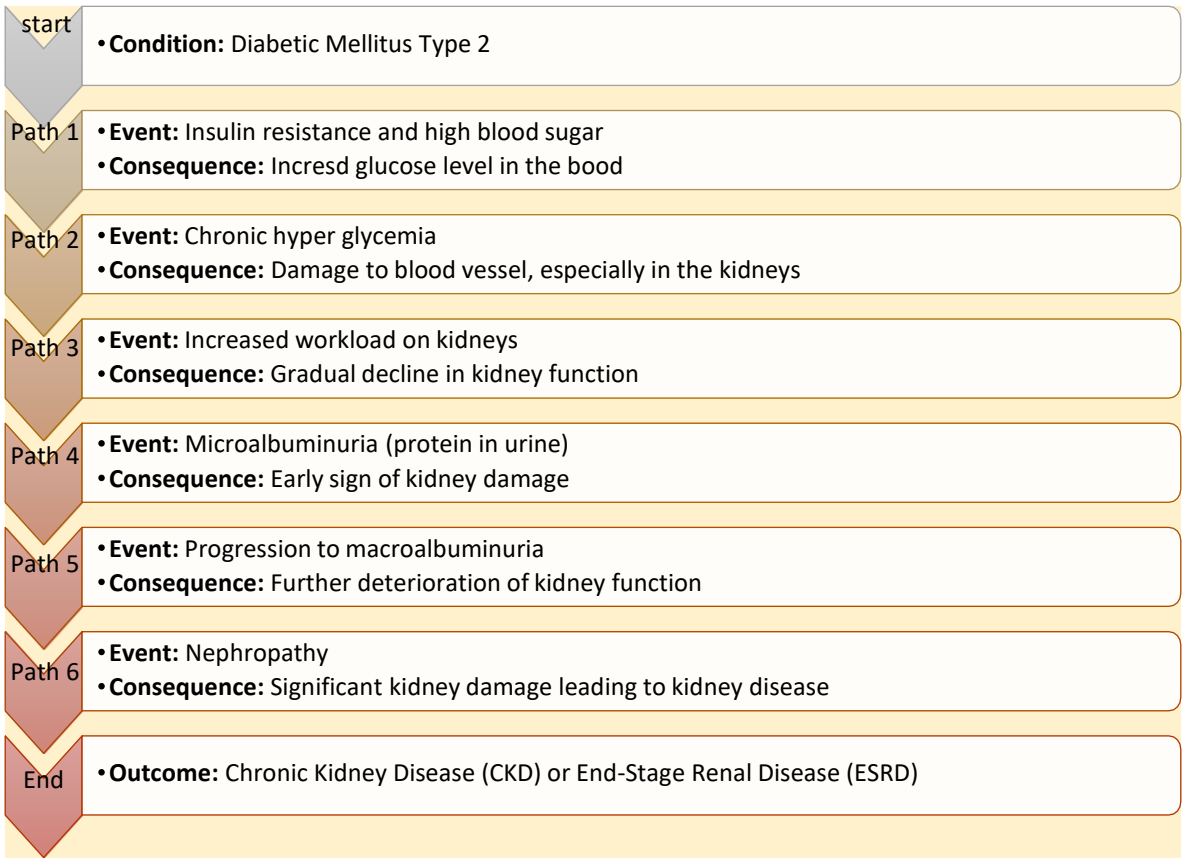

Fig. 2 Flowchart to illustrate how diabetes can lead to kidney disease.

Here are some common classes of anti-diabetes drugs and their potential effects on kidney function:

Biguanide

Potential effect - Metformin belongs to the class of anti-diabetic drugs known as biguanides. Its potential effects on kidney function include a relatively low risk of causing kidney issues. Metformin is generally considered safe for most individuals, but caution is advised in patients with pre-existing kidney problems. In rare cases, it can lead to a condition called lactic acidosis, particularly if there is significant impairment in kidney function.

Drug - Metformin

Considerations – Caution in individuals with severe renal impairment due to the recommended use of metformin at different stages [3, 4].

Stage 1-2, GFR 60 ml/min No contraindication for use of metformin. Monitor renal function annually.

Stage 3a GFR 45-59ml/min No contraindication for use of metformin. Monitor renal function every 3-6 months.

Stage 3b GFR 30-44 ml/min the use of metformin should be carefully evaluated. Consider reduce your dose. Monitor kidneys function every 3 months.

Stage 4-5 GFR<30ml/min Stop use of metformin, do not initiate metformin.

Sulfonylureas

Potential Effect - Sulfonylureas are a class of oral medications commonly used to treat type 2 diabetes. They stimulate insulin release from the pancreas, helping to lower blood sugar levels. Potential side effects may include hypoglycemia (low blood sugar), weight gain, and gastrointestinal issues. Long-term use may also affect cardiovascular outcomes. It's crucial to go over the advantages and possible risks with your healthcare professional.

Drugs - Glibenclamide, Glimepiride, Gliclazide

Considerations - Dose adjustment may be needed in patients with impaired liver function [5].

SGLT-2 Inhibitors

Potential effect - SGLT-2 inhibitors, a class of medications used to treat type 2 diabetes, have shown potential benefits for kidney function. They may reduce the risk of kidney disease progression and cardiovascular events in people with diabetes. These inhibitors work by blocking glucose reabsorption in the kidneys, leading to increased glucose excretion in urine. This mechanism may help lower blood sugar levels and reduce the workload on the kidneys, offering potential renal protective effects. However, individual responses can vary, and it's crucial to consult a healthcare professional for personalized advice.

Drug - Dapagliflozin

Considerations: Monitor and analysis for potential side effects like dehydration and urinary tract infections [6].

DPP-4 Inhibitors

Potential effect - DPP-4 inhibitors, another class of medications used for type 2 diabetes, generally have a neutral or slightly beneficial impact on kidney function. They work by increasing the levels of incretin hormones, which help regulate blood sugar. Unlike some other diabetes medications, DPP-4 inhibitors are not primarily eliminated through the kidneys, making them a suitable option for individuals with mild to moderate kidney impairment.

Drug - Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin

Considerations: Suitable for patients with mild to moderate renal impairment [7].

GLP-1 Receptor Agonists

Potential effect - GLP-1 is an incretin secreted in the gastrointestinal tract in response to food intake. GLP-1 regulates blood sugar levels and reduces the chance of hypoglycemia. Studies suggest that these medications may have renoprotective effects, including reducing albuminuria and preserving glomerular filtration rate (GFR). Additionally, by delaying stomach emptying and suppressing hunger via a central mechanism, it aids in weight loss.

Clinical studies suggest that GLP-1 receptor agonists can reduce the risk of kidney complications in people with diabetes.

Drugs - Exenatide, liraglutide

Considerations: Some evidence and suggests renal benefits; suitable for patients with kidney disease [8].

Insulin

Potential effect - Insulin itself does not have a direct impact on kidney function. However, maintaining proper blood glucose levels through insulin therapy is crucial for preventing diabetes-related kidney complications. Uncontrolled diabetes can lead to kidney damage over time, causing diabetic nephropathy. Insulin helps regulate blood sugar levels, and by keeping glucose within the target range, it contributes to preventing or slowing down kidney problems associated with diabetes. Regular monitoring of blood glucose levels and adherence to prescribed insulin regimens are essential.

Considerations - Adjustments may be needed in patients with renal impairment to avoid hypoglycemia [9,10].

Thiazolidinediones (TZDs) OR Glitazones

Potential Effect - Thiazolidinediones (TZDs), a class of medications used to treat type 2 diabetes, may have both positive and negative effects on kidney function. On the positive side, some studies suggest that TZDs may have renal protective effects, including a potential reduction in albuminuria and preservation of glomerular filtration rate (GFR). However, it's important to note that there are also concerns associated with TZDs. One specific TZD, rosiglitazone, has been linked to an increased risk of fluid retention and edema, which can potentially impact kidney function. Additionally, TZDs may lead to weight gain and have been associated with an increased risk of heart failure.

Drug - Pioglitazone

Considerations: Monitor for signs of edema and cardiovascular issues [11].

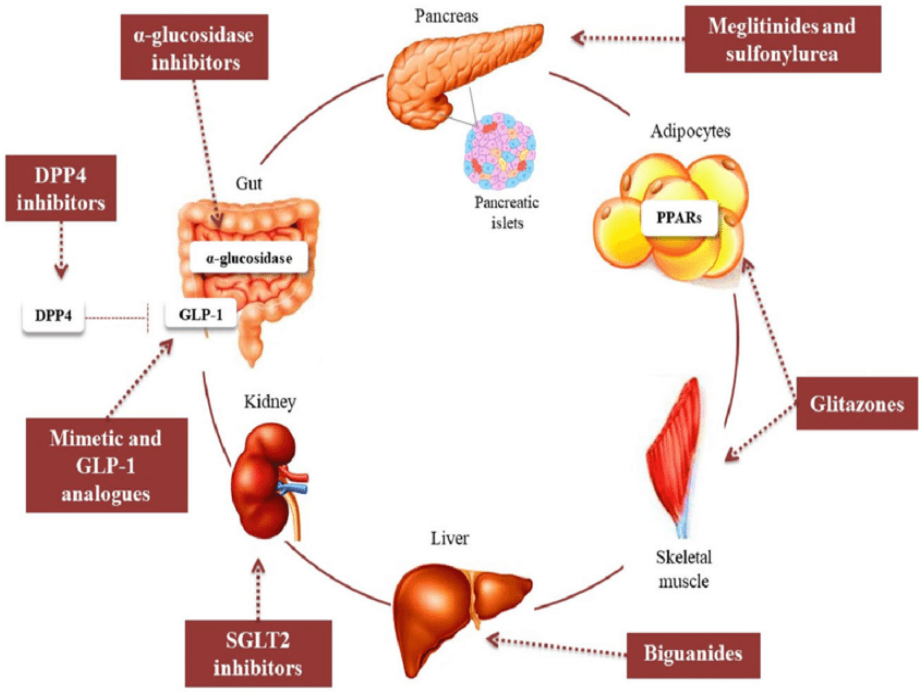

Fig. 3 Anti-diabetes drugs and their potential effects on kidney function in cycle form

Key Risk Factors for Antidiabetic Drugs and Kidney Disease:

1. Pre-existing Kidney Conditions: Individuals with pre-existing kidney disease or impaired renal function are at a higher risk of developing complications when using certain antidiabetic medications. Certain anti-diabetic drugs can pose risks to kidney function. Metformin, a commonly prescribed drug, may cause lactic acidosis in individuals with impaired kidney function. Sulfonylureas and insulin might lead to hypoglycemia, especially in patients with compromised kidney function who may have difficulty clearing these drugs from their system. Reduced kidney function may impact drug clearance, necessitating dosage adjustments. Additionally, uncontrolled diabetes can contribute to the progression of CKD.
2. Drug-Induced Nephrotoxicity: Some antidiabetic drugs, especially certain classes like sodium-glucose cotransporter-2 (SGLT2) inhibitors, have been associated with an increased risk of drug-induced nephrotoxicity. Some of these drugs, including certain sulfonylureas and nonsteroidal anti-inflammatory drugs (NSAIDs), can contribute to kidney damage. Nephrotoxicity may

manifest as elevated creatinine levels or progress to conditions like acute kidney injury (AKI) or chronic kidney disease.

3. Dehydration: Certain antidiabetic medications, such as SGLT2 inhibitors, may increase the risk of dehydration. Dehydration is a risk factor for kidney dysfunction. In a dehydrated state, blood volume decreases, impairing drug clearance in the kidneys and increasing the concentration of substances, including medications. This heightened concentration raises the potential for drug-induced kidney damage. Additionally, dehydration reduces renal blood flow, hindering kidney function. For individuals with pre-existing kidney conditions, this exacerbates the risk of complications. Maintaining proper hydration is crucial to mitigate these risks, emphasizing the importance of fluid intake for individuals managing diabetes and kidney health.
4. Cardiovascular Disease: Patients with cardiovascular disease may be at an increased risk of kidney-related issues when using antidiabetic drugs, as cardiovascular health is closely linked to renal function. Diabetes itself increases the likelihood of cardiovascular complications, and certain anti-diabetic medications may impact cardiovascular health. Chronic high blood sugar levels can contribute to atherosclerosis and increase the risk of heart disease. Additionally, some medications, such as certain types of sulfonylureas, may pose cardiovascular risk.
5. Age: Older individuals may have a higher risk of kidney complications due to age- related decline in renal function. Dosage adjustments may be necessary for elderly patients. Furthermore, advancing age is often associated with a higher prevalence of chronic conditions, including diabetes and hypertension, which are key contributors to kidney disease [12].

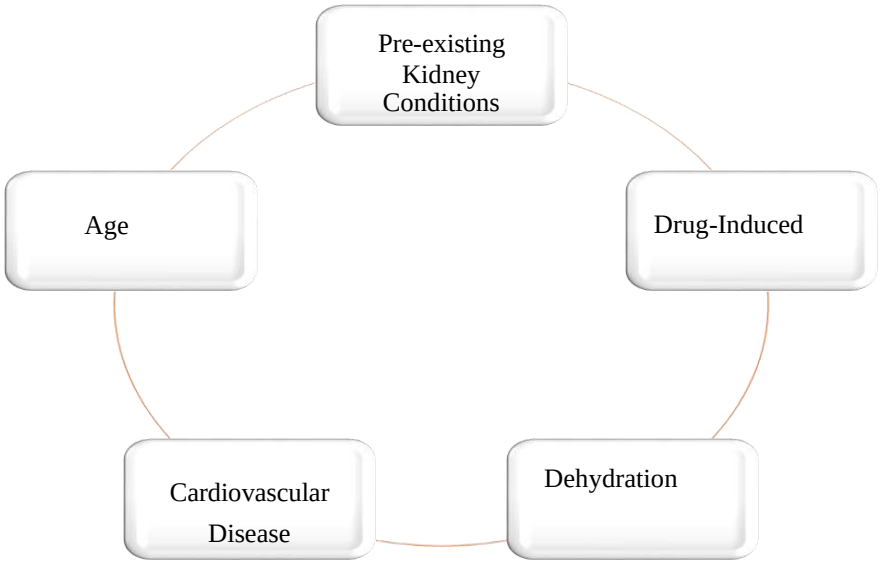

Fig. 4 Key Risk Factors for Antidiabetic Drugs and Kidney Disease in cycle form

Pathophysiology of effect of antidiabetic drug on kidney disease and functions:

The pathophysiology of the effect of antidiabetic drugs on kidney disease involves multiple factors.

Diabetes can lead to nephropathy, and certain antidiabetic medications aim to
mitigate these effects.

1. Glucose Control: Antidiabetic drugs help regulate blood glucose levels, reducing the risk of hyperglycemia-associated kidney damage. Prolonged hyperglycemia can lead to increased oxidative stress, inflammation, and damage to renal structures.
2. Renin-Angiotensin-Aldosterone System (RAAS): Some antidiabetic medications, like ACE inhibitors and ARBs, target the RAAS. They help manage blood pressure and reduce stress on the kidneys by dilating blood vessels and decreasing fluid retention.
3. Inflammation and Fibrosis: Chronic hyperglycemia triggers inflammatory responses and fibrosis in the kidneys. Certain antidiabetic drugs, such as SGLT-2 inhibitors, have shown renal protective effects by reducing inflammation and fibrosis.
4. Glomerular Filtration Rate (GFR): Diabetes can impact GFR, affecting kidney function. Medications like SGLT-2 inhibitors can influence GFR positively by reducing hyperfiltration and preserving renal function.
5. Albuminuria: Diabetes can cause proteinuria, specifically albuminuria, indicating kidney damage. Medications like ACE inhibitors and ARBs can help reduce proteinuria by relaxing blood vessels and decreasing pressure in the glomerulus.
6. Mitochondrial Dysfunction: Hyperglycemia contributes to mitochondrial dysfunction, leading to oxidative stress. Some antidiabetic drugs, such as metformin, may exert protective effects by improving mitochondrial function and reducing oxidative stress.
7. Regular Kidney Function Monitoring: Monitor renal function regularly, including serum creatinine and estimated glomerular filtration rate (eGFR), to detect changes early and adjust medications accordingly.
8. Dose Adjustments: Modify drug doses based on renal function to prevent drug accumulation and potential toxicity, as impaired kidney function can alter drug metabolism and excretion.
9. Pharmacovigilance: Stay vigilant for adverse drug reactions and promptly address any signs of worsening kidney function or electrolyte imbalances [13-14].

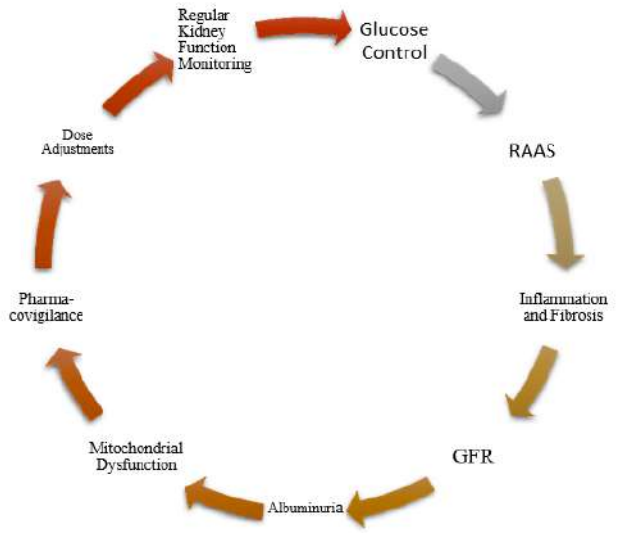

Fig. 5 Pathophysiology of effect of antidiabetic drug on kidney disease and functions in cycle form

Clinical Practice recommendation for the use of anti-diabetic drugs in renal impaired patients

Class	Drug	Use in case of renal impairment (eGFR in ml/min)		Use in patient on dialysis
Meglitinides	Repaglinide	Yes		Yes
	Nateglinide	With caution		No
Biguanide	Metformin	GFR>60	Yes	No

		GFR:45-60	Reduce dose; use with caution, only in the absenceof condition	No
Sulfonylureas	Glibenclamide	GFR>60	Yes	No
	Glimepiride	GFR<60	No	No
	Gliclazide	GFR>60	Yes	No
		GFR: 40-60	With caution	
		GFR<40	No	
Alpha glucosidase inhibitor	Acarbose	GFR>60	Yes	No
		GFR<60	No	No
Glitazone	Pioglitazone	GFR>60	Yes	Limited experience; caution use
		GFR<60	With caution,risk of water and sodium retention	
DPP-4 Inhibitors	Sitagliptin	GFR>50	Yes	Limited experience; usewith caution.
		GFR:30-60	50mg/day	
		GFR<30	25mg/day:Limited experience	
	Vildagliptin	GFR>50	Yes	No
		GFR<50	No	
	Saxagliptin	GFR>50	Yes	No; limited experience
		GFR:30-50	2.5 mg/day	
		GFR:15-30	2.5 mg/day;limited experience	
	Linagliptin	GFR>50	Yes	No experience; use withcaution
		GFR<50	Yes, limited experience	
GLP-1 receptor agonist	Exenatide	GFR>60	Yes	No
		GFR:30-60	Limited experience, with caution	No
		GFR<30	No	No
	Liraglutide	GFR>50	Yes	No
		GFR<50	No	No
SGLT-2 Inhibitors	Empagliflozin	GFR<30	10mg/day	Yes
	Dapagliflozin	GFR<30	No	Yes, use with caution

Treatment of Diabetic Kidney Disease: Current and Future

Current Treatment

[A]. Multidisciplinary treatment of DKD: Multidisciplinary treatment of DKD involves a comprehensive approach that includes glycemic control, blood glucose control, blood pressure and lipid control with RAS inhibitors, appropriate weight management, and guidance for diet and smoking cessation[2]. A systematic review and meta-analysis found that multidisciplinary treatment of DKD can improve kidney function, reduce proteinuria, lower blood pressure, and enhance health-related quality of life.

- Glycemic control: Maintaining optimal blood glucose levels is essential to prevent or slow down the development of AKD. The target hemoglobin A1c (HbA1c) level for most patients with diabetes

and AKD is <7%. However, the target may vary depending on the individual risk factors, comorbidities, and preferences. The choice of antidiabetic drugs should consider the kidney function, safety, efficacy, and potential benefits on kidney and cardiovascular outcomes. Some of the recommended drugs for patients with AKD are metformin, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and glucagon-like peptide 1 (GLP-1) receptor agonists.

- Blood pressure control: Hypertension is a common and modifiable risk factor for AKD. The target blood pressure for most patients with diabetes and AKD is <140/90 mmHg [2]. However, lower targets may be considered for some patients with high cardiovascular risk or albuminuria. The first-line drugs for blood pressure control in patients with AKD are renin-angiotensin system (RAS) inhibitors, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) [23]. These drugs have been shown to reduce proteinuria, slow down the decline of kidney function, and lower the risk of cardiovascular events in patients with AKD. However, they should be used with caution and regular monitoring of serum potassium and creatinine levels, as they may cause hyperkalemia and acute kidney injury in some cases. Other antihypertensive drugs, such as calcium channel blockers, diuretics, or beta-blockers, may be added as needed to achieve the target blood pressure.

- Lipid control: Dyslipidemia is another common and modifiable risk factor for AKD. The target low-density lipoprotein (LDL) cholesterol level for most patients with diabetes and AKD is <100 mg/dL. However, lower targets may be considered for some patients with high cardiovascular risk or albuminuria. The first-line drugs for lipid control in patients with AKD are statins, such as atorvastatin, rosuvastatin, or simvastatin [23]. These drugs have been shown to lower the LDL cholesterol level, reduce the risk of cardiovascular events, and possibly slow down the progression of AKD in patients with diabetes. However, they should be used with caution and regular monitoring of liver function tests, as they may cause hepatotoxicity or myopathy in some cases. Other lipid-lowering drugs, such as ezetimibe, fibrates, or omega-3 fatty acids, may be added as needed to achieve the target LDL cholesterol level [16].

[B]. RAS inhibitors: RAS inhibitors, such as losartan and irbesartan, are commonly used drugs for the treatment of DKD that have gained federal regulatory approval in patients with diabetes manifesting albuminuria; however, relatively few patients are prescribed optimal guideline-recommended doses of the RAS inhibitors, partly due to hyperkalemia and hypotension. Renin-angiotensin system (RAS) inhibitors are a type of medication that can lower blood pressure and protect the kidneys from damage in people with diabetes. RAS inhibitors include angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers
(ARBs). They work by blocking the effects of a hormone called angiotensin II, which causes blood vessels to narrow and increases blood volume and pressure.

However, RAS inhibitors are not a cure for DKD, and they may not work for everyone. Some people may have side effects from RAS inhibitors, such as cough, low blood pressure, high potassium levels, or allergic reactions. RAS inhibitors may also interact with other medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, or lithium. Therefore, it is important to consult with your doctor before starting or changing any medication for Diabetic kidney disease [17-19].

[C]. SGLT-2 inhibitors: SGLT-2 inhibitors are a new class of drugs that have shown efficacy against DKD in clinical trials, such as the Canagliflozin and Renal Events in Diabetes with

Established Nephropathy Clinical Evaluation (CREDENCE) trial. SGLT-2 inhibitors are a class of drugs that lower blood sugar levels by blocking the reabsorption of glucose in the kidneys. They are used to treat type 2 diabetes, but they also have benefits for people with diabetic kidney disease (DKD), which is a complication of diabetes that can lead to kidney failure. SGLT-2 inhibitors have been shown to slow down the progression of DKD by reducing the amount of protein (albumin) in the urine, which is a sign of kidney damage. They also lower blood pressure and improve heart function, which are important factors for preventing kidney failure. SGLT-2 inhibitors can be used in people with DKD who have different levels of kidney function, including those who have a low glomerular filtration rate (GFR), which is a measure of how well the kidneys filter waste from the blood. Some studies have found that SGLT-2 inhibitors can even improve kidney function in some people with advanced DKD [20-23].

However, SGLT-2 inhibitors are not suitable for everyone, and they may have some side effects, such as urinary tract infections, genital infections, dehydration, low blood sugar, or diabetic ketoacidosis (a serious condition where the body produces too much acid from breaking down fat). Therefore, it is important to consult with your doctor before starting or changing any medication for DKD.

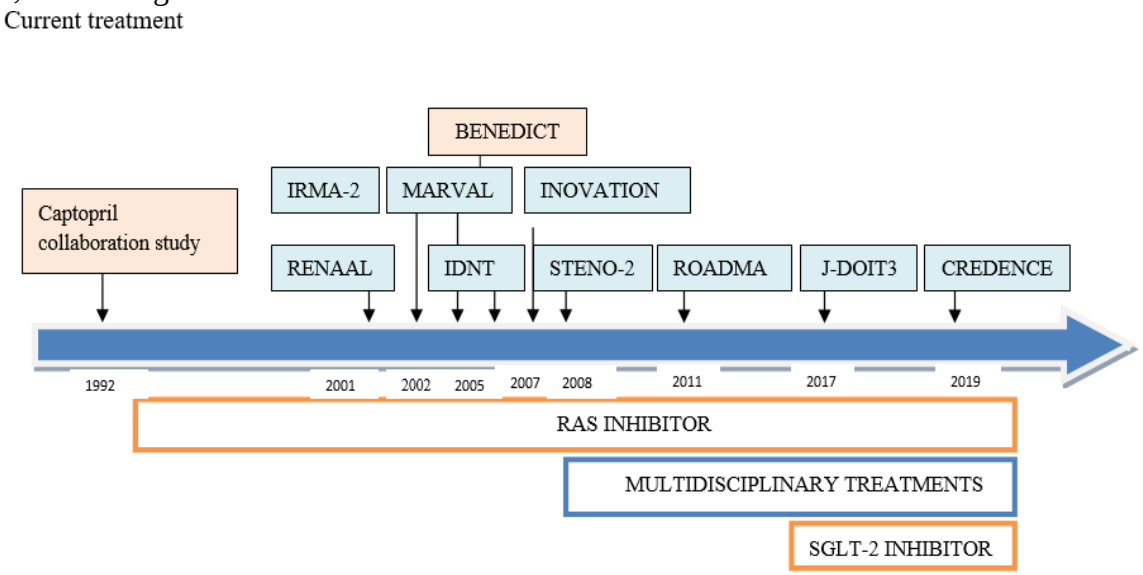

Fig. 6 Time course of current treatment

Future treatment of DKD

[A]. Hypoxia-inducible factor prolyl hydroxylase inhibitor: HIF-PHI are a novel class of drugs that stabilize hypoxia-inducible factors (HIF), which are transcription factors that regulate the cellular response to hypoxia (low oxygen). HIF-PHI can increase the endogenous production of erythropoietin (EPO), a hormone that stimulates red blood cell formation, and thus treat anemia, a common complication of CKD. HIF-PHI can also improve iron utilization and suppress hepcidin, a hormone that inhibits iron absorption and release. HIF-PHI may also have renoprotective effects in DKD, as they can counteract the metabolic alterations and oxidative stress that are induced by hyperglycemia and contribute to kidney damage. HIF-PHI can modulate the expression of genes involved in glucose metabolism, lipid metabolism, inflammation, fibrosis, and angiogenesis, and thus potentially prevent or delay the development of DKD [24].

However, the long-term effects and safety of HIF-PHI in DKD patients are still unclear, and more

studies are needed to confirm their efficacy and optimal dosing [25].

[B]. Epigenetic regulator: Epigenetic regulators are molecules that control gene expression without altering the DNA sequence. They include DNA methylation, histone modifications, and non-coding RNAs. Epigenetic regulators are involved in various biological processes, such as cell differentiation, development, and metabolism. Epigenetic regulators are also implicated in the pathogenesis of diabetic kidney disease (DKD), which is a major complication of diabetes and the leading cause of end-stage kidney disease (ESKD). Hyperglycemia, oxidative stress, inflammation, and other factors can induce epigeetic changes in the kidney cells, such as podocytes, mesangial cells, and tubular cells, and alter their function and phenotype.

Epigenetic changes can persist even after the normalization of blood glucose levels, and contribute to the metabolic memory phenomenon, which is the continued progression of diabetic complications despite adequate glycemic control. Epigenetic changes can also be inherited by the offspring of diabetic parents and increase their susceptibility to DKD. Epigenetic regulators are potential therapeutic targets for DKD, as they can modulate the expression of genes involved in kidney damage and repair, such as fibrosis, inflammation, angiogenesis, and apoptosis. Several epigenetic modifiers, such as DNA methylation inhibitors, histone deacetylase inhibitors, histone methyltransferase inhibitors, and microRNA mimics or inhibitors, have been tested in animal models and cell cultures of DKD, and showed promising results in improving renal function and structure [26].

However, the clinical application of epigenetic modifiers for DKD is still challenging, as they may have off-target effects, toxicity, and poor bioavailability. More studies are needed to identify the specific epigenetic signatures and mechanisms of DKD, and to develop more selective and safe epigenetic modifiers [27].

[C]. AGE Inhibitor: AGEs are molecules that are formed by the non-enzymatic reaction of sugars with proteins, lipids, or nucleic acids [28]. AGEs can accumulate in various tissues and organs, especially under hyperglycemic conditions, and cause oxidative stress, inflammation, and tissue damage. AGEs are involved in the pathogenesis of diabetic kidney disease (DKD), which is a major complication of diabetes and the leading cause of end-stage kidney disease (ESKD) [29,30]. AGEs can bind to their receptors (RAGE) on the surface of kidney cells, such as podocytes, mesangial cells, and tubular cells, and activate various signaling pathways that lead to renal dysfunction and fibrosis [31].

AGE inhibitors are agents that can prevent or reduce the formation or accumulation of AGEs or block their interaction with RAGE. AGE inhibitors can be classified into three categories:

1. Inhibitors of AGE formation, such as aminoguanidine, pyridoxamine, and benfotiamine.
2. Breakers of AGE crosslinks, such as alagebrium and ALT-711.
3. Blockers of AGE-RAGE axis, such as sRAGE and FPS-ZM1.

AGE inhibitors have shown renoprotective effects in animal models and cell cultures of DKD, as they can attenuate the oxidative stress, inflammation, and fibrosis induced by AGEs 124. However, the clinical evidence of AGE inhibitors for DKD is still limited and inconclusive, as most of the trials were small, short-term, or poorly designed.

Some of the challenges and limitations of AGE inhibitors for DKD include: (1) the lack of reliable biomarkers to measure the levels and effects of AGEs; (2) the complexity and heterogeneity of AGEs and their receptors; (3) the potential side effects and toxicity of some AGE inhibitors; and (4) the possible interactions and synergies with other anti-diabetic drugs.

[D]. Nrf2 activator: Nrf2 is a transcription factor that regulates the expression of more than 300 genes involved in antioxidant, anti-inflammatory, and detoxification responses. Nrf2 is normally bound and inhibited by its negative regulator, Kelch-like ECH-associated protein 1 (Keap1), in the cytoplasm. Under oxidative stress or exposure to electrophilic compounds, Nrf2 dissociates from Keap1 and translocates to the nucleus, where it binds to the antioxidant response elements (ARE) in the promoters of its target genes [32,33]. Nrf2 activation has been shown to have renoprotective effects in diabetic kidney disease (DKD), which is a major complication of diabetes and the leading cause of end-stage kidney disease (ESKD). Hyperglycemia, inflammation, and other factors can induce oxidative stress and damage in the kidney cells, such as podocytes, mesangial cells, and tubular cells. Nrf2 activation can counteract these insults by upregulating the expression of genes that encode for antioxidant enzymes, phase II detoxification enzymes, anti-apoptotic proteins, and anti-fibrotic factors [34].

Nrf2 activators are agents that can induce or enhance the activation of Nrf2 and its downstream pathways. They can be classified into three categories: (1) direct activators, which interact with cysteine residues in Keap1 and disrupt its binding to Nrf2; (2) indirect activators, which modulate the phosphorylation or ubiquitination of Nrf2 or Keap1; and (3) dual activators, which have both direct and indirect mechanisms.

Several natural and synthetic Nrf2 activators have been tested in animal models and cell cultures of DKD and showed promising results in improving renal function and structure. Some examples of Nrf2 activators are sulforaphane, cinnamic aldehyde, bardoxolone methyl, ebselen, and dimethyl fumarate. However, the clinical evidence of Nrf2 activators for DKD is still scarce and inconclusive, as most of the trials were small, short-term, or terminated due to safety concerns.

Some of the challenges and limitations of Nrf2 activators for DKD include:

1. the lack of specific and sensitive biomarkers to measure the activity and efficacy of Nrf2 activators.
2. the complexity and heterogeneity of Nrf2 signaling and its interactions with other pathways.
3. the potential side effects and toxicity of some Nrf2 activators, such as increased blood pressure, liver injury, and tumor growth.
4. The possible interactions and synergies with other anti-diabetic drugs.

[E]. Incretin-based drug: Incretin-based drugs have been shown to have beneficial effects on diabetic kidney disease (DKD), which is a major complication of diabetes and the leading cause of end-stage kidney disease (ESKD). Incretin-based drugs can lower blood glucose levels and reduce the risk of hypoglycemia, which are important factors for preventing or delaying the progression of DKD.

Several clinical trials have demonstrated the efficacy and safety of incretin-based drugs for DKD, either as monotherapy or in combination with other anti-diabetic drugs. For example, GLP-1RAs, such as liraglutide, semaglutide, dulaglutide, and albiglutide, have been shown to reduce the risk of major adverse kidney events, such as doubling of serum creatinine, end-stage kidney disease, or death from renal causes, in patients with type 2 diabetes and cardiovascular disease or high cardiovascular risk. DPP-4Is, such as sitagliptin, linagliptin, saxagliptin, and alogliptin, have also been shown to slow down the decline of estimated glomerular filtration rate (eGFR) and reduce albuminuria in patients with type 2 diabetes and DKD. GIP analogs, such as efpeglenatide and tirzepatide, are still under development and have shown promising results in

improving glycemic control and renal function in phase 2 trials [35].

However, the long-term effects and safety of incretin-based drugs for DKD are still unclear, and more studies are needed to confirm their optimal dosing, timing, and combination. Some potential risks of incretin-based drugs include gastrointestinal adverse events, pancreatitis, thyroid cancer, and allergic reactions.

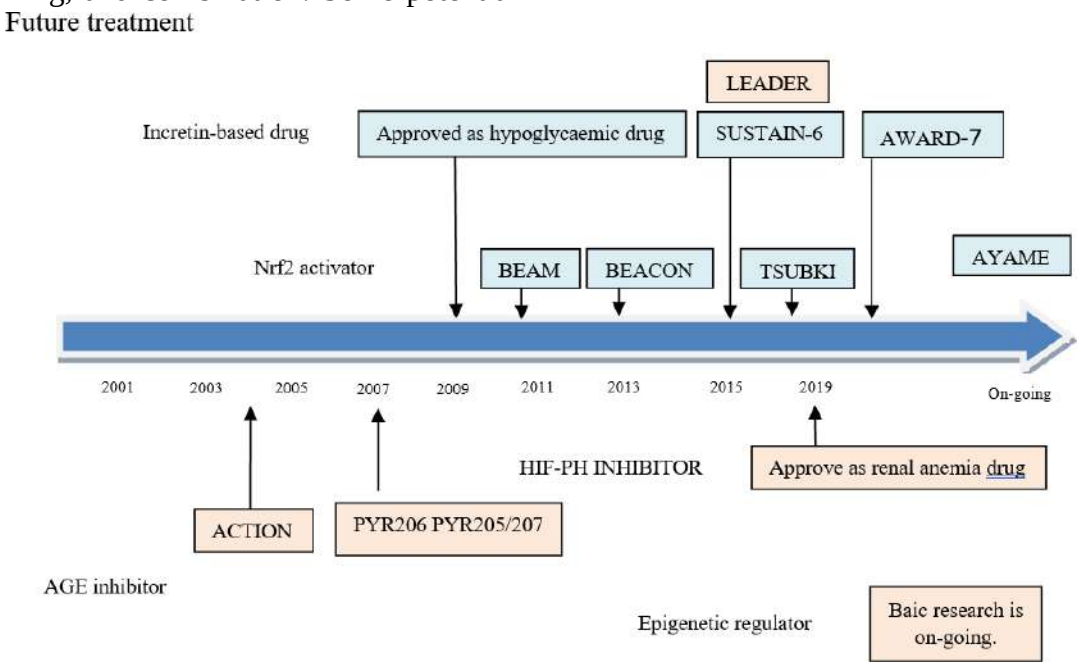

Fig. 7 Time course of current treatment

CONCLUSION:

In conclusion, the intricate relationship between antidiabetic drugs and kidney disease necessitates a meticulous approach in diabetes management. Uncontrolled diabetes heightens the risk of chronic kidney disease, emphasizing the pivotal role of effective glycemic control. Tailoring antidiabetic drug regimens based on renal function, considering the varying impacts of drug classes, and addressing key risk factors are essential for optimizing treatment. Regular monitoring, early intervention, and lifestyle modifications play crucial roles in minimizing adverse effects. The multifaceted pathophysiology involving glucose control, modulation of RAAS, anti-inflammatory effects, and mitochondrial improvements underscores the need for vigilant pharmacovigilance. Personalized, guideline-driven approaches, including consideration of eGFR and dialysis status, are pivotal in clinical practice. While current treatments involve a comprehensive strategy, ongoing research into innovative approaches holds promise for enhancing outcomes in individuals with diabetes and kidney disease.

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