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Management of patients with diabetic and chronic kidney disease

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ABSTRACT

Diabetes is an important problem with its prevalence, difficulties in its treatment and complications that can be fatal. Chronic kidney disease, which often accompanies diabetic patients, complicates the current clinical picture of patients, reduces or complicates treatment options. For this reason, the treatment and follow-up of diabetic patients with chronic kidney disease needs a unique and holistic approach.

Keywords: Diabetes mellitus, chronic kidney disease, diabetes treatment, oral antidiabetic agents

INTRODUCTION

Diabetes is increasing at an unbelievable rate all over the world and, together with the complications it brings, is now becoming an epidemic that threatens humanity (1). Chronic kidney disease (CKD), which often accompanies diabetes patients, is a serious and frequently encountered complication that negatively affects the quality of life of these patients, the success of their treatment, and may even cost the lives of the patients.

Chronic kidney disease is defined as urinary albumin excretion of more than 30 mg in 24 hours (microalbuminuria) and/or GFR value less than 60 ml/min/1.73 m^2 in intermittent controls, and this condition persists for more than 3 months (2,3). Contrary to this generally accepted definition with clear boundaries, the definitions of diabetic kidney disease and diabetic nephropathy are not so clear. The KDIGO 2020 guideline avoids using the definition of diabetic kidney disease on the grounds that it may connote the conclusion that CKD is caused by traditional diabetes pathophysiology in all cases. However the use of the definition of 'diabetic kidney disease' is acceptable provided one is aware of this limitation. On the other hand, the term diabetic nephropathy is defined as an outdated and not agreed upon definition and avoided using this definition (4). In a study conducted in the USA, the incidence of CKD in type 2 diabetes patients was investigated, and researchers reported that this rate was between 34.5 and 42.3% in the literature, and they reported this rate as 38.3% in their own study (5). In this study, the stages of patients with CKD were also examined, and it was seen that 9.1% of type 2 diabetes patients had stage 1, 9.4% had stage 2 and 11.2% had stage 3A CKD. In addition, it revealed that 0.7% of all patients had stage 5 CKD.

Stages	Patient Rate %
Stage 1	9.1
Stage 2	9.4
Stage 3A	11.2
Stage 3B	5.5
Stage 4	2.4
Stage 5	0.7
Unstageable	61.7

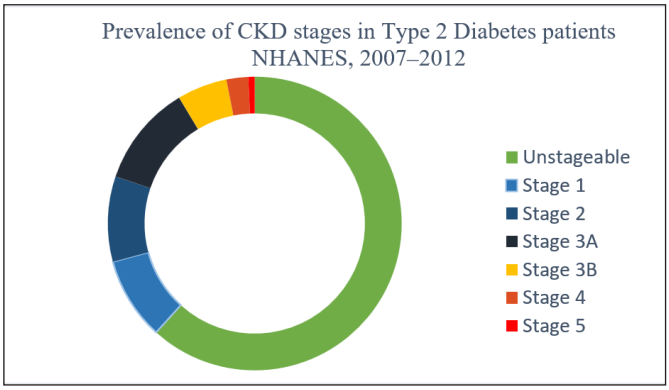

Table and Figure 1. Prevalence of CKD stages in Type 2 Diabetes patients. NHANES, 2007-2012 (5)

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The CREDIT study provides important data on CKD in our country (6). In the study, the incidence of CKD in Turkey was determined as 15.7%, and CKD was observed in 32.4% of diabetic patients. To put it another way, more than a quarter (26.6%) of CKD patients at any stage have diabetes.

Stages	Patient Rate %
Stage 1	22.5
Stage 2	39.4
Stage 3	33.8
Stage 4	2.8
Stage 5	1.6

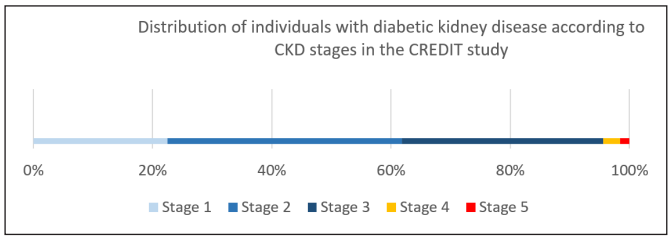

Table and Figure 2. Distribution of individuals with diabetic kidney disease according to CKD stages in the CREDIT study (6)

To summarize, the incidence of chronic kidney disease in type 2 diabetes patients has been reported up to 40% (7). In these patients, the risk of developing end-stage renal disease increases up to 20% in 20 years (8). In addition, it has been demonstrated that diabetic nephropathy is the most common cause of end-stage renal disease in adults (9). The coexistence of diabetes and chronic kidney disease, which causes increased cardiovascular risk and difficulties in glycemic control, should be recognized early; The treatment should be planned individually, paying attention to treatment complications, and closely monitored.

PHYSIOPATOLOGY OF DIABETIC RENAL DISEASE

In diabetic kidney disease; there are changes in renal hemodynamics and increased renin-angiotensin-aldosterone-system (RAAS) activity, pathological changes in glucose metabolism, increased inflammatory process, hypoxia and oxidative damage (10). These various mechanisms cause structural damage and functional deficiencies in the kidney and ultimately kidney fibrosis.

Hyperglycemia causes vasodilation in the afferent arteliol through various vasoactive mediators (IGF-1, glucagon, nitric oxide, VEGF and prostaglandin). At the same time, with the increase of angiotensin II, vasoconstriction develops in the efferent arteliol. This mechanism, which is responsible for the hyperfiltration seen in early diabetic kidney disease; It contributes to an increase in intraglomerular pressure and hypertrophy in the glomeruli, and in the following process, it contributes to fibrosis in the glomeruli (10).

The hyperglycemic state additionally leads to various metabolic pathologies such as increased protein kinase C (PKC) activation, alterations in the polyol pathway, and increased advanced glycosylated product. The increase in PKC level exacerbates hyperfiltration by contributing to vasodilation in the afferent arteliol and vasoconstriction in the efferent arteliol in the nephron through the increase of prostaglandin E2 and NO. In addition, PKC activation causes microalbuminuria by increasing capillary permeability through Vascular endothelial growth factor (VEGF) increase and causes pathological changes in the histological structure of the nephron by increasing transforming growth factor (TGF-B). The change in the polyol pathway, which is a pathway in carbohydrate metabolism, causes an increase in oxidative stress and a tendency to apoptosis in the cell. High glucose levels cause an increase in advanced glycosylated products. These products accumulate in the tissue and cause oxidative stress, as well as contribute to kidney damage by triggering the production of growth factor and various cytokines that cause fibrosis (11).

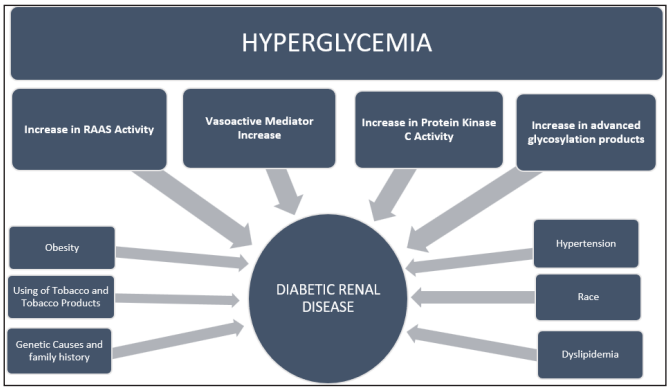

Figure 3. Pathophysiology of diabetic kidney disease (8)

It is visualized from the article Diabetic Kidney Disease: Pathophysiology and Therapeutic Targets.

In summary, hyperglycemia is the main risk factor for the development of diabetic kidney disease through many pathological mechanisms, and should be evaluated together with the severity of hyperglycemia and the length of time spent in the hyperglycemic state. In addition to hyperglycemia; hypertension, dyslipidemia, obesity, history of tobacco and tobacco products use, ethnic predisposition should be investigated. Finally, genetic predisposition should be evaluated by questioning family history of DM, RAS polymorphism, and insulin resistance.

CHALLENGES IN TREATMENT OF DIABETIC RENAL DISEASE

When planning treatment for glycemic control in diabetic kidney disease, it is extremely important to evaluate oral antidiabetic drugs in terms of albumin binding, metabolism and renal elimination for the success of medical treatment and avoiding treatment-related complications. When arranging treatment with insulin, it should be kept in mind that the peripheral tissues of the patient show resistance to insulin and there is a decrease in insulin degradation, and that insulin doses need to be regulated (12).

It is known that the main source of glucose in the bloodstream in a healthy person originates from the liver via glucogenolysis and gluconeogenesis. However, what should not be overlooked is that the share of the liver in circulating glucose is roughly 70-75%, and the remaining 20-25% is provided by the kidney via gluconeogenesis (13). As this explains why patients with diabetes and kidney disease are more vulnerable to hypoglycemia, this information should always be considered when determining target blood glucose levels in patients.

Low effort capacity, decrease in exercise, loss of muscle mass and anorexia are frequently observed in diabetic kidney patients. In the presence of these morbidities, it becomes difficult to implement therapeutic lifestyle changes and the patient's response to treatment decreases. In addition, complications associated with diabetic kidney disease; infection, malignancy, gastroparesis should always be kept in mind when evaluating a patient. It should be noted that the solutions used for dialysis in end-stage renal disease patients followed up with peritoneal dialysis contain high amounts of glucose, this glucose passes into the blood from the peritoneum and consequently contributes to hyperglycemia and weight gain (14). In the presence of these factors mentioned above, it is clear that the treatment and follow-up of the patient will be difficult and complex.

In diabetic kidney patients, there are various difficulties in the evaluation of glycemic control as well as in providing glycemic control. Glycated hemoglobin (HbA1c) is the first criterion to be evaluated for the success of diabetic treatment in clinical practice. The relationship between the factors causing the increase and decrease of HbA1c value and the pathophysiology of chronic kidney disease should be well understood. Shortening of erythrocyte lifespan, hemolysis, transfusion, history of erythropoietin (EPO) use indicate low HbA1C value. In addition, increased carbamile Hb in renal failure, iron deficiency, hypertriglyceridemia, hyperbilirubinemia, metabolic acidosis; It increases the HbA1C value (15). These factors, which often accompany chronic kidney patients, cause the HbA1C value to give erroneous results and as a result; It may lead to erroneous assessment of the patient's condition and incorrect treatment planning.

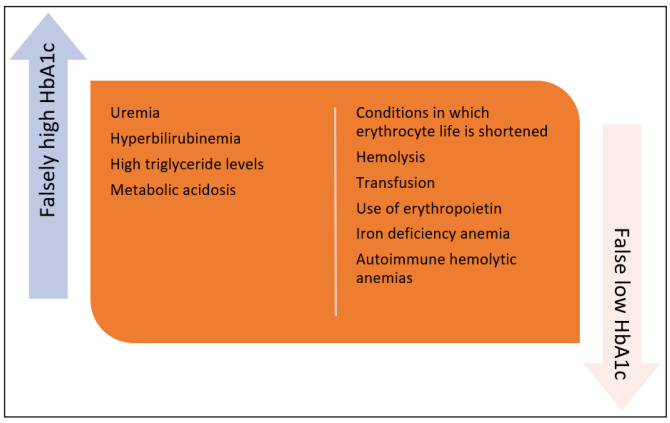

Figure 4. Factors affecting Glycated hemoglobin (15)

While planning the treatment, it should be taken into consideration that chronic kidney patients may be in uremic or acidosis state, and that some biochemistry test techniques may give erroneous results in these non-ideal conditions, and consequently may mislead treatment and follow-up.

Nausea and vomiting due to the uremic picture is a common picture. If there is nausea-vomiting due to diabetic ketosis, this situation may be mistakenly thought to be due to uremia, and the diagnosis of ketosis may be delayed.

ORAL ANTIDIABETIC THERAPY IN PATIENTS WITH CKD

Medical treatment of the patient; cost, goodness in glycemic control, side-effect profile, comorbidities should be taken into consideration, and it should be planned with clinical experience. The treatment of the patient should not be approached with a narrow perspective focused only on regulating the patient's blood sugar; it is necessary to provide weight loss, to keep cardiovascular risks under control by monitoring the lipid profile, to stop the progression of kidney disease, to protect and maintain beta cell function, to protect bone tissue and bone health, and to aim to provide all these without exposing the patient to hypoglycemia. Finally, protecting the patient from polypharmacy and considering the patient's wishes will ensure treatment compliance and the success of the treatment.

1-Insulin Secretagogues

Sulfonylureas: They bind to Sulfonylurea receptor 1 (SUR1) receptors in pancreatic beta cells (16). They increase insulin secretion from beta cells by inhibiting the receptor's ATP-dependent potassium channels. To be effective, the beta-cell function must be present. In other words, if c-peptide

is extremely low in long-term diabetics, these drugs are not effective. Today, 2nd generation sulfonylureas are used. Advantages: They reduce HbA1c by 1-2%, they are powerful drugs and cheap.

Table 3. Oral antidiabetics

Insulin secretagogues	
Sulfonylureas	Gliclazide, glimeprid, glipizide, glibenclamide, glibornuride
Meglitinides	Repaglinide, nateglinide
Drugs that increase insulin sensitivity	
Biguanides	Metformin
Thiazolidinedione derivatives	Pioglitazone
Alpha glucosidase inhibitors	Acarbose, miglitol, voglibose
Insulinomimetic drugs	
Incretin-based therapies	
Dipeptidyl peptidase 4 (DPP4) inhibitors	Sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin
Glucagon-like peptide 1 (GLP 1) analogues*	Exenatide, liraglutide, dulaglutide, semaglutide, lixisenatide
Amylin analogues*	Pramlintide
Sodium glucose co-transporter 2 inhibitors	Dapagliflozin, empagliflozin, canagliflozin, ertugliflozin

*Subcutaneous (qv. Treatment with GLP-1 analogues in CKD)
* Subcutaneous (Not available in our country.)

In treating type 2 diabetes, sulfonylureas can be combined with other oral antidiabetics and insulin. However, they are not given together because they have the exact mechanism of action as the meglitinide group. They are not used together when switching to intensified insulin therapy because of the high risk of hypoglycemia. Maturity onset is effective in patients with diabetes of young (MODY).

The most critical side effects are hypoglycemia, and because they secrete insulin, they cause weight gain, just like insulins. They may cause cross-reactivity in those allergic to sulfonamides. They can cause nausea, liver enzyme elevation, and hematological side effects. They are tightly bound to circulating albumin and interact with warfarin, sulfonamides, fibrates, and acetaminophen. They can accelerate the loss of beta cells and shorten the transition time of patients to insulin (17).

- Gliclazide/Glipizide: Not recommended for use below eGFR 30 ml/min/1.73 m^2. In the eGFR range of 30-60 ml/min/1.73 m^2, the dose should be reduced by 50%.
- Glimepiride: Its use is not recommended if the eGFR is 30 ml/min/1.73 m^2.
- Glibenclamide: Its use is contraindicated if eGFR is below 30 ml/min/1.73 m^2. It should not be used if eGFR is between 30-60 ml/min/1.73 m2; if possible, the dose should be reduced by 50% (18).

Meglitinides: They act by binding to a different region of the SUR1 receptor and making short-term inhibition. They are especially used to lower postprandial blood sugar. They differ pharmacologically from sulfonylureas; they can be used in allergic to sulfonamides. There are two drugs available, repaglinide and nateglinide. They are used three times a day, before each meal. Since the liver metabolizes repaglinide, it can be used in renal failure (19). It can be given at low doses in patients with a GFR of 20-40 ml/min/1.73 m^2. It should not be used in patients with GFR<20 ml/min/1.73 m^2. Nateglinide undergoes hepatic metabolism, and its renal metabolites are also active. Therefore, caution should be exercised in both kidney and liver failure. They cause less hypoglycemia than sulfonylureas, and their weight-gaining effects are similar.

- Repaglinide: Not recommended if eGFR is 30 ml/min/1.73 m^2.
- Nateglinide: It is contraindicated if the eGFR is below 15 ml/min/1.73 m^2. The dose should preferably be reduced by 50% in the range of eGFR 15-30 ml/min/1.73 m^2. According to clinical studies, it has been reported that there is no need for dose adjustment if the eGFR is 15-30 ml/min/1.73 m^2 (18).

2-Drugs that Increase İnsulin Sensitivity

Biguanides (metformin): Metformin, the only member of the biguanide drug family in use, has gained a unique place in the treatment of diabetes (20). Metformin suppresses hepatic gluconeogenesis and lipogenesis by increasing the activation of AMP protein kinase enzyme. It also decreases the conversion of lactate to pyruvate. Metformin; can provide a decrease of almost 1.5% in HbA1C value and 50 mg/dL in fasting plasma glucose (21). Despite its strong effect on fasting blood sugar, it is considered safe for hypoglycemia as it does not affect insulin secretion. Due to its side effects on the gastrointestinal system and a slight increase in GLP1, it reduces the appetite. In this way, it has been shown that it helps patients to maintain their body weight and even reduces body weight in obese patients (22). Some studies indicate that metformin has a cardiac protective effect apart from and independently of its contribution to glycemic control. Its cardiovascular protective feature is decrease in total cholesterol, LDL and VLDL, HDL neutral or increase; It is associated with a decrease in oxidative stress, a decrease in blood pressure, and a decrease in platelet aggregation (23). According to these studies, metformin may make the heart tissue more resistant to ischemia and post-ischemia reperfusion injury in diabetic and non-diabetic patients. Researchers have reported that this cardiac protective effect of metformin is independent of hyperglycemia control,

with changes in the mitochondrial structure through receptor interactions (24). The use of metformin, which is known as the first drug to be used in the treatment of diabetes with the mentioned advantages, in chronic kidney patients requires close follow-up due to the metabolic complications of the drug and the need for dose regulation. The most common side effects in metformin use are temporary problems such as gas, bloating, cramps, diarrhea and metallic taste in the mouth, originating from the gastrointestinal tract and that can be managed with low initial doses (25). It has been observed that metformin may cause B12 deficiency in the long term (26), and B12 levels should be monitored in patients using metformin for more than 4 years. However, the main side effect of metformin is lactic acidosis, with a mortality rate of 50%. Although the mechanism of action of metformin has not yet been fully elucidated, it is known that it accelerates glucose breakdown via the anaerobic pathway and increases lactate formation as a result of this process. Although it has been reported to occur in 9 patients per 100,000 patient-years, considering the prevalence of diabetes and the frequency of use of metformin, it is clear how serious and widespread this problem is (27). Emphasizing that lactate is used almost as a unit of measurement when evaluating the severity of tissue hypoxia, especially in patients with sepsis; It should be noted that hypoperfusion and hypoxemia are important predisposing causes for lactic acidosis. When evaluating a patient in terms of lactic acidosis risk, first of all; The patient should be examined for acute and chronic renal failure, uncompensated heart failure, acute pulmonary decompensation, active liver disease. While taking the patient's medical history, whether he has had lactic acidosis related to metformin before and alcohol consumption should be questioned. In addition, care should be taken against an existing infection or sepsis in the patient.

Metformin can be used with or without food; The daily dose is 500-2550 mg (2-3 times a day), the daily dose of metformin extended-release form is 500-2000 mg (1-2 times a day). Turkish Society of Endocrinology and Metabolism recommends not to start GFR <45 ml/min and to start half dose with GFR 45-60 ml/min. The American Drug Administration (FDA) recommends not to start GFR <30ml/min and dose reduction to GFR 30-45ml/min. It is recommended to stop 24 hours before contrast (such as angiography, etc.) procedures and start again if creatinine measurement is normal 24 hours later. Metformin should not be used in cases of shock, hypoxia, COPD, acute decompensated (resistant, class IV) heart failure, and severe renal failure (should not be started if GFR <45 ml/min; should be discontinued if GFR <30 ml/min). Liver failure, chronic alcoholism, peripheral arterial disease, pregnancy and lactation period, primary surgical intervention, advanced age (over 80 years) are contraindications.

As a result, metformin; is the drug group with the best results among oral agents. It has been shown to reduce deaths from all causes in patients with coronary artery disease. It can be combined with other diabetes medications and insulins. It does not gain weight, does not cause hypoglycemia, and is inexpensive. It should be continued unless there are contraindications. According to current guidelines (ADA, EASD, IDF, TEMD), "It is still the first drug to be given at the time of diagnosis in the treatment of type 2 DM.

- If the GFR is over 45 ml/min/1.73 m^2, it can be used without dose adjustment. Between the GFR 45-30 ml/min/1.73 m^2, the dose should be reduced by 50%.
- It is contraindicated if the GFR is below 30 ml/min/1.73 m^2 (18).

Thiazolidinediones (pioglitazone): The starting dose is 15-30 mg, the maximum dose is 45 mg, once a day. If edema does not develop for 1-3 months at a low dose and the glycemic response is insufficient the dose increases. They decrease glucose production in the liver and increase peripheral insulin sensitivity. Peroxisome proliferator-activated receptor (PPAR) makes gamma activation (28). It has a high HbA1c reducing effect (0.5-1.4% decrease in HbA1c). It is metabolized by CYP 2C8 and CYP 3A4 and excreted in bile. They do not cause hypoglycemia, are generally well-tolerated, increase HDL levels, decrease triglycerides and reduce secondary cardiovascular events. It has been found to reduce carotid intima-media thickness, improve endothelial functions, decrease blood pressure, improve fibrinolytic and coagulation factors, and slow restenosis in coronary stents. It primarily reduces insulin resistance by acting on adipose tissue. Benefits have been demonstrated in non-alcoholic fatty liver disease.

They can prevent the progression to diabetes in prediabetics. It is seen that glitazones provide a significant reduction in the risk of type 2 diabetes as a group, and even this effect is much greater than that obtained with metformin and has a beneficial effect close to lifestyle adjustments. However, despite these findings, glitazones in prediabetic patients are not recommended. Because potential side effects such as fluid retention, weight gain, heart failure exacerbation, osteoporotic fractures, and bladder cancer preclude the benefits. The cost of using it as a preventive treatment is also relatively high. The same benefit can be achieved with lifestyle adjustments in prediabetes, which is an increasingly common and important public health problem.

It should not be used in congestive heart failure (CHF) as it increases sodium reabsorption and consequent water retention. The risk of edema is higher in insulin users, women, obese, pre-existing edema, and those with congestive heart failure. Salt restriction is done, diuretics are used if necessary. CHF and anasarca edema are seen in 2% of patients. It can also cause anemia, weight gain, increased liver enzymes, worsen Graves' ophthalmopathy. It can increase the risk of fractures in postmenopausal women and older men, increasing respiratory tract infections. It should not be given to patients with bladder cancer or unexplained hematuria. In addition, it is contraindicated in those with elevated ALT (over 2.5 times), CHF classes I-IV, conical severe renal failure, pregnancy, type 1 DM, macular edema, adolescents, and children (29). According to the results of some studies, rosiglitazone has been discontinued in our country due to an increase in myocardial infarction.

As a result, there are limitations in using pioglitazone due to its side effects. It is included in current guidelines by specifying its side effects. Metformin treatment can be considered insufficient or in double or triple combinations. Combining it with an SGLT2i makes sense, which would counteract its oedematous effect. It has protective effects on β-cell function and reduces the conversion to diabetes. When placing an indication, the decision should be made according to the patient's characteristics, considering the possible side effects, benefits, and harms.

- Although there is no need for dose regulation according to clinical studies, it is recommended to be used with caution and dose reduction if necessary due to the risk of fluid retention below GFR 30 ml/min/1.73 m^2 (18).

3- Alpha Glucosidase Inhibitors

Acarbose is the only agent available in our country; it has 50-100 mg tablets (dose 50 or 100 mg tablets three times a day). The tablets are taken by swallowing with some liquid before the meal or chewing with the first bites. They prevent carbohydrate absorption by blocking the breakdown of polysaccharides into monosaccharides in the intestine. The intestinal flora metabolizes it, its absorption is minimal, and its metabolites are inactive. Compared to other oral antidiabetics, they are relatively weakly effective. HbA1c is reduced by 0.5-1.3%. They can provide glycemic control without gaining weight, do not cause hypoglycemia, and prevent the progression to diabetes in prediabetics (30).

There are side effects, bloating, diarrhea, abdominal pain (10-25%), and rarely iron deficiency. Although it does not cause hypoglycemia in monotherapy, it can cause hypoglycemia when used with sulfonylurea, glinide, and insulin. Hepatotoxicity can be seen rarely. Contraindicated in inflammatory bowel disease, chronic ulceration, malabsorption, partial bowel obstruction, cirrhosis, pregnancy, and lactation

- Contraindicated below GFR25 ml/min/1.73 m^2 (18).

4- Insulinomimetic Drugs

Incretin-acting drugs (Dipeptidyl peptidase four inhibitors): Inhibition of the DPP-4 enzyme, which provides rapid degradation of the GLP-1 molecule in the postprandial period, emerges as a new group of antidiabetic drugs that increase the levels of endogenous and natural incretins, GLP-1 and GIP. They increase insulin secretion in a glucose-dependent manner. They reduce glucagon secretion (31). They are neutral in terms of weight and have no gastrointestinal side effects. Their costs are high. They reduce HbA1c by 0.6-1.1%. They can be used together with other oral antidiabetics' insulin and can reduce insulin requirements, which indirectly helps the patient lose weight. Since the risk of hypoglycemia is higher in the sulfonylurea combination, they can be used with metformin in elderly patients. They have good tolerability, do not cause hypoglycemia, and improve islet cell functions by increasing pancreatic alpha and beta-cell responsiveness. They do not increase the risk of cardiovascular disease. Saxagliptin and alogliptin alone increase hospitalization for heart failure (32).

As a side effect; They can cause headache, nasopharyngitis, upper respiratory tract infection, gastrointestinal side effects (especially with sitagliptin), acute pancreatitis, urinary system infections, hepatic dysfunction (especially with vildagliptin and alogliptin), inflammatory bowel diseases, skin reactions, arthralgia, myalgia. Linagliptin is eliminated from the enterohepatic system and can be used without dose changes in chronic renal failure. Others require dose adjustment according to GFR.

- Sitagliptin: If the GFR is in the range of 30-50 ml/min/1.73 m^2, the dose should be reduced by 50%. When the GFR is below 30 ml/min/1.73 m^2, the dose can be reduced by 75%. If possible, it should not be used under GFR 30 ml/min/1.73 m^2.
- Vildagliptin: It can be given in half dose when the GFR is 30 ml/min/1.73 m^2. It should preferably not be used if the GFR is below 15 ml/min/1.73 m^2.
- Saxagliptin: If the GFR is between 15-50 ml/min/1.73 m^2, the dose should be reduced by 50%. It is contraindicated if the GFR is below 15 ml/min/1.73 m^2.
- Linagliptin can be used without dose adjustment, including in patients receiving routine dialysis.

- Alogliptin: If the estimated glomerular filtration rate (e-GFR) is 30-60 ml/min/1.73 m^2, the dose can be reduced by 50%, and if the eGFR is 15-30 ml/min/1.73 m^2, it can be used by reducing it by 75%. Alogliptin should not be used in patients with an eGFR of 15 ml/min/1.73 m^2 (18).

5- Sodium Glucose Co-transporter 2 Inhibitors

Sodium-glucose co-transporter-2 inhibitors (SGLT2I) prevent glucose reabsorption in the proximal tubule in the kidney, causing glucose loss from the blood to the urine. This mechanism lowers blood sugar independently of insulin and provides calorie loss and reduction in body weight. In addition, lost glucose exerts diuretic activity by providing diuresis and natriuresis with an osmotic effect (33). It has been observed that SGLT2I has cardiovascular and renal protective activity, and this activity is thought to have reasons other than its contribution to glycemic control. SGLT2I may have a renal protective effect independent of blood sugar regulation by lowering intraglomerular pressure or causing hyperfiltration of the nephron. From a cardiac point of view, SGLT2I may have a cardioprotective effect by providing natriuresis and its effectiveness against cardiac fibrosis and directing energy metabolism from carbohydrates to ketone bodies (34). SGLT2 inhibitors have become a prominent drug family in patients with complicated diabetes, with their broad efficacy outside of blood sugar regulation.

In addition to glycemic control, the primary purpose of using antidiabetic drugs in diabetic patients should be to slow the progression of kidney disease, reduce cardiovascular events and prolong life. Essential treatment approaches to achieve this goal; lifestyle changes (healthy diet, weight loss, salt reduction, smoking cessation, and physical activity), blood pressure control with RAS blockers, and statin use. While targeting glycemic control, the organ protective properties of the drugs used should be taken into account, and first of all, a drug with evidence that it reduces the progression of heart failure, albuminuria, and CKD should be given. In the light of the scientific data of the studies mentioned in the previous section, SGLT-2 inhibitors are the first group of drugs to be selected in this case. The first drug to be added after SGLT-2 inhibitors should be metformin. SGLT-2 inhibitors and metformin, which have a low risk of hypoglycemic complications, are effective against diabetes complications separately and can be combined.

- Dapagliflozin: e-GFR should not be used below 60 ml/min/1.73 m^2.
- Empagliflozin: If the e-GFR is 45 ml/min/1.73, it is not recommended to be used because it will be ineffective in the treatment.
- Canagliflozin: It can be used by reducing the dose (100 mg/day) in the range of e-GFR 45-60 ml/min/1.73 m^2. If the e-GFR is below 45 ml/min/1.73 m^2, it is not recommended to be used because it will be ineffective in the treatment (18).

INSULIN THERAPY IN CKD PATIENT

In the uremic environment, the effect of insulin is increased as its metabolism will be impaired due to its breakdown. In addition, decreased appetite due to uremic status in CKD patients and weight loss occur over time, leading to a decrease in blood sugar. As the renal dysfunction increases, the need for insulin in most of these patients decreases in the following periods, and insulin is not needed in a significant part of them. Particular attention should be paid to hypoglycemia in these patients. In principle, it is recommended to halve the insulin dose when the urea-creatinine elevation begins.

TREATMENT WITH GLP-1 ANALOGUES IN PATIENT WITH CKD

In patients with diabetic kidney disease, when needed, it is recommended to use GLP-1 receptor agonists with known kidney and heart-protective effects after SGLT-2 inhibitor and metformin treatment. In studies on this subject, a significant reduction in renal outcomes, especially in new-onset moderate-to-severe albuminuria and ESRD risk, has been observed with GLP-1 receptor agonists.

Among the drugs available in our country, exenatide can be used if the e-GFR is above 30 ml/min/1.73 m^2. Liraglutide can be used above e-GFR 15 30 ml/min/1.73 m^2. These drugs can cause abdominal pain, nausea, and vomiting. It is recommended to start with a low dose (exenatide 2x5 mcg/day subcutaneously) and continue in patients with impaired renal function.

- Exenatide: It is recommended to be careful when increasing the dose from 5 mcg to 10 mcg in the GFR range of 30-50 ml/min/1.73 m^2. e-GFR is contraindicated below 30 ml/min/1.73 m^2.
- Lixisenatide: Contraindicated below e-GFR 30 ml/min/1.73 m^2.
- Liraglutide: Contraindicated below e-GFR 15 ml/min/1.73 m^2.
- Dulaglutide: If the GFR is below 15 ml/min/1.73 m^2, it should not be used if possible, and the dose should be reduced if necessary.
- Albiglutide: It should not be used under e-GFR <15 ml/min/1.73 m^2 (18).

Table 4. Dose regulation of oral antidiabetics according to e-GFR level

		Estimated glomerular filtration rate					
Pharmaceutical group	**Active substance**	**>90**	**90-60**	**60-45**	**45-30**	**30-15**	**<15**
Biguanides	Metformin	No dose adjustment required			Should be reduced by 50%	Contraindicated	
Sulfonylureas	Gliclazide Glipizide	No dose adjustment required		Should be reduced by 50%		Should not be used	
	Glimepiride	No dose adjustment required				Should not be used	
	Glibenclamide	No dose adjustment required	Should not be used/reduced by 50% if necessary			Contraindicated	
Meglitinides	Repaglinide	No dose adjustment required				Should not be used	
	Nateglinide	No dose adjustment required				Should be reduced by 50%	Contraindicated
Thiazolidinedione	Pioglitazone	No dose adjustment required				Dose should be reduced	
Dipeptidyl peptidase 4 inhibitors	Acarbose	No dose adjustment required				Contraindicated if GFR<25	
	Sitagliptin	No dose adjustment required		If GFR is <50, the dose should be reduced by 50%.		Should not be used, if necessary, the dose should be reduced by 75%	
	Vildagliptin	No dose adjustment required				Dose should be reduced by 50%	Contraindicated
	Linagliptin	No dose adjustment required					
	Alogliptin	No dose adjustment required		Dose should be reduced by 50%		Dose should be reduced by 75%	Contraindicated
Sodium Glucose Co-transporter 2 Inhibitors	Dapagliflozin	No dose adjustment required		Should not be used			
	Canagliflozin	No dose adjustment required		Dose should be reduced	Not recommended for use		
	Empagliflozin	No dose adjustment required			Not recommended for use		
Glucagon-like peptide1 (GLP 1) analogues	Exenatide	No dose adjustment required		Care should be taken in increasing the dose of GFR <50		Contraindicated	
	Lixisenatide	No dose adjustment required				Contraindicated	
	Liraglutide	No dose adjustment required					Contraindicated

It is adapted from the resource named 'TEMD Diabetes Mellitus and Its Complications Diagnosis, Treatment and Follow-up Guide-2020' (18).

CONCLUSION

When determining glycemic control targets in CKD patients; The potential benefit-risk ratio of the patient should be considered, and it should be aimed to avoid treatment-related hypoglycemic complications and aim for improvement in complications. It should not be forgotten that hypoglycemia can cause mortality much faster than hyperglycemia. Hyperglycemia is a common problem; Often, the reason is the wrong insulin treatment regimen or non-compliance with the treatment, and inadequate insulin absorption should be evaluated. Infrequent and resistant hypoglycemic events; Low-calorie intake should be questioned, and an underlying infection or malignancy should be considered. Avoiding drugs such as long-acting antidiabetics and beta-blockers that impair the counterregulatory response in these patients; will make it easier for the metabolism to protect itself from hypoglycemia, as well as to show symptoms in a possible hypoglycemic situation, making it possible for the patient and the doctor to notice hypoglycemia and take precautions.

While planning the treatment of the patient, not only the drugs, but also the lifestyle and diet should be regulated. The general medical condition of the patient, the cultural and socio-economic conditions of the patient should be taken into account.

ETHICAL DECLARATIONS

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REFERENCES

1. Huizinga MM, Rothman RL. Addressing the diabetes pandemic: a comprehensive approach. Indian J Med Res 2006; 124: 481-4.
2. Levey AS, Coresh J. Chronic kidney disease. Lancet 2012; 379: 165-80.
3. Toto RD. Microalbuminuria: definition, detection, and clinical significance. J Clin Hypertens (Greenwich) 2004; 6: 2-7.
4. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int 2020; 98: S1-S115.
5. Wu B, Bell K, Stanford A, et al. Understanding CKD among patients with T2DM: prevalence, temporal trends, and treatment patterns-NHANES 2007-2012. BMJ Open Diabetes Res Care 2016; 4(1): e000154.
6. Süleymanlar G, Utaş C, Arinsoy T, et al. A population-based survey of Chronic REnal Disease In Turkey--the CREDIT study. Nephrol Dial Transplant 2011; 26: 1862-71.
7. Jitraknatee J, Ruengorn C, Nochaiwong S. Prevalence and risk factors of chronic kidney disease among type 2 diabetes patients: a cross-sectional study in primary care practice. Sci Rep 2020; 10: 6205.
8. Ghaderian SB, Hayati F, Shayanpour S, Beladi Mousavi SS. Diabetes and end-stage renal disease; a review article on new concepts. J Renal Inj Prev 2015; 4: 28-33.
9. Reikes ST. Trends in end-stage renal disease. Epidemiology, morbidity, and mortality. Postgrad Med 2000; 108.
10. Lin YC, Chang YH, Yang SY, Wu KD, Chu TS. Update of pathophysiology and management of diabetic kidney disease. J Formos Med Assoc 2018; 117: 662-75.
11. Toth-Manikowski S, Atta MG. Diabetic Kidney Disease: Pathophysiology and Therapeutic Targets. J Diabetes Res 2015; 2015: 697010.
12. Snyder RW, Berns JS. Use of insulin and oral hypoglycemic medications in patients with diabetes mellitus and advanced kidney disease. Semin Dial 2004; 17: 365-70.
13. Gerich JE, Meyer C, Woerle HJ, Stumvoll M. Renal gluconeogenesis: its importance in human glucose homeostasis. Diabetes Care 2001; 24: 382-91.
14. Duong U, Mehrotra R, Molnar MZ, et al. Glycemic control and survival in peritoneal dialysis patients with diabetes mellitus. Clin J Am Soc Nephrol 2011; 6: 1041-8.
15. Welsh KJ, Kirkman MS, Sacks DB. Role of Glycated Proteins in the Diagnosis and Management of Diabetes: Research Gaps and Future Directions. Diabetes Care 2016; 39: 1299-306.
16. Thulé PM, Umpierrez G. Sulfonylureas: a new look at old therapy. Curr Diab Rep 2014; 14: 473.
17. Costello RA, Nicolas S, Shivkumar A. Sulfonylureas. In: StatPearls. Treasure Island (FL): StatPearls Publishing; February 23, 2022.
18. TEMD Diabetes Mellitus and Its Complications Diagnosis, Treatment and Follow-up Guide-2020
19. Black C, Donnelly P, McIntyre L, Royle PL, Shepherd JP, Thomas S. Meglitinide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev 2007; 2007: CD004654.
20. Flory J, Lipska K. Metformin in 2019. JAMA 2019; 321: 1926-7.
21. Dunn CJ, Peters DH. Metformin. A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. Drugs 1995; 49: 721-49.
22. Golay A. Metformin and body weight. Int J Obes (Lond) 2008; 32: 61-72.
23. Lv Z, Guo Y. Metformin and its benefits for various diseases. Front Endocrinol (Lausanne) 2020; 11: 191.
24. Zhang J, Huang L, Shi X, et al. Metformin protects against myocardial ischemia-reperfusion injury and cell pyroptosis via AMPK/NLRP3 inflammasome pathway. Aging (Albany NY) 2020; 12: 24270-87.
25. Corcoran C, Jacobs TF. Metformin. In: StatPearls. Treasure Island (FL): StatPearls Publishing; May 2, 2022.
26. Tomkin GH, Hadden DR, Weaver JA, Montgomery DA. Vitamin-B12 status of patients on long-term metformin therapy. Br Med J 1971; 2: 685-7.
27. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: current perspectives on causes and risk. Metabolism 2016; 65: 20-9.
28. Gillies PS, Dunn CJ. Pioglitazone. Drugs 2000; 60: 333-45.
29. Singh G, Can AS, Correa R. Pioglitazone. In: StatPearls. Treasure Island (FL): StatPearls Publishing; February 17, 2022.
30. McIver LA, Tripp J. Acarbose. [Updated 2021 Aug 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https: //www.ncbi.nlm.nih.gov/books/NBK493214/
31. Ahrén B. DPP-4 inhibitors. Best Pract Res Clin Endocrinol Metab 2007; 21: 517-33.
32. Clifton P. Do dipeptidyl peptidase IV (DPP-IV) inhibitors cause heart failure? Clin Ther 2014; 36: 2072-9.
33. Saisho Y. SGLT2 Inhibitors: the Star in the treatment of type 2 diabetes? Diseases 2020; 8: 14.
34. Çavuşoğlu Y, Altay H, Cahn A, et al. Sodium glucose co-transporter 2 inhibitors in heart failure therapy. Kalp yetersizliği tedavisinde sodyum glukoz ko-transporter 2 inhibitörleri. Turk Kardiyol Dern Ars 2020; 48: 330-54.