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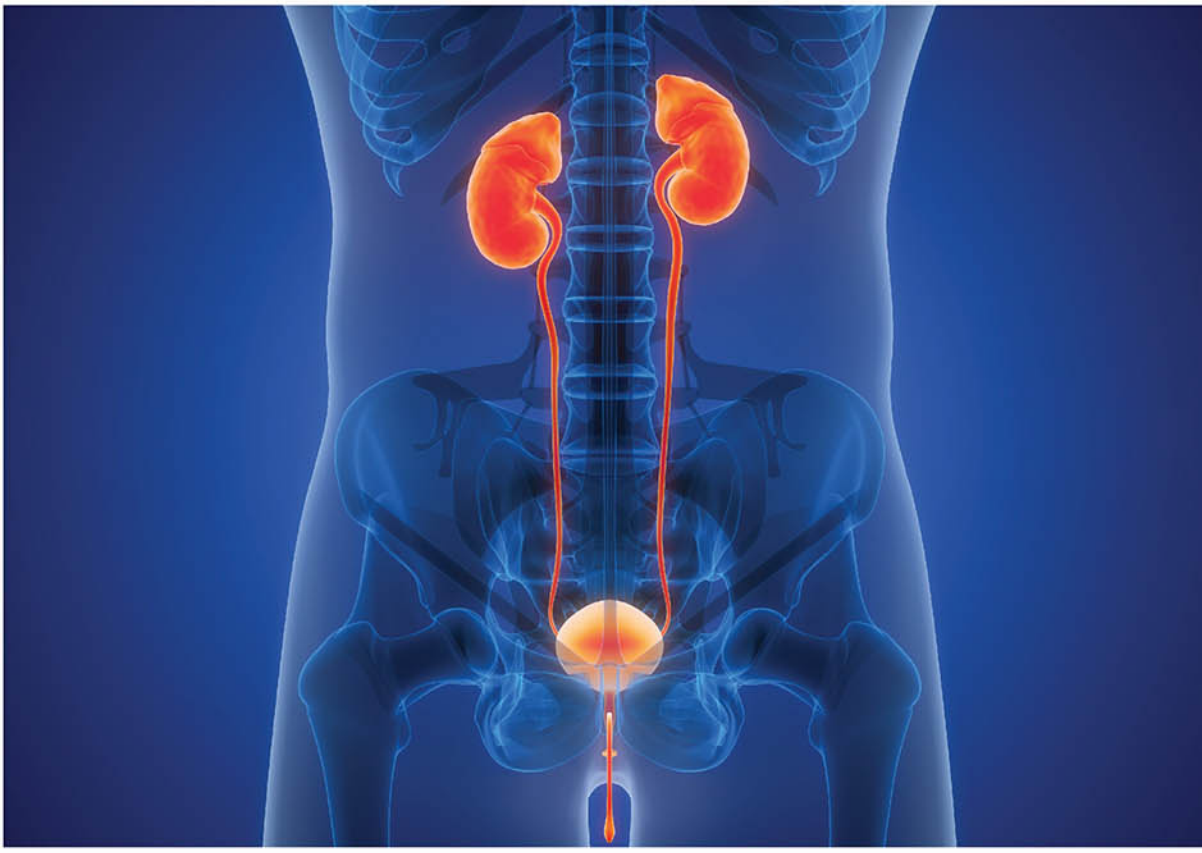
2nd Edition

# Clinical Approach to Renal Diseases in Diabetes



T Dhinakaran

*Foreword*
D Shantharam

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CHAPTER 7

# Diabetic Nephropathy—Treatment: Hyperglycemia Control

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**Keywords**

Importance of glycemic control: Glycemic control and glomerular filtration rate; Treatment of glycemia—drugs: Oral hypoglycemic agents, dose modification for sulfonylureas: Metformin and lactic acidosis, α-glucosidase inhibitors; Thiazolidinediones: Glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl peptidase-4 (DPP-4) inhibitors; Insulin usage: Role of synthetic insulins; sodium-glucose cotransporter-2 (SGLT-2) inhibitor in diabetic kidney disease (DKD).

## INTRODUCTION

Clinical nephropathy in diabetes is defined by the presence of proteinuria >300 mg/24 hours. This stage is referred to as overt nephropathy or clinical nephropathy. Progression from incipient nephropathy or microalbuminuria (MA) to clinical nephropathy is variable. Several studies have shown that there is a 25–32% progression from MA to macroalbuminuria in 10 years. From the stage of clinical diabetic nephropathy (DN), there is an inevitable and variable progression to stage 4 DN, which is characterized by a progressive fall in glomerular filtration rate (GFR).

A clinical diagnosis of DN is based on history of long-standing diabetes plus or minus retinopathy and urine examination which reveals macroalbuminuria (an albumin/creatinine ratio >300 mg/g). There is usually pedal edema in the majority with hypertension in 80–90% of patients.

Once the diagnosis of DN is made, the treatment options include the following:

- Glycemic control
- Hypertension therapy

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- Proteinuria treatment and renoprotection
- Dyslipidemia therapy
- Other supportive measures
- Coronary artery disease—risk reduction
- End-stage renal disease (ESRD) therapy

## GLYCEMIC CONTROL

Hyperglycemia therapy is a must to control the progression of proteinuria, prevent hyperglycemia-related problems, such as ketoacidosis, hyperosmolar syndrome, and macrovascular complications. In normoalbuminuric patients with type 1 diabetes mellitus (T1DM) disease, poor glycemic control is an independent predictor of progression to development of proteinuria (albuminuria) and/or ESRD. Two landmark trials conducted with patients with early-stage T1DM or type 2 diabetes mellitus (T2DM) disease showed that intensive blood glucose control early in the course of disease exhibits a long-lasting favorable effect on the risk of diabetic kidney disease (DKD) development.[15,16] This "legacy effect," also named "metabolic memory," suggests that early intensive glycemic control can prevent irreversible damage, such as epigenetic alterations, associated with hyperglycemia. With the onset of proteinuria, the hyperglycemia management becomes easier in some patients due to the increased endogenous availability of insulin. This is due to the reduced metabolism of insulin due to renal damage. In addition, there is reduced renal gluconeogenesis. Even then hyperglycemia control is a tight rope walk due to the brittle nature of diabetes in DN.

### Course of Overt/Clinical Diabetic Nephropathy

Clinical nephropathy with proteinuria >300 mg/g of creatinine is the starting point of declining GFR. The decline in GFR occurs over several years and shows high variability between individuals. It may range from 1 mL/min/year in some to 24 mL/min/year in the rapidly progressive persons.[1] After the onset of overt nephropathy, the GFR decline is similar between type 1 and type 2 as shown in many studies.[2] In T1DM, 50% develop ESRD within 10 years and 78% within 18 years.[3] In T2DM,only about 20% progress to ESRD within 20 years after overt nephropathy. This is because of the higher cardiovascular-related mortality occurring before they develop ESRD, and others may develop nondiabetic nephropathy.

### Importance of Glycemic Control

The efficacy of strict glycemic control depends in part upon the stage at which it is begun and the degree of normalization of glucose metabolism; the evidence is best established in T1DM.

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Intensive insulin therapy has the following benefits with respect to the kidney:

- It can partially reverse the glomerular hypertrophy and hyperfiltration (both in the basal state and after a protein load) that are thought to be important risk factors for glomerular injury.
- It can delay the development of elevated albumin excretion. Intensive therapy to near-normal glycemia reduces the onset or progression of DN for years compared to less intensive therapy.[4]
- It can stabilize or decrease protein excretion in patients with increased albumin excretion, although this effect may not be apparent until relative normoglycemia has been maintained for at least 2 years. Furthermore, the restoration of euglycemia with pancreas transplantation in patients with T1DM prevents recurrent nephropathy in a renal allograft.[5]

The importance of tight glycemic control for protection against microvascular complications and cardiovascular disease (CVD) in diabetes was established in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study for T1DM.[6] Although, the role of glycemic control on microvascular disease in T2DM was documented in the United Kingdom Prospective Diabetes Study (UKPDS), its role in reducing cardiovascular risk has not been established clearly for T2DM, as in T1DM.

## Glycemic Control and Glomerular Filtration Rate

Multiple observational studies have shown that the rate of fall of GFR correlates very highly with glycohemoglobin levels in patients with T1DM, even with advanced disease. Parving et al.[7] found similar rates of decline in GFR (3.8–4.4 mL/min/year) for patients with persistent albuminuria >200 μg/min, while receiving angiotensin-converting enzyme (ACE) inhibitors as part of an aggressive approach to blood pressure control. But, there was a significant positive correlation between the rates of decline in GFR and glycated hemoglobin (HbA1c). Breyer et al.[8] in a large, prospective double-blind study of 409 T1DM patients, with overt nephropathy, using captopril, showed importance of HbA1c in predicting progressive nephropathy. They found the glycemic control, to be important in T1DM, in retarding the progression of chronic kidney disease (CKD), in addition to use of ACE inhibitor.

In DCCT, the risk analysis for every 1% increase in HbA1c showed a higher risk of 31% for MA, 71% greater risk for overt nephropathy in the conventionally treated group, whereas the risks in the intensive treatment group were 29% for MA, and 57% for overt nephropathy. Similarly,[9] in UKPDS study, for each 1% reduction in HbA1c, there was a 37% risk reduction for microvascular disease. In the group with normal HbA1c (6%), the risk was lowest.

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These observations confirm the role of hyperglycemia by showing greater risk for patients with higher HbA1c values. The effect of glycemic control on GFR decline is not as clear in T2DM as in T1DM.[10] A study of 108 patients, consisting of 74 with MA and 34 with overt nephropathy, was done to assess the role of hyperglycemia control, over and above intensified BP control with ACE inhibitor on the renal functional decline. Patients who had HbA1c >8.5–9%, showed the maximum decline in GFR. There was a fall of 1.3 mL/min/year in the group with MA, and it was 3.0 mL/min/year in the macroalbuminuria group, when studied for up to 4 years. It shows the better effect of glycemia control in early stages of proteinuria for controlling the GFR decline. Another prospective study showed a survival benefit, with glycemic control, even at the stage of ESRD starting hemodialysis.[11] Thus tight blood sugar control offers renoprotection across the spectrum of DN with more pronounced benefit in the earlier stages.

## Glycemic Control Targets

The price paid for strict glycemic control is hypoglycemia. In the DCCT, the incidence of hypoglycemia was threefold in the intensively treated patients. The incidence was a little less and of lesser severity in T2DM as shown in the UKPDS study. One has to strike a balance between the benefits of intensive therapy and the increased incidence of hypoglycemia. Is there a threshold of metabolic control at which there is maximal protection with minimal hypoglycemic events?

No clinical trial date has yet demonstrated a macrovascular benefit with intensive therapy in patients with long-standing T2DM and data from the ACCORD study suggests that lowering HbA1c to near normal may be unsafe in patients with a long history of diabetes and at high risk for CVD. Thus, a reasonable goal of therapy might be an HbA1c value of ≤7.0% for most patients. In order to achieve the HbA1c goal, a fasting glucose of 70–130 mg/dL (3.9–7.2 mmol/L) and a postprandial glucose (90–120 minutes after a meal) <180 mg/dL (10 mmol/L) are usually necessary.

The results of the ACCORD study suggest that a target HbA1c of 7.0–7.9% (achieving a median of 7.5%) rather than <6.5% (achieving a median of 6.4%) may be safer for patients with long-standing T2DM who are at high risk for CVD. The current American Diabetes Association and European Association for the Study of Diabetes consensus algorithm recommends an HbA1c of < 7% for most patients due to the benefits of reducing microvascular complications.[12] However, these guidelines also recommend tailoring HbA1c goals for individual patients. Less stringent treatment goals may be appropriate for patients with a history of severe hypoglycemia, patients with limited life expectancies, very young children or older adults, and individuals with comorbid conditions. The American Association of Clinical Endocrinologists recommends a target of HbA1c <6.5%, although

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this recommendation was made prior to publication of the ACCORD and ADVANCE results.[13]

## TREATMENT OF GLYCEMIA—DRUGS

Overall glycemic control is more important than the use of any particular antidiabetic drug, especially in retarding microvascular disease as shown in various clinical trials. What is more important is the appropriate selection of drugs based on individual clinical picture, and the right drug to achieve glycemia with less adverse effects.

With CKD and declining GFR, choice of drugs becomes more difficult and demanding. The therapy has to be based on periodic GFR measurement, as the prevailing stages of CKD will decide the drug selection and its dose. Any harmful or protective effect beyond sugar control should be taken note of while prescribing drugs.

So, before choosing the drug and the dose in DN, it is very prudent and practical to stage CKD, as it influences the prescription in many ways, as we will see when we discuss about the individual drugs.

## STAGES OF CHRONIC KIDNEY DISEASE

These two types of staging need not run parallel in all diabetic patients **(Table 1)**. A fall in GFR may occur even with normoalbuminuria and MA and it usually denotes a tendency to rapid progression of CKD. The risk stratification is shown as green—low risk and red—highest risk of progression to ESRD and mortality.

Patients in CKD stage 3–5 are more prone to hypoglycemia.[14] With insulin therapy such hypoglycemic incidents are due to reduced renal clearance of insulin with falling GFR and also reduced insulin degradation in peripheral tissues. Hypoglycemia is also an issue with oral hypoglycemic agents (OHAs), in diabetes with GFR <30 mL/min, especially with drugs that are renally excreted. The hypoglycemia in diabetic CKD could also be due to reduced neoglucogenesis from the kidney due to reduced nephron mass. These observations stress the importance of close monitoring of glucose levels and appropriate dose modifications of OHA to avoid hypoglycemia.

## ORAL HYPOGLYCEMIC AGENTS

The full complement of oral agents for hyperglycemia can still be used in DN with additional care and consideration **(Table 2)**.

### Sulfonylureas

Sulfonylureas (SUs) increase endogenous insulin secretion (secretagogues). They bind to SU receptor, cause closure of adenosine triphosphate (ATP)-

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**TABLE 1: Comparison of stages of nephropathy in diabetes and in CKD *(For color version, see Plate 2)*.**

| Prognosis of CKD by GFR and albuminuria categories | | | | Albuminuria categories Description and range | | |
|---|---|---|---|---|---|---|
| | | | | A1 | A2 | A3 |
| | | | | Normal to mildly increased | Moderately increased | Severely increased |
| | | | | • <30 mg/g<br>• <3 mg/mmol | • 30–299 mg/g<br>• 3–29 mg/mmol | • ≥300 mg/g<br>• ≥30 mg/mmol |
| GFR categories (mL/min/1.73 $m^2$) Description and range | G1 | Normal or high | ≥90 | | | |
| | G2 | Mildly decreased | 60–90 | | | |
| | G3a | Mildly to moderately decreased | 45–59 | | | |
| | G3b | Moderately to severely decreased | 30–44 | | | |
| | G4 | Severely decreased | 15–29 | | | |
| | G5 | Kidney failure | <15 | | | |

Green: Low risk (if no other markers of kidney disease, no CKD); Yellow: Moderately increased risk; Orange: High risk; Red: Very high risk.
(CKD: chronic kidney disease; GFR: glomerular filtration rate)
*Source*: KDIGO, 2012.

**TABLE 2: Oral pharmacologic therapy for hyperglycemia.**

*Insulin secretagogues*:
- Sulfonylureas:
  - Glibenclamide
  - Gliclazide
  - Glipizide
  - Glimepiride
- Meglitinides:
  - Repaglinide
  - Nateglinide
  - Mitiglinide

*α-glucosidase inhibitors*:
- Acarbose
- Miglitol
- Voglibose

*Insulin sensitizers*:
- Thiazolidinediones:
  - Rosiglitazone
  - Pioglitazone

*Biguanides*:
- Metformin newer agents
- GLP-1—mimetics
- DPP-4 inhibitors
- SGLT-2 inhibitors

(DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT-2: sodium-glucose cotransporter-2)

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sensitive potassium channels in β cells of pancreas, cell membrane depolarization, influx of calcium, and insulin release.

As kidney function declines, the clearance of SUs or their active metabolites also declines and increases the risk of hypoglycemia. Therefore, the initial dose, subsequent dose titrations, and maintenance dosage should be conservative in patients with any degree of kidney dysfunction.

Long-acting SU such as glibenclamide should be used with caution even in early stages of diabetic CKD and should generally be avoided in stages 3–5. Similarly, chlorpropamide can be used at a reduced dose in patients with a GFR of 50–70 mL/min/1.73 $m^2$, but should be avoided if GFR is <50 mL/min/1.73 $m^2$.

There are concerns that first-generation secretagogues may be associated with increased cardiovascular risk and mortality.[16] The UKPDS and more recently the ADVANCE study demonstrated that newer agents, such as glipizide and gliclazide, do not appear to confer such a risk and are associated with benefits when used to achieve tighter glycemic control.[17]

The first-generation SU drugs, such as acetohexamide, tolazamide, and chlorpropamide are contraindicated in diabetic CKD patients. Among the second-generation SUs,[18] short-acting glipizide and gliclazide can be used without dose modification; glipizide has 98–99% protein (especially albumin) binding and has a half-life of 2.5 hours in T2DM patients. Gliclazide also has a very short half-life and is not renally eliminated; glimepiride can be used at a low dose in stage 2–3 CKD, but may have to be avoided in stage 5 and during dialysis.

## Meglitinides

These also act as secretagogues. The drugs in this category are nateglinide, repaglinide, and mitiglinide. Their rapid action helps to control postprandial blood sugar levels. When used with metformin, they are effective in HbA1c reduction. Repaglinide shows an increase in half-life, when used for 1 week, with single or multiple dosing. This happens in patients with creatinine clearance (CrCl) <30 mL/min. This does not happen with normal GFR. The peak plasma concentrations did not increase due to low CrCl.[19,20] Nateglinide, which is metabolized by cytochrome P450 (CYP450) enzyme, has metabolites that have insulin secreting activity. Because of the hypoglycemic action of the metabolites, hypoglycemia is common in CKD, and should be avoided in stage 3–4 CKD. Mitiglinide acts on pancreatic β cells and induces insulin secretions. Hypoglycemia is uncommon in diabetic CKD. The half-life of mitiglinide in stage 3 CKD may be prolonged to 3.22 hours, compared to 1.48 hours in normal renal function. Because of this, it has to be used with restraint in patients with renal impairment. This drug is not marketed in India.

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**TABLE 3: Dose adjustments for insulin secretagogues.**

| Drug | Dosing recommendation CKD stage 3, 4, or kidney transplantation | Dosing recommendation dialysis |
|---|---|---|
| *First-generation sulfonylureas* | | |
| Acetohexamide | Avoid | Avoid |
| Chlorpropamide/ Glibenclamide | • Reduce dose by 50% when GFR <70 and ≥50 mL/min/1.73 $m^2$<br>• Avoid when GFR <50 mL/min/1.73 $m^2$ | Avoid |
| Tolazamide | Avoid | Avoid |
| Tolbutamide | Avoid | Avoid |
| *Second-generation sulfonylureas* | | |
| Glipizide | • Preferred sulfonylurea<br>• No dose adjustment is necessary | • Preferred sulfonylurea<br>• No dose adjustment is necessary |
| Gliclazide | • Preferred sulfonylurea<br>• No dose adjustment is necessary | • Preferred sulfonylurea<br>• No dose adjustment is necessary |
| Glibenclamide | Avoid | Avoid |
| Glimepiride | Initiate at low dose, 1 mg daily | Avoid |
| *Meglitinides* | | |
| Repaglinide | No dose adjustment is necessary. Initiate at 0.5 mg dose when GFR <40 mL/min/1.73 $m^2$ | • No dose adjustment is necessary<br>• Initiate at low dose |
| Nateglinide | Initiate at low dose, 60 mg before each meal | Avoid |
| Mitiglinide | • No dose adjustment is necessary<br>• Not available in India | Initiate at low dose, 5 mg before each meal |

(CKD: chronic kidney disease; GFR: glomerular filtration rate)

### *Dose Adjustments for Insulin Secretagogues*

The dose adjustments for insulin secretagogues have been provided in the **Table 3**.

## Metformin

Metformin, a very effective agent and with many benefits in T2DM, has some limitations in the CKD patients. This drug works quite differently than SU and meglitinides. It works by improving insulin sensitivity at the muscle and adipose tissue, improve glucose uptake and at the level of the liver decreases hepatic glucose output.[21]

Next to insulin, metformin is the most commonly used and studied drug in T2DM. It acts by reducing hepatic glucose output and suppresses

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gluconeogenesis in fasting state. It does not cause weight gain.[22] In obese diabetes, when used alone in newly diagnosed T2DM, it reduced the risk of myocardial infarction (MI) by 30%, as observed in the UKPDS.[23] It has mild anorectic effects and gastrointestinal (GI) disturbance. Metformin is absorbed in small intensive and is 50–60% bioavailable. It does not undergo any metabolism in liver and is excreted in urine unchanged. It has a major tubular secretion via organic cation transporter 2 and so renal clearance is about three-to-fivefold higher than CrCl. After consumption, about 90% is eliminated in urine and it has a plasma half-life of 6.2 hours. In CKD, with reduced CrCl, the renal clearance will be reduced, and the plasma half-life of metformin is prolonged.[24] Therefore, it is better to avoid metformin in grade 3 to 5 CKD and during dialysis.[25] This is because of the tendency for lactic acidosis—in severe CKD, especially with other compounding factors for lactic acidosis.

### *Metformin Contraindications*

*Decreased kidney function*: Metformin can be used safely when the estimated glomerular filtration rate (eGFR) is ≥45 mL/min/1.73 $m^2$. If the eGFR is between 30 and 44 mL/min/1.73 $m^2$, metformin treatment should not be started.

- Congestive heart failure
- Liver disease
- Alcoholism
- Use of iodinated contrast media for radiologic studies
- Surgical procedure
- *Other states that might contribute to lactic acidosis*: Hypoxia, hypotension, and sepsis.

### *Metformin-induced Lactic Acidosis*

- Serious metabolic complication due to metformin accumulation
- Incidence of 0.03 cases per 1,000 patient-years, but fatal in ~50% of cases
- Risk rises with increasing kidney dysfunction and advancing age
- Medical emergency
- Suspected in patients with diabetes with metabolic acidosis but no evidence of ketoacidosis.

Current prescribing guidelines warn against the use of metformin in patients with eGFR <44 mL/min/1.73 $m^2$. Metformin is eliminated renally and cases of lactic acidosis have been described in patients with renal failure.

## Alpha-glucosidase Inhibitors

The α-glucosidase inhibitors are another class of oral agents. These drugs primarily work by impairing glucose absorption secondary to decreased

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digestion of carbohydrates. They are effective therapies either as an adjunct to diet or in combination with other oral agents or insulin.

In the brush border of the small intestine, dietary oligosaccharides, trisaccharides, and disaccharides are hydrolyzed by the α-glucosidase enzyme. The inhibitor of this gut enzyme will reduce the breakdown of complex carbohydrates. So, less of glucose is formed and absorbed, thereby reducing postprandial hyperglycemia. They have no effect on insulin secretion. These drugs cause flatulence and diarrhea frequently.[26,27] Acarbose, an α-glucosidase inhibitor, reduced postprandial hyperglycemia and showed reduction in CVD risk and also slowing of renal disease progression.[28] Acarbose is mainly metabolized in GI tract by digestive enzyme and intestinal bacteria. About 51% will be excreted unabsorbed in the faces within 96 hours. Because of its action being confined to the GI tract, very low level of the drug reaches the systemic circulation and it does not produce hypoglycemia. Only <2% is absorbed as an active drug. But, in patients with CrCl <25 mL/min, the drug may show 5–6 times increase in peak plasma levels. Since, the clinical result of such higher peak levels has not been studied, it is recommended to avoid acarbose when CrCl is <30 mL/min.

*Voglibose* is another drug in this category, used at dose of 0.2–0.3 mg TID, with better GI tolerance. It has the same usage and limitations as acarbose.

*Miglitol,* another α-glucosidase inhibitor, is not metabolized in humans or in any other animal species studied thus far. Miglitol is eliminated by renal excretion as unchanged drug.[27] Patients with CrCl <25 mL/min, taking miglitol 25 mg three times daily exhibited a greater than twofold increase in miglitol plasma levels when compared to subjects with CrCl >60 mL/min **(Table 4)**. Dose adjustment to correct the increased plasma concentrations is not feasible because miglitol acts locally. However, treatment of patients

**TABLE 4: Alpha-glucosidase inhibitors: use and limitations.**

| Characteristics | Acarbose | Miglitol | Voglibose |
|---|---|---|---|
| Therapeutic dose (mg/day) | 75–300 | 75–300 | 0.6–0.9 |
| Half-life (h) | 2 | 2 | Not absorbed in blood |
| Administration | With each meal preprandially | With each meal preprandially | With each meal preprandially |
| Dose reduction with renal impairment | KDOQI: Not recommended in patients with sCr >2 mg/dL | KDOQI: Not recommended in patients with sCr >2 mg/dL, no dose adjustment is necessary in patients with CrCl > 25 mL/min | Better not to use if sCr >2 mg/dL |

(CrCl: creatinine clearance; KDOQI: Kidney Disease Outcomes Quality Initiative; sCr: serum creatinine)

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with CrCl <25 mL/min with miglitol is not recommended because the safety of miglitol in these patients has not yet been elucidated.

## Thiazolidinediones

The thiazolidinediones (TZDs) are a class of drugs that have certainly received a lot of attention. They have proved their effects in glycemia and have the potential for pleiotropic effects. Like metformin, these are insulin-sensitizing agents that work both at the level of muscle and adipose tissue, as well as to reduce hepatic glucose output.

Since all other drugs in this category except pioglitazone have been withdrawn due to various hepatic and cardiac morbidities, the focus is on pioglitazone only.

Rosiglitazone and pioglitazone are potent peroxisome proliferator-activated receptor-γ (PPARγ) agonists belonging to a class of oral antidiabetic agents known as TZDs. PPARγ agonists are insulin sensitizers that reduce insulin resistance, increase glucose uptake in muscles and adipose tissue, and decrease hepatic glucose production. The available glitazone (pioglitazone) has an adequate oral bioavailability and is extensively metabolized by the liver. Pioglitazone is metabolized by CYP3A4 and CYP2C8/9. Metabolites of pioglitazone are more active than those of rosiglitazone and are excreted predominantly in bile **(Box 1)**.

The pharmacokinetic profile of pioglitazone was found to be similar in healthy subjects and patients with moderately or severely impaired renal function who did not require dialysis.[28]

However, TZDs have the potential to cause or exacerbate heart failure and should be used with caution in patients with hepatic injury. Furthermore, it was reported that rosiglitazone is associated with a significant increase in the risk of MI and has been withdrawn.[29] In contrast, pioglitazone improved the cardiovascular outcome in T2DM patients who were not dependent on dialysis therapy.[30]

Thiazolidinedione can cause fluid retention, hemodilution, and gain in weight. This weight gain is due to adipose tissue accumulation in subcutaneous tissue combined with vasodilatory actions.[31] There is a definite risk of heart failure, when insulin is combined with TZDs. The risk is 2–3% when the combination is used and is about 1% with use of TZD alone. So, a caution is required with the use of TZD, especially along with insulin.[32]

**BOX 1 Monitoring recommendations for pioglitazone.**

- Liver function test (LFT) before initiation of therapy:
  - Do not start treatment if alanine transaminase (ALT) >2.5 × upper limit of normal (ULN)
- Liver function test "periodically" thereafter
- Discontinue treatment if ALT >3 × ULN or jaundice develops

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From a nephrologist point of view, probably the biggest issue with the TZDs is edema and heart failure. There has recently been a combined statement from the American Diabetes and American Heart Association that these should be used with caution in patients with heart failure. In class I/II heart failure, they may be used, but they should be started at low dose with very gradual dose escalation and perhaps allowing even more time than usual to achieve the HbA1c goals. These organizations have actually recommended that the TZDs not be used in patients with class III or IV heart failure.[32]

*Pleiotropic actions*: Rosiglitazone and pioglitazone have been reported to:

- *Reduce insulin requirements*:
  - Play various roles in lipid metabolism, fibrinolysis, coagulation, and platelet aggregation
  - Ameliorate albuminuria
  - Protect against impairment of endothelial function
  - Have an anti-inflammatory effect **(Fig. 1)**.[33]

When used for the clinical management of T2DM and ESRD, TZDs are primarily metabolized in the liver and will not accumulate in patients with CKD. They might also improve uremia-associated insulin resistance and confer benefits at the metabolic, inflammatory, vascular, and hemodynamic levels.[34] It has been reported that pioglitazone administration is associated with mean decrease in triglyceride levels and mean increase in high-density lipoprotein cholesterol without consistent changes in the mean levels of total cholesterol or low-density lipoprotein cholesterol in nonuremic patients.[35] The potential vascular benefits with TZD are shown in **Figure 1**.

There has been a lot of interest in the potential vascular benefits due to PPARγ activation by TZDs, based on a lot of good experimental data, but in terms of clinical trial data, doctors are still waiting to see whether or not these agents add anything to usual treatment. There have been a couple of studies

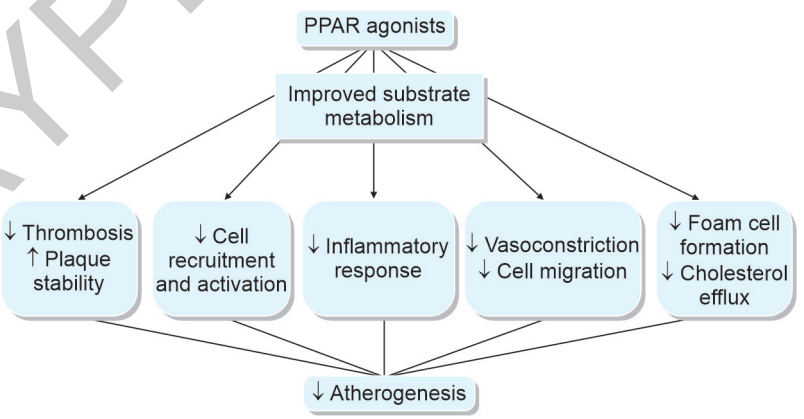


**FIG. 1:** Potential vascular benefits of proliferator-activated receptor (PPAR) activation with thiazolidinediones.[36]

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that suggest some benefit, but at this point, the relative benefit beyond glycemic control still remains to be established.

### *Thiazolidinediones Summary*

- Decrease plasma glucose and insulin levels, but do not produce hypoglycemia when used alone.
- Lower blood pressure and lipids
- Mechanism of action involves binding to nuclear receptors (PPARs) that regulate gene expression
- May have direct effects on the kidney (decreased albuminuria) and other vascular targets, but difficult to separate from effects to improve risk factors
- Fluid retention and edema may be limiting side effect in CKD and/or chronic heart failure.

### *Dose Adjustments for Insulin Sensitizers*

The dose adjustments for insulin sensitizers have been provided in **Table 5**.

## Glucagon-like Peptide-1 (Incretin) Mimetics

Glucagon-like peptide-1 (GLP-1) belongs to the incretin class of hormones, which exert an influence over multiple physiologic functions, including a rapid blood glucose-lowering effect in response to enteral nutrient absorption. Thus, GLP-1 is a potent blood glucose-lowering agent with many potential beneficial effects and may be able to modulate the progression of T2DM.[37] Native GLP-1 is rapidly metabolized by dipeptidyl peptidase-4 (DPP-4), which is found in many tissues and cell types as well as in the circulation. Clearance of native GLP-1 and its metabolites is largely mediated by the kidneys.[38] Incretins, such as GLP-1, enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into the circulation from the gut. Exenatide and liraglutide are

**TABLE 5: Dose adjustment for insulin sensitizers.**

| Drug | Dosing recommendation CKD stage 3, 4, or kidney transplant | Dosing recommendation dialysis |
|---|---|---|
| *Biguanides* | | |
| Metformin | Use with caution with kidney dysfunction defined as eGFR <45 mL/min/1.72 $m^2$ | Avoid |
| *Thiazolidinediones* | | |
| Pioglitazone | No dose adjustment is necessary | No dose adjustment is necessary |

(CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate)

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# Clinical Approach to
# Renal Diseases in Diabetes

Renal diseases in diabetes mellitus is an inevitable and major accompaniment of diabetes. Both the clinical course and therapeutic advances have been striking and impressive in the past decade. The cardiorenal orchestration with diabetes mellitus is omnipresent and lethally collaborating and goes by the name Cardiorenal Metabolic Disease. The progress made in these directions is elaborated in the second edition of the book. New information has been included in almost all the chapters, notably in chapters 1, 2, 4, 6, 7, 8, and 10 to 12. The simple and free flow of reading is ensured throughout the book. This book will serve as a reference as well as a textbook for postgraduates, physicians, and specialists dealing with diabetes and its accompanying complications.

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