Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

COMPREHENSIVE DIABETES & CKD MANAGEMENT

ALL PATIENTS
- Glycemic control
- Blood pressure control
- Lipid management
- Exercise
- Nutrition
- Smoking cessation

MOST PATIENTS
- SGLT2 inhibitors
  Patients with T2D (Type 2 Diabetes) and CKD (Chronic Kidney Disease)
- RAS inhibition
  Patients with T2D albuminuria, and hypertension

SOME PATIENTS
- Aspirin
  Secondary prevention in established cardiovascular disease
  Primary prevention among high-risk individuals
- Dual antiplatelet therapy
  After acute coronary syndrome or percutaneous coronary intervention

Developed with support from Novo Nordisk

Original infographic by Dr Michelle Lim @whatsthegfr
We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated.  

**RECOMMENDATION**

- For patients with diabetes, albuminuria, and normal blood pressure, treatment with an ACEi or ARB may be considered.
- Advise contraception in women who are receiving ACEi/ARB therapy.
- Discontinue ACEi/ARB in women who are considering pregnancy or who become pregnant.
- Manage hyperkalemia by other measures to reduce serum potassium rather than decreasing the dose or stopping ACEi/ARB immediately.
- Use only one agent at a time for RAS blockade since the combination of an ACEi with an ARB, or the combination of an ACEi or ARB with a direct renin inhibitor, is potentially harmful.
- Mineralocorticoid receptor antagonists are effective in refractory hypertension but can cause hyperkalemia or a reversible decline in GFR, particularly among patients with low eGFR.

**TREATMENT ALGORITHM**

- **Initiate ACEi or ARB**
  - Monitor serum creatinine and potassium within 2-4 weeks of starting/dosing.
  - **Normokalemia**
    - <30% increase in creatinine
      - Increase dose of ACEi/ARB or continue on maximally tolerated dose
      - Moderate potassium intake
        - Consider: diuretics, sodium bicarbonate, or GI cation exchangers
    - >30% increase in creatinine
      - Review concurrent drugs
      - Reduce dose or stop ACEi/ARB as last resort
      - Reduce/stop ACEi/ARB in symptomatic hypotension, uncontrolled hyperkalemia or to reduce uremic symptoms when eGFR <15
  - **Hyperkalemia**
    - Review for causes of AKI
      - Correct volume depletion
      - Reassess concomitant medications: (e.g., diuretics, NSAIDs)
      - Consider renal artery stenosis
    - >30% increase in creatinine
      - Review concurrent drugs
      - Moderate potassium intake
        - Consider: diuretics, sodium bicarbonate, or GI cation exchangers
      - Reduce dose or stop ACEi/ARB as last resort
    - >30% increase in creatinine
      - Review for causes of AKI
        - Correct volume depletion
        - Reassess concomitant medications: (e.g., diuretics, NSAIDs)
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GLYCEMIC MONITORING & TARGETS

RECOMMENDATION

- We recommend using HbA1c to monitor glycemic control in patients with diabetes and CKD
- We recommend an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis

Frequency of monitoring HbA1c

- Twice yearly for patients with diabetes
- Up to four times yearly if glycemic target not met or with change in therapy

Continuous glucose monitoring (CGM) and self-monitoring of blood glucose (SMBG)

Can provide a glucose management indicator (GMI) to index glycemia for individuals in whom HbA1c is unreliable

- Daily monitoring may help prevent hypoglycemia
- CGM metrics (e.g., time in range and time in hypoglycemia) may be considered as alternatives to HbA1c for defining glycemic targets
- Newer CGM devices may offer advantages for certain individuals depending on their values, goals and preferences

Choice of antihyperglycemic agents

- Advanced CKD substantially increases the risk of hypoglycemia in patients treated with oral agents and insulin
- Consider agents (metformin, SGLT2i, GLP-1 RA and DPP-4i) that pose a lower risk of hypoglycemia especially with patients not using CGM/SMBG
- Doses of agents might need to be reduced according to level of CKD
- CGM/SMBG may facilitate safe achievement of lower HbA1c targets in conjunction with use of agents that are not associated with hypoglycemia

Accuracy and precision of HbA1c

- Declines with advanced CKD (G4-G5)
- Low reliability particularly in patients treated by dialysis

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FACTORS GUIDING DECISIONS ON INDIVIDUAL HbA1c TARGETS

**HbA1c**

- <6.5%
- <8.0%

- CKD G1
- CKD G5

- Absent/minor
- Present/severe

- Few
- Many

- Long
- Short

- Present
- Impaired

- Available
- Scarce

- Low
- High

Severity of CKD

Macrovascular complications

Comorbidities

Life expectancy

Hypoglycemia awareness

Resources for hypoglycemia management

Propensity of treatment to cause hypoglycemia

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LIFESTYLE INTERVENTIONS IN PATIENTS WITH DIABETES & CKD

**RECOMMENDATION**

- We suggest maintaining a protein intake of 0.8 g protein/kg (weight)/day for those with diabetes and CKD not treated with dialysis 2C
- We suggest that sodium intake be <2 g of sodium/day (< 5 g of sodium chloride/day) in patients with diabetes and CKD 2C
- We recommend that patients with diabetes and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes/week, or to a level compatible with their cardiovascular and physical tolerance 1D
- We recommend advising patients with diabetes and CKD who use tobacco to quit using tobacco products 1D

**NUTRITION INTAKE**

- Encourage a varied diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts
- **Reduce intake** of processed meats, refined carbohydrates, and sweetened beverages
- **Aim for 1.0 – 1.2 g protein/kg/day** in patients treated with hemodialysis, and particularly peritoneal dialysis
- **Shared decision-making** should be a cornerstone of patient-centered nutrition management. Accredited nutrition providers, registered dietitians and diabetes educators, community health workers, peer counselors, or other health workers should be engaged in the multidisciplinary nutrition care of patients with diabetes and CKD
- **Health care providers** should consider cultural differences, food intolerances, variations in food resources, cooking skills, comorbidities, and cost when recommending dietary options to patients and their families.

**PHYSICAL ACTIVITY**

- Recommendations for physical activity should consider **age, ethnic background, presence of other comorbidities, and access to resources**
- Advise patients to **avoid sedentary behavior**
- **Tailor advice** on intensity of physical activity and type of exercises for patients at higher risk of falls
- Encourage patients with obesity, diabetes, and CKD to **lose weight**, particularly if eGFR ≥30 ml/min/1.73 m²

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ANTIHYPERGLYCEMIC THERAPIES

RECOMMENDATION

★ We recommend treatment for patients with T2D, CKD and eGFR ≥30 with SGLT2i 1A and metformin 1B.
★ In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i, or who are unable to use those medications, we recommend a long-acting GLP-1 RA 1B.

TREATMENT ALGORITHM

Lifestyle therapy
First-line therapy
Additional therapy

Physical activity
Nutrition
Weight loss

Metformin
X eGFR <30
X Dialysis
⚠ Reduce dose if eGFR <45

SGLT2 inhibitor
X Do not initiate if eGFR <30
X Dialysis & Transplant

GLP-1 receptor agonist

DPP-4 inhibitor
Insulin
Sulfonylurea (SU)
Thiazolidinedione (TZD)
Alpha-glucosidase inhibitor (AGI)

Most patients with T2D, CKD, and an eGFR ≥30 would benefit from treatment with both metformin and an SGLT2i.
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**METFORMIN**

**RECOMMENDATION**

We recommend treatment for patients with T2D, CKD and eGFR ≥30 with metformin

**BENEFITS**

- Effective as an antihyperglycemic agent; can be used to treat transplant recipients as well for those with eGFR ≥30
- Efficacy comparable to thiazolidinediones and sulfonylureas
- Reduced risk of hypoglycemia compared to sulfonylureas and insulin
- May be helpful with weight control
- May offer protection against cardiovascular events

**CAUTION**

- Closer monitoring required when eGFR <60
- Doses should be halved when eGFR <45
- Conflicting reports of lactic acidosis
- Gastrointestinal side effects particularly with immediate release formulations
- Interferes with intestinal vitamin B12 absorption

**TREATMENT ALGORITHM**

- **eGFR < 30**
  - Stop metformin; do not initiate metformin

- **Only initiate metformin if eGFR ≥ 30**

  - **eGFR ≥ 60**
    - Immediate release
      - Initial 500 mg or 850 mg once daily
      - Titrate upwards by 500 mg/d or 850 mg/d every 7 days until maximum dose
    - OR
      - Extended release
        - If GI side effects from immediate release
          - Initially 500 mg daily
          - Titrate upwards by 500 mg/d every 7 days until maximum dose
  - **eGFR 45-59**
    - Monitor kidney function
      - At least annually
    - Monitor Vitamin B12
      - Annually if on metformin for >4 years or at risk of vitamin B12 deficiency
  - **eGFR 30-44**
    - Subsequent dose adjustment
      - **eGFR ≥ 60**
        - Continue same dose
      - **eGFR 45-59**
        - Continue same dose but consider dose reduction in certain conditions
      - **eGFR 30-44**
        - Halve dose

Original infographic by Dr Michelle Lim @whatsthegfr

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We recommend treatment for patients with T2D, CKD and eGFR ≥30 with SGLT2i (1A).

**Benefits**
- Can reduce major adverse cardiovascular events (MACE)
- Reduces risk of hospitalization due to heart failure
- Helps slow progression of CKD and albuminuria

**Caution**
- May need to be withheld when patients are at greater risk of ketosis (e.g. fasting, surgery, critical illness)
- Consider reducing dose of concurrent thiazide or loop diuretics if at risk of hypovolemia
- Not yet adequately studied for use in patients with kidney transplants; therefore recommendations do not apply to this population

**CAUTION**
- A reversible decrease in eGFR may occur and generally not an indication to discontinue therapy
- Can lower glycemic target be safely achieved by adding an SGLT2i?
  - Yes
    - Add SGLT2i
    - Educate on potential adverse effects
    - Follow up on glycemia
    - Monitor for adverse effects
  - No
    - Discontinue/decrease dose of current antihyperglycemic medication (other than metformin)

Once an SGLT2i is initiated, it is reasonable to continue this even if eGFR falls below 30, unless it is not tolerated or when dialysis is initiated or a transplant is received

Original infographic by Dr Michelle Lim

Developed with support from Novo Nordisk
GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1 RA)

**RECOMMENDATION**

In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA.

**BENEFITS**

- Long-acting GLP-1 RA substantially improve blood glucose and HbA1c control
- May be helpful with weight control
- Can help lower blood pressure
- Can reduce major adverse cardiovascular events (MACE)
- Risk of hypoglycemia is generally low but doses of sulfonylureas or insulin may need to be reduced if used concomitantly
- Substantially reduces albuminuria and likely helps preserve eGFR

**CAUTION**

- Gastrointestinal side effects can be minimized by starting with a low dose and titrating up slowly
- Should not be used in conjunction with DPP-4 inhibitors
- Prioritize agents with documented cardiovascular benefits
- Can cause a slight increase in heart rate
- Avoid in individuals at risk of medullary thyroid tumors
- Avoid in individuals with a history of acute pancreatitis

**DOSING + ADJUSTMENTS IN CKD**

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<thead>
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<th>GLP-1 RA</th>
<th>Dose</th>
<th>CKD dose adjustment</th>
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<tbody>
<tr>
<td>Dulaglutide</td>
<td>0.75 and 1.5 mg</td>
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<tr>
<td></td>
<td>Once weekly</td>
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<tr>
<td>Exenatide</td>
<td>10 µg</td>
<td>Use if eGFR &gt;15</td>
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<tr>
<td></td>
<td>Twice daily</td>
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<td>Exenatide Extended release</td>
<td>2 mg</td>
<td>Use if CrCl &gt;30</td>
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<td>Liraglutide</td>
<td>0.6, 1.2, and 1.8 mg</td>
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<td></td>
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<td>Lixisenatide</td>
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<tr>
<td>Semaglutide Injectable</td>
<td>0.5 mg and 1 mg</td>
<td>Limited data for severe CKD</td>
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<td>Semaglutide Oral</td>
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</table>

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SELF-MANAGEMENT EDUCATION PROGRAMS

RECOMMENDATION

- We recommend that a structured self-management educational program be implemented for care of people with diabetes and CKD.

- Health care systems should consider implementing a structured self-management program for patients with diabetes and CKD, taking into consideration local context, cultures, and availability of resources.

Increase engagement with medication, glucose monitoring and complications screening programs

Reduce risk to prevent or better manage diabetes-related complications

Encourage adoption and maintenance of healthy lifestyles

Improve diabetes-related knowledge, beliefs and skills

Improve vascular risk factors

Improve emotional and mental well-being, treatment satisfaction, and quality of life

Improve self-management and self-motivation


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TEAM-BASED INTEGRATED CARE

RECOMMENDATION

We suggest that policymakers and institutional decision-makers implement team-based, integrated care focused on risk evaluation and patient empowerment to provide comprehensive care in patients with diabetes and CKD.

GOALS OF CARE

- Treat to glycemia, BP, and lipids targets
- Use of organ-protective drugs (RASi, SGLT2i, GLP-1 RA, statins)
- Ongoing support to promote self-care

Identify the population

- Establish a register
- Perform comprehensive risk assessment including blood/urine and eye/foot examination every 12-18 months

Stratify risk

- Assess cardiometabolic risk factors every 2-3 months, and kidney function (eGFR and ACR) every 3-12 months

Empower and support

- Identify special needs at each visit
- Reinforce self-management (e.g., self-monitoring of BP, glucose, weight)
- Provide counseling on diet, exercise, and self-monitoring, and recall defaulters at the clinic visit

Optimize treatment

- Review treatment targets and use of organ-protective medications at each visit
- Assess risk factor control

Team-based integrated care, supported by decision-makers, should be delivered by physicians and nonphysician personnel preferably with knowledge of CKD

Periodic audits should be conducted to identify care gaps and provide feedback to practitioners with support to improve quality of care

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