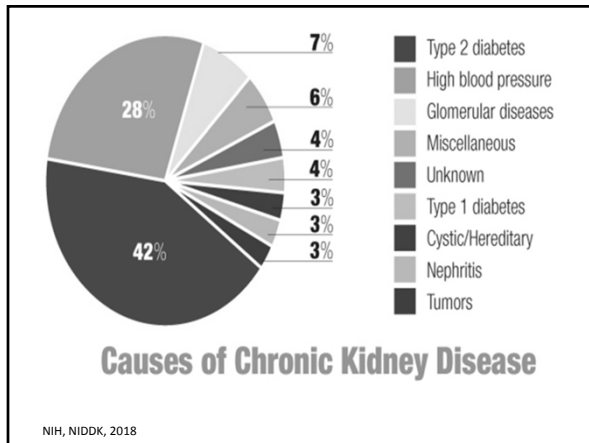


Chronic Kidney Disease (CKD) and Diabetes

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Objectives

- Learn epidemiology of CKD and diabetes
- Understand classifications of diabetes and stages of CKD
- Comprehend the pharmacokinetics of anti-hyperglycemia agents in people with CKD
- Use knowledge to educate patients about diabetes and CKD



Epidemiology

Diabetes	Chronic Kidney Disease (CKD)
29 million Americans have diabetes	30 million Americans have CKD (>1 in 7)
Diabetes and Chronic Kidney Disease (CKD)	
247,000 people living with kidney failure is from diabetes	
In 2013, diabetes led to >51,000 new cases of kidney disease	
>35% of people with DM greater than 20 years old have CKD	
Greater in non-Hispanic blacks (13.2%) than Hispanics (12.8%) and Asian Americans (9%) and non-Hispanic whites (7.6%)	Greater in non-Hispanic blacks (16%) than in non-Hispanic whites (13%)

National Kidney Foundation, 2016; CDC, 2017

Criteria for Testing for Diabetes or Prediabetes in Asymptomatic Adults:

Testing should be considered in overweight (BMI ≥ 25 kg/m² or ≥ 23 kg/m² in Asian Americans) or obese adults who have one or more of the following risk factors:

- First-degree relative with diabetes
- High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- History of CVD
- Hypertension ($\geq 140/90$ mmHg or on therapy for hypertension)
- HDL cholesterol level ≤ 35 mg/dL (0.90 mmol/L) and/or a triglyceride level ≥ 250 mg/dL (2.82 mmol/L)
- Women with polycystic ovary syndrome
- Physical inactivity
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

Criteria for Testing for Diabetes or Prediabetes in Asymptomatic Adults:

- Patients with prediabetes (A1C $\geq 5.7\%$ [39 mmol/mol], IGT, or IFG) should be tested yearly
- Women who were diagnosed with GDM should have lifelong testing at least every 3 years
- For all other patients, testing should begin at age 45 years
- If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status

ADA, 2018

Criteria for Diagnosis of Diabetes:

FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h
OR

2-h PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT.
The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.
OR

A1C $> 6.5\%$ (48 mmol/mol).
The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.
OR

In a patient with **classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).**

(In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.)
ADA, 2018

Classifications of Diabetes:

Type 1 Diabetes Mellitus (T1DM)	Type 2 Diabetes Mellitus (T2DM)	Gestational Diabetes Mellitus (GDM)	Specific Types of Diabetes due to Other Causes
Due to autoimmune b-cell destruction, usually leading to absolute insulin deficiency	Due to a progressive loss of b-cell insulin secretion frequently on the background of insulin resistance	Diagnosed in second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation	Monogenic diabetes syndromes, diseases of the exocrine pancreas, and drug- or chemical-induced diabetes, in the treatment of HIV/AIDS, or after organ transplantation

ADA, 2018

Chronic Kidney Disease Stages

GFR stages, descriptions and range (ml/min per 1.73m ²)	Stage	Normal or high	Mildly decreased	Moderately to severely decreased	Normal to mildly increased	Moderately increased	Severely increased
					<3 mg/mmol	3-29 mg/mmol	≥ 30 mg/mmol
Stage 1 (G1)	Normal or high	≥ 90					
Stage 2 (G2)	Mildly decreased	60-90					
Stage 3 (G3a)	Mildly to moderately decreased	45-59					
Stage 3 (G3b)	Moderately to severely decreased	30-44					
Stage 4 (G4)	Severely decreased	15-29					

Kidneyhealth.ca, 2018

What is the most important predictor for people with diabetes developing CKD?

Blood pressure:

Guidelines	BP Category	Systolic BP	Diastolic BP
AHA/ACC, 2017	Normal	<120	<80
	Elevated	120-129	and <80
	Hypertension Stage 1	130-139	or 80-89
ADA, 2018	Hypertension Stage 2	≥ 140	or ≥ 90
	Goal	<140	and <90

What are signs that people with diabetes may be developing CKD?

- Proteinuria
- High blood pressure
- Leg swelling or cramps
- Increased need to urinate (especially at night)
- Abnormal GFR

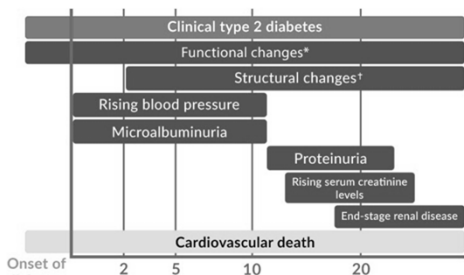
National Kidney Foundation, 2016

What are signs that people with diabetes may be developing CKD?

- Lower insulin requirements or less anti-diabetic agents
- Nausea and or vomiting
- Weak, pallor, and anemia
- Itching
- Diabetic eye disease

National Kidney Foundation, 2016

Natural History of Type 2 Diabetic Kidney Disease



Diabetes Council, 2016

Conditions Associated with Falsely Elevated or Lowered A1c

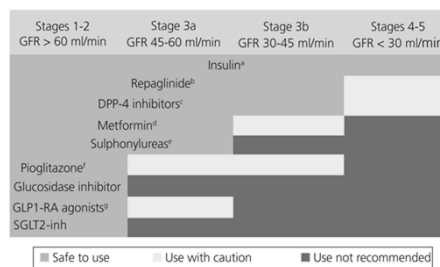
Test	False Decrease	False Increase
A1c	Anemia from acute or common blood loss (hemolytic anemia)	Anemia associated with decreased RBC turnover (iron deficiency, B12, folate deficiency)
	Splenomegaly	Asplenia
	Red blood cell transfusion	Uremia
	Pregnancy	Chronic alcohol or opioid consumption
	Vitamin E ingestion	Severe hypertriglyceridemia (>1750)
	Iron supplements	High-dose aspirin
	ESRD on HD	

J Gen Intern Med 2014

Glycemic Target Recommendations for People with Diabetes and CKD

Guidelines and Consensus Reports	Recommendations
ADA standards of care in diabetes 2018	Less stringent HbA1c goals (<8%) may be appropriate for people with advanced complications, such as CKD
DKD: ADA consensus conference report 2014	HbA1c < 8% when GFR <60 ml/min per 1.73 m ² due to hypoglycemic risks Rely on SMBG for diabetes management due to imprecision of HbA1c
KDOQI clinical practice guidelines for diabetes and CKD, 2012 update	Recommend not to treat to a HbA1c <7% given risk for hypoglycemia Suggest that target HbA1c >7% with people with comorbidities such as CKD

Therapeutic Agents with People with Diabetes and CKD



Biguanide Drug Class Metformin (Glucophage)

- Improve insulin sensitivity
 - decreases gluconeogenesis in the liver, decreases

FREE AT SOME RETAIL PHARMACIES

- Low risk for hypoglycemia
- Can result in modest weight loss
- Diarrhea, gastrointestinal discomfort is most common side effect
 - Titrate dose up weekly and/or try ER/XR options

ADA 2018; Glucophage 2018; FDA 2016

Biguanide Drug Class Metformin (Glucophage)

- GFR:
 - < 45, consider reducing dose by 50% or to half maximal dose (max effective dose is 2000 mg/day)
 - 30 to 45, initiation not recommended
 - <30, contraindicated
- Life threatening
- Risk for Lactic Acidosis
 - Extremely rare (estimated incidence of 0.03 to 0.06 per 1000 patient-years)

Sulfonylureas

- Lowers blood sugars by stimulating release of insulin from the pancreatic beta cells
- Hypoglycemia is major adverse effect
 - 2014 UK trail showed severe hypoglycemia
 - ≥ 75 , AKI or CKD, dementia/cognitive impairment
- Glipizide (glucotrol) is first choice, start with 2.5mg daily
- Start glimepiride (amaryl) conservatively
- Avoid use with glyburide (diabeta)
- Consider use of meglitinides

JNP 2018; Diabetes Obesity Metabolism 2014

Dipeptidyl Peptidase-4 (DPP4) Inhibitors

- Increase post-prandial incretin concentrations and glucose-dependent insulin secretion
- Weight neutral and low risk for hypoglycemia
- GI side effects. Less than 1% risk for pancreatitis
- Glucose-lowering effect and tolerability is similar in people with and without diabetes.

ADA 2018, JNP 2018, FDA 2018

Dipeptidyl Peptidase-4 (DPP4) Inhibitors

DPP-4 Inhibitor	Dose Recommendations
Sitagliptin (Januvia)	GFR >50 – 100mg daily GFR 30 to 50 – 50mg daily GFR <30 -25 mg daily—Can use in patients on dialysis
Saxagliptin (Onglyza)	GFR <50 – 2.5mg daily
Linagliptin (Tradjenta)	No dose adjustment
Alogliptin (Nesina)	GFR 30 to 60 – 12.5 mg daily GFR <30 – 6.25 mg daily

ADA 2018, JNP 2018, FDA 2018

Glucagon-Like Peptide-1 Receptor Agonists

- Mimics endogenous incretin effects
 - Enhances insulin secretion, inhibits glucagon, delays gastric emptying, and induces satiety
- Daily or weekly injections
- Similar GI side effects as DPP-4I
- Weight loss benefit
- All GLP-1RAs can be used in mild CKD
- GI side effects cause a risk of volume depletion and AKI

ADA 2018, JNP 2018, FDA 2018

Glucagon-Like Peptide-1 Receptor Agonists

GLP-1 Receptor Agonists	Dose Recommendations
Exenatide BID (Byetta) or weekly Bydureon	GFR <30 , not recommended
Dulaglutide (Trulicity) weekly	
Liraglutide (Victoza) daily	No dose adjustment
Lixisenatide (Adlyxin) weekly	GFR 60-89, no dose adjustment GFR 30-59, no dose adjustment, monitor for ADRs and changes in kidney function GFR 15-29, limited clinical experience, monitor GFR <15 , not recommended due to lack of data
Semaglutide (Ozempic) weekly	No dose adjustment; thyroid c cell tumors in rodents; Increase risk for DR complications with those with hx of DR

ADA 2018, JNP 2018, FDA 2018

Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors

- Work in the proximal tubules of the kidney to reduce glucose and sodium reabsorption
- Modest reductions in weight and blood pressure
- Common side effects GU and UTI (women $>$ men)
- Initial transient rise in serum creatinine in people with moderate CKD
- Risk factors for ketoacidosis are infection, low carb diet or low calorie intake, reduction of exogenous insulin, discontinuation of an oral insulin secretagogue and alcohol use.
- Stop 2 weeks prior to surgery due to risk of euglycemic ketoacidosis

ADA 2018, JNP 2018, FDA 2018

Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors

SGLT-2 Inhibitors	Dose Recommendations
Canagliflozin (Invokana)*	GFR 45-59, 100 mg daily GFR <45, discontinue
Dapagliflozin (Farxiga)*	GFR <60, do not initiate GFR 30-60, not recommended GFR <30, contraindicated
Empagliflozin (Jardiance)	GFR <45, contraindicated and do not initiate Reduced cardiovascular death and events by 1.6% along with reduction in heart failure hospitalization

*Increased risk of AKI. Hypovolemia, heart failure, NSAIDs, diuretics, and ACEI/ARBs are factors that predispose people to AKI

ADA 2018, JNP 2018, FDA 2018

Insulin and People with T2DM

- Eventually require insulin to achieve adequate A1C control
- Weight gain is a risk but basal insulin had less weight gain and hypoglycemia compared to prandial or mixed insulin
 - Obesity is risk factor for CKD
- Exogenous insulin is primarily excreted by the kidney
- Risk for hypoglycemia with declining GFR
 - GFR <20 results in increased half-life and decreased insulin requirements
 - GFR <10 or people starting dialysis, require 50% dose decrease

ADA 2018, JNP 2018

Insulin Pen and Vials 2018

Diabetes Forecast

Insulin Pumps 2018

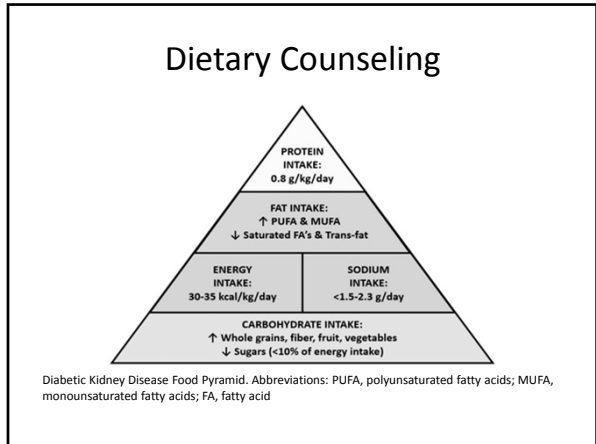
Diabetes Forecast

Glucometers 2018

Diabetes Forecast

Continuous Glucose Monitoring Systems 2018

Diabetes Forecast



- ### Hypoglycemia Prevention and Treatment
- Prevention:
 - Monitor blood glucose levels
 - Monitor GFR/serum creatinine levels
 - Must eat with prandial insulin, SU, meglitinides
 - Call health care provider when sick
 - Treatment:
 - BG <70, 15 gms of fast-acting carbs (4 glucose tabs, 1 juice box, 1 dextrose drink)
 - BG <50, 30 gms of fast-acting carbs (8 glucose tabs, 2 juice box, 2 dextrose drinks)
 - Glucagon given if patient unable to eat/drink, given by someone other than the person with hypoglycemia
 - Recheck BG in 15 minutes after treatment and repeat as needed
- ADA 2018

- ### Hyperglycemia Prevention and Treatment
- Prevention/Treatment:
 - Assess for symptoms of hyperglycemia
 - Monitor blood glucose levels
 - Take medications as prescribed
 - Do not skip prandial insulin, SU, or meglitinide when eating
 - Increase water intake
 - Exercise
 - Limit amount of carbohydrates and change to lower glycemic index foods/fruits
- ADA 2018

- ### Sick Day Counseling
- | | |
|------------------|---|
| S Sugar | <i>Check blood glucose at least every 2-3 hours</i> |
| I Insulin | <i>Continue to take insulin</i> |
| C Carbs | <i>High glucose, stick with SF fluids
Low glucose, can drink carb containing fluids</i> |
| K Ketones | <i>Check urine or blood for ketones
Increase water intake</i> |
- Diabetescouncil, 2018

Sick Day Counseling

- People with diabetes who become ill and are unable to maintain adequate fluid intake should hold medications which will

Increase risk for decline in kidney function	Have reduced clearance and increase risk for adverse effects
Angiotensin-converting enzyme inhibitors	Metformin
Angiotensin receptor blockers	Sulfonylureas (gliclazide, glimepiride, glyburide)
Direct renin inhibitors	
Non-steroidal anti-inflammatory medications	
Diuretics	
SGLT2 inhibitors	

Canadian Diabetes Association, 2018

- ### Sick Day Counseling
- S** sulfonylureas
 - A** Acetaminophen
 - D** Decongestants

Cough syrups should be sugar-free
 Nasal decongestants, like pseudoephedrine, increase blood pressure and may increase blood sugars also
 - M** Metformin
 - A** Aspirin
 - N** nonsteroidal anti-inflammatory
 - S** SGLT2 inhibitors
- Canadian Diabetes Association, 2018

Summary

- T2DM is the most common cause of CKD, and blood pressure treatment decreases progression of CKD
- Blood glucose monitoring is required in people with diabetes and CKD, since A1C is not always reliable
- Screening for proteinuria is required annually or more frequently if proteinuria worsens
- GFR should be checked every 3-6 months to monitor progression of CKD and need for medication dose adjustments
- People with diabetes and CKD benefit from sick day counseling and education on prevention and treatment of hypoglycemia and hyperglycemia