Blood Glucose Control in Diabetic nephropathy

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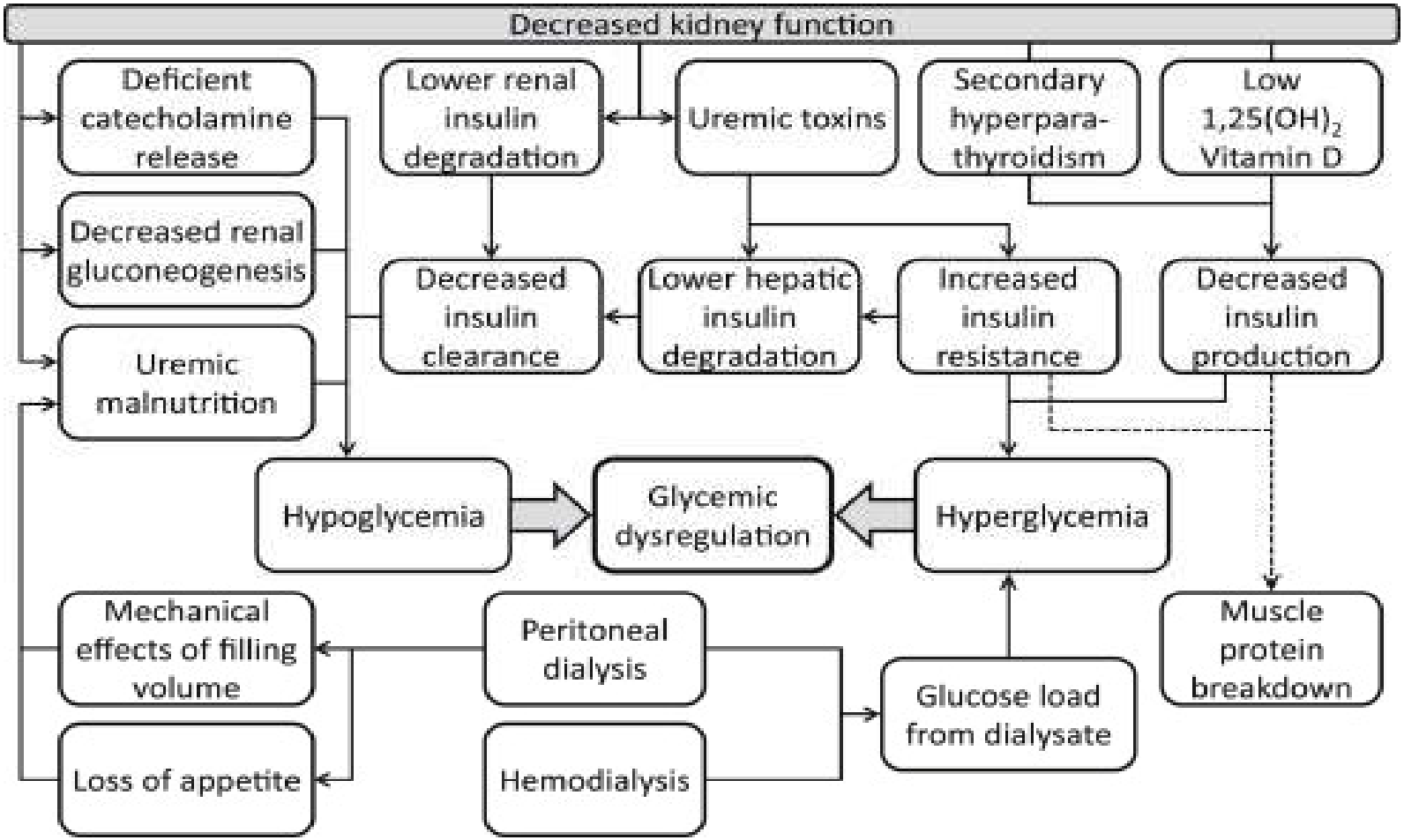
Blood Glucose Control in Diabetic nephropathy(DN)

- According to the National Diabetes Statistics Report 2014,
- in 2012, 29.1 million Americans(9.3% of the population) had DM
- Among Americans ≥65 years of age, 25.9% (11.8 million people)
- In 2013, a total of 1 469 000 new cases of diagnosed DM among adults (aged 18–79 years) were reported in the USA
- DM is the leading cause of kidney failure (44% of all new cases in 2011).
- In 2011, a total of 228 924 American people of all ages with kidney failure secondary to DM were treated with chronic dialysis or underwent kidney transplant



Overview of glucose/insulin homeostasis in chronic kidney disease. Disturbances of glucose metabolism include insulin resistance and glucose intolerance. Several factors contribute to hyperglycemia, which may coexist with hypoglycemia.

Mark E. Williams, Rajesh Garg

Glycemic Management in ESRD and Earlier Stages of CKD

American Journal of Kidney Diseases, Volume 63, Issue 2, Supplement 2, 2014, S22–S38

Assessment of Glycemic Control

Monitoring of blood glucose

- insulin-treated diabetes
- Patients treated with sulfonylureas or meglitinides

HbA1c

serial measurements (two to four times yearly)

Glycated albumin

Fructosamine

Assessment of Glycemic Control

HbA1c

- false elevations: interference from carbamylated hemoglobin in agar gel electrophoresis method
- The Boronate-agarose affinity chromatography and the thiobarbituric acid methods are techniques for analyzing HbA1c that can be used reliably in ESRD
- Other factors that affect the accuracy of these assays:

  reduced red blood cell life span, recent transfusion, iron deficiency, accelerated erythropoiesis due to administration of erythropoietin, and metabolic acidosis.

Assessment of Glycemic Control

Goals of therapy(HbA1c target)

Nondialysis CKD patients

- approximately 7 percent

(K/DOQI and KDIGO guidelines)

Dialysis patients:

- Patients <50 years and without significant comorbid conditions 7 to 7.5 percent
- Older patients with multiple comorbid conditions 7.5 to 8 percent

Glycemic Control

Non pharmacologic therapy

- Weight reduction:

For patients with BMI ≥25

- Diet: caloric restriction

depletion of hepatic glycogen stores, reducing hepatic glucose output

- Exercise:

  30 to 60 minutes of moderate-intensity aerobic activity on most days of the week (at least 150 minutes per week)

  It leads to increased responsiveness to insulin

Glycemic Control

Pharmacologic therapy

- For most patients presenting with A1C at or above target level (ie, >7.5 to 8 percent), pharmacologic therapy should be initiated at the time of diabetes diagnosis.
- After three to six-month trial of lifestyle modification

Glycemic Control

Insulin therapy

(The indications for initiating insulin therapy are the same as for the general diabetic population)

- Patients who fail therapy with oral agents
- Ketonuria and/or weight loss
- For patients presenting with severe hyperglycemia (FBS >250 mg/dL, random glucose consistently >300 mg/dL, A1C >9.5 insulin remains the preferred initial therapy

Glycemic Control

Insulin dose adjustment in CKD

- GFR >50mL/min: no dose adjustment (10 units or 0.2 units/kg)
- GFR 10 - 50 mL/min: dose should be reduced to approximately 75 percent of baseline
- GFR is <10 mL/min: dose should be reduced 50 percent

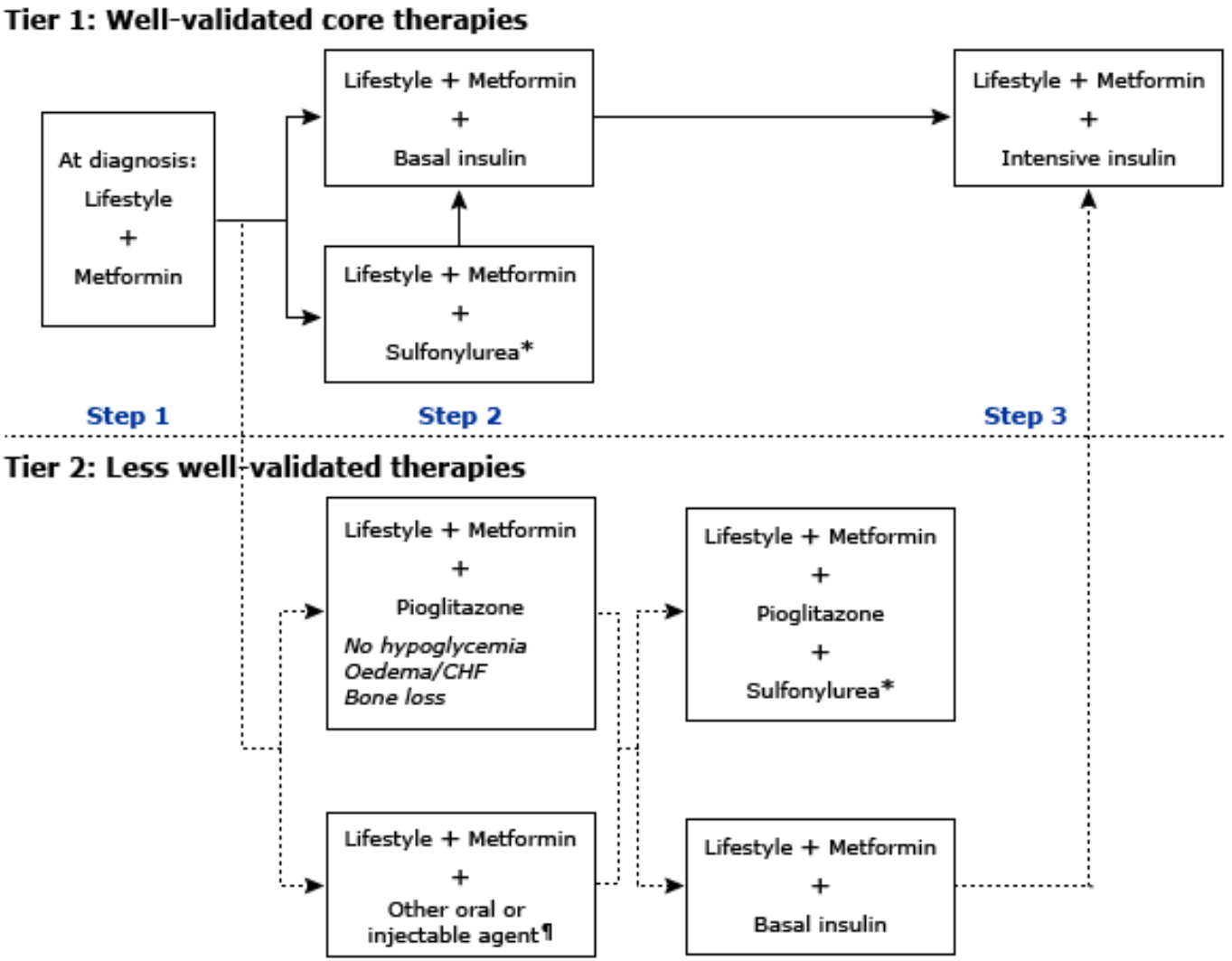
Glycemic Control

First line oral hypoglycemic agents:

the ADA/EASD consensus guideline (grade 2B)

- **Metformin**
- **Short-acting sulfonylurea**, such as glipizide for patients with contraindications to metformin
- **Repaglinide** for patients who are intolerant of or are not candidates for metformin or sulfonylureas

Management of type 2 diabetes



Glycemic Control:Oral medications

Metformin

- Increases insulin sensitivity
- Decreases hepatic gluconeogenesis

does not cause hypoglycemia and may lead to weight loss

- The most common side effects:

diarrhea, bloating and cramping

Vitamin B12 deficiency (rare)

Glycemic Control:Oral medications

Metformin dose adjustment:

- **eGFR ≥45-59: use caution with dose and follow renal function closely (every 3–6 months)**
- **eGFR ≥30-44: max dose 1000 mg/day, Follow renal function every 3 months, Do not start as new therapy**
- **eGFR<30: avoid use**
- **Per FDA, do not use if serum Cr ≥ 1.5 mg/dL in men ≥ 1.4 mg/dL in women**

Glycemic Control:Oral medications

Prevention of lactic acidosis:

- Stop metformin in the presence of situations that are associated with hypoxia or an acute decline in kidney function:

sepsis/shock, hypotension, acute myocardial infarction, and use of radiographic contrast or other nephrotoxic agents

(KDIGO guidelines)

Glycemic Control:Oral medications

Sulfonylureas

Sulfonylureas bind to the sulfonylurea receptor on the pancreatic beta-cells and lead to increased insulin secretion

- **Glipizide**: Less than 10 % of is cleared renally

use with caution with an eGFR <30 ml/min/1.73

- **Glyburide** : avoid with eGFR <60 ml/min/1.73 m^2
- **Gliclazide**: No dose adjustment

Glycemic Control:Oral medications

Glinides

- Nateglinide and repaglinide
- increase insulin secretion by closing a sulfonylurea receptor/ATP-dependent potassium channel on the beta-cells of the pancreas
- result in a rapid and short duration of insulin release and should be taken prior to meals

Glycemic Control:Oral medications

Repaglinide

- eGFR <30 ml/min/1.73 m^2, start at the lowest dose (0.5 mg) with slow upwards titration

Nateglinide should not be used with an eGFR <60 ml/min/1.73 m^2

- nateglinide can be used in dialysis patients

Glycemic Control:Oral medications

Thiazolidinediones

pioglitazone, rosiglitazone

- increase insulin sensitivity

are metabolized by the liver

side effects: fluid retention, bone loss

should not be used in advanced heart failure

Glycemic Control:Oral medications

Alpha-glucosidase inhibitors

Acarbose, Miglitol

- Decrease the breakdown of oligo-and disaccharides in the small intestine, slowing ingestion of carbohydrates and delaying absorption of glucose after a meal
- Side effects: bloating, flatulence, and abdominal cramping
- serum Cr >2 mg/dl: avoid use

Glycemic Control:Oral medications

Dipeptidyl peptidase-4 inhibitors

- Dipeptidyl peptidase 4 (DPP 4) inhibitors decrease the breakdown of incretin hormones such as GLP-1

(leads to insulin secretion, decreasing glucagon release, slow gastric emptying)

sitagliptin, saxagliptin, linagliptin, and alogliptin

- Approximately 80 % of sitagliptin is cleared by the kidney

Glycemic Control:Oral medications

Sitagliptin

- eGFR ≥50: 100 mg daily
- eGFR 30–49: 50 mg daily
- eGFR < 30: 25 mg daily

Saxagliptin

- eGFR > 50: 2.5 or 5 mg daily
- GFR ≤ 50: 2.5 mg daily

Linagliptin

- No dose adjustment

Alogliptin

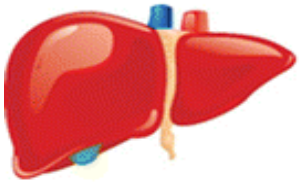
- eGFR >60: 25 mg daily
- eGFR 30–59: 12.5 mg daily
- eGFR <30: 6.25 mg daily

Glycemic Control:Oral medications

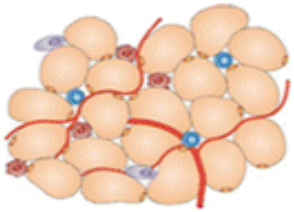
DPP-4 inhibitors:

- exhibit cytoprotective functions against various diabetic complications affecting the liver, heart, kidneys, retina, and neurons
- improve the proteinuria, filtration barrier remodeling, and the circulating and kidney tissue DPP-4 activity
- DPP-4 targeting improves oxidative stress-related glomerulopathy and the associated proteinuria

Ref. Bae, E. DPP-4 inhibitors in diabetic complications: role of DPP-4 beyond glucose control. J. Arch. Pharm. Res. (2016) 39: 1114.



NAFLD
NASH
Liver fibrosis

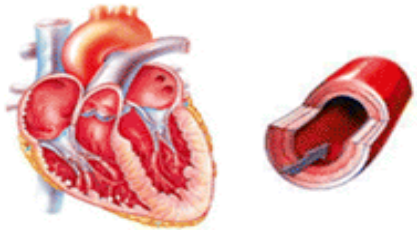


Adipocyte hypertrophy
ATM accumulation

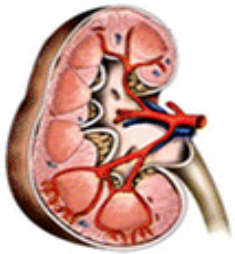
Insulin secretion
β cell mass

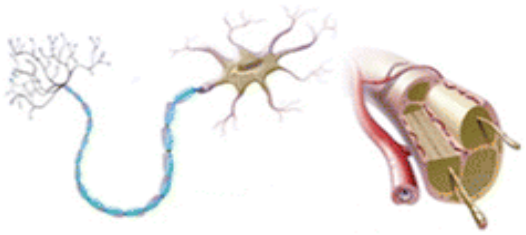
DPP-4 Inhibitors (Gliptins)

Atherosclerosis
CV diseases



Diabetic nephropathy





Glycemic Control:Oral medications

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

- SGLT2 inhibitors reduce glucose absorption from the kidney
- weight loss, intravascular volume contraction, AKI,DKA ,UTI

Glycemic Control:Oral medications

Canagliflozin

- eGFR 45 - 60: max dose 100 mg once daily
- eGFR <45, avoid use

Dapagliflozin

- eGFR < 60, avoid use

Empagliflozin

- eGFR < 45, avoid use

Glycemic Control

Glucagon-like peptide 1 (GLP-1) Receptor Agonists

- leading to insulin release, delayed glucagon secretion and delayed gastric emptying

Exenatide (regular and extended-release) and liraglutide

- use with metformin and/or sulfonylureas also with insulin
- leading to a reduction in appetite and often weight loss

Glycemic Control

GLP-1 Receptor Agonists

- Common side effect:

pancreatitis, nausea, renal failure and worsening of chronic renal impairment(exetinide)

- Albiglutide and dulaglutide are other GLP-1 receptor agonists that can also be dosed once weekly.

Glycemic Control

Exenatide

- eGFR 30–50: use caution
- eGFR <30: avoid use

Liraglutide

- No dose adjustment but use caution when starting or titrating the dose

Albiglutide

- No dose adjustment needed

Dulaglutide

- No dose adjustment needed

Glycemic Control

Hemodialysis patients

- Insulin: usually use rather than oral agents

(K/DOQI guidelines)(grade 2C)

- Oral agents: patients who are already on these agents and have acceptable glycemic control

Preferred agents are **glipizide** or **repaglinide**

Glycemic Control

Peritoneal dialysis patients

oral agents:

- For patients who were already on oral agents with good glycemic control prior to starting dialysis
- For patients who develop diabetes after starting dialysis

the preferred oral agent is glipizide,Repaglinide

Insulin:

- Most peritoneal dialysis patients require to maintain good glycemic control
- subcutaneous or intraperitoneal insulin