IN THE NAME OF GOD

Control of hyperglycemy in CKD patients

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Diabetology & Metabolic Syndrome

REVIEW

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Interactions between kidney disease and diabetes: dangerous liaisons

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CLINICAL DIABETES
AND ENDOCRINOLOGY

REVIEW ARTICLE Open Access

Management of diabetes mellitus in patients with chronic kidney disease

Glucose homeostasis in kidney disease

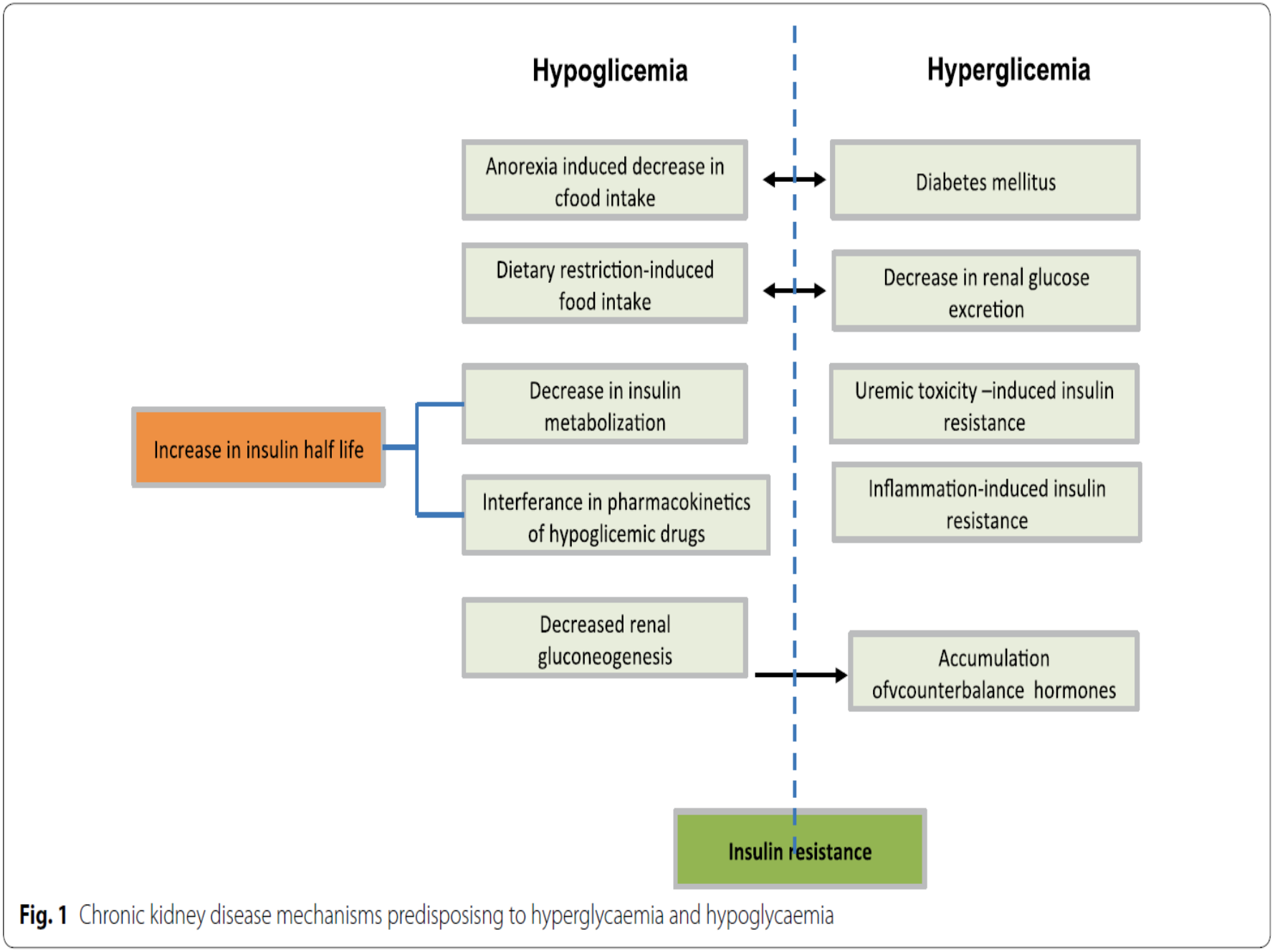

Fig. 1 Chronic kidney disease mechanisms predisposisng to hyperglycaemia and hypoglycaemia

- **Glycemic monitoring in CKD**

-Blood glucose concentration

-Home glucose monitoring or self-monitoring (SM)

-Glycated hemoglobin

- ***Important factors causing technical interferen*Interference**

factors **increasing** HbA1c:

- **renal** impairment (increased urea binds to hemoglobin, producing **carbamylated** hemoglobin that interferes with HbA1c measurement)

-use of **acetylsalicylic acid** (binds to hemoglobin, producing acetylated hemoglobin, which interferes with HbA1c measurement

-hypertriglyceridemia; and **hyperbilirubinemia**.

- factors **decreasing** HbA1c measurements include hemoglobin glycation inhibition factors (e.g., **vitamins C and E)**

- ***Clinical conditions*** *that interfere with the method Interference*

factors **increasing** HbA1c:

- **polycythemia**, **anemia** due to **iron deficiency**, **folic acid**, or **vitamin B12**; **chronic alcoholism; and opiates**.

- Factors **decreasing** HbA1c measurements include conditions that shorten the half-life of red blood cells:

- hemolytic anemia, hemorrhages, **lead poisoning**, **erythropoietin deficiency** secondary to **renal failure**, **multiple myeloma**, **hypothyroidism**, leukemia, and severe burns with loss of fluid and proteins **.**

- ***Limitations of glycated hemoglobin in CKD***

- HbA1c is a measure for the mean level of blood glucose in the **past 90** days.
- **50 % for the last month**, **25 % for the 2nd month ago**, and **25 %** for the **3rd and 4th month ago**.

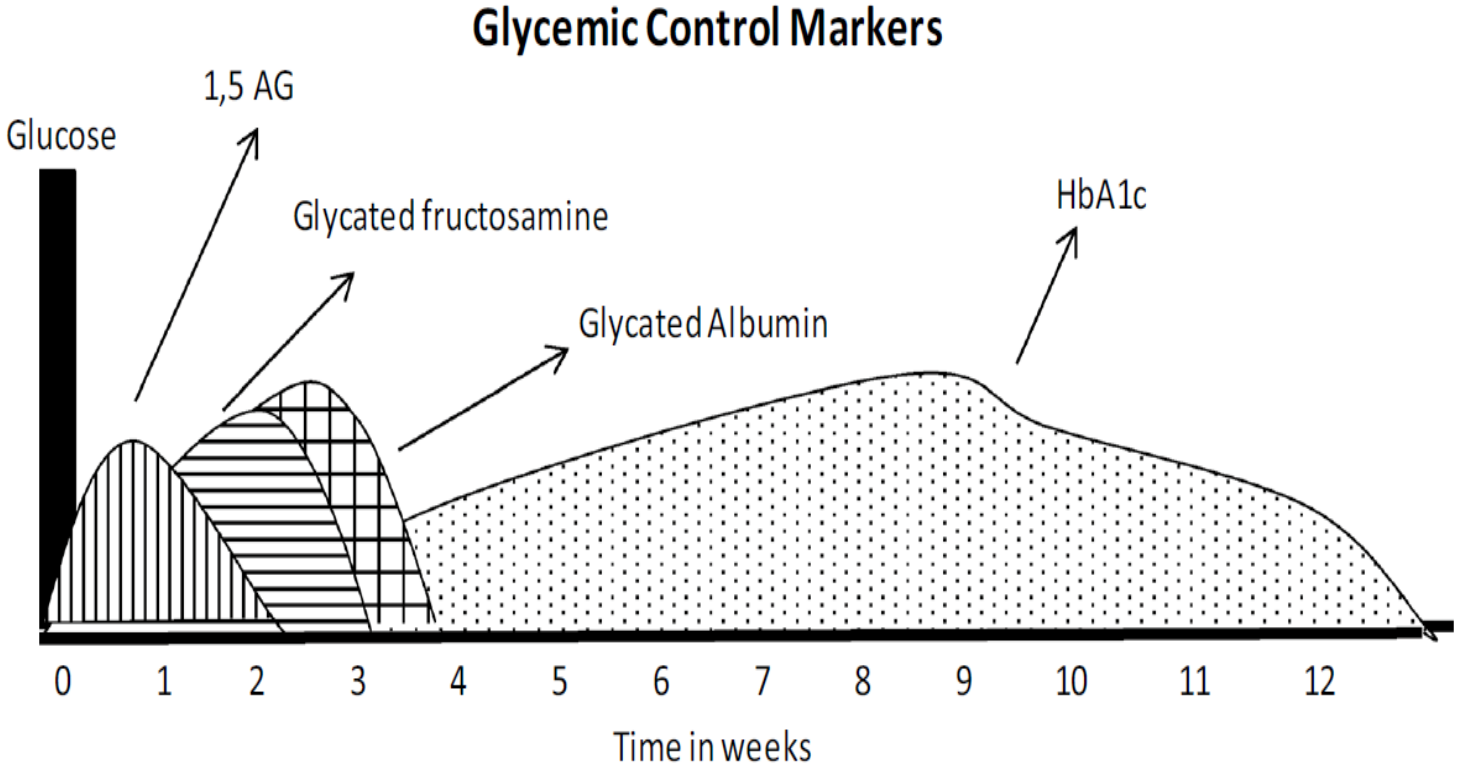

Fig. 2 Correlation between each marker and the time of hyperglycemia that each indicates

- discrepancy between HbA1c and other measurements of glycemic control can be partly due to the different **life span of erythrocytes**.

- **Decreased erythropoiesis**, caused by **iron** or vitamin **B12 deficiency** or **aplastic anemia**, leads to an **increased number of aged** red blood cells and a subsequent **progressive increase of HbA1c**, unrelated to glycemic control

- Anemia due to iron deficiency increases HbA1c up to **2 %,** which can be **reverted by iron supplementation**.

- decrease in HbA1c is observed after the administration of **erythropoietin, iron, and vitamin B12**, and in cases of **hemolytic anemia**

- **General approach of DM treatment in CKD**

- Studies show that reducing **HbA1c to values ≤7 % influences** the reduction of **microvascular** complications caused by DM, and if implemented **early**, it is also associated with a reduced occurrence of **macrovascular** complications

- **secondary prevention** when the kidney disease is already established, glycemic control remains a major therapeutic to progression of CKD
- The ADVANCE trial showed that intensive control was able to reduce albuminuria, nephropathy, and the need for hemodialysis
- the ACCORD trial showed a significant reduction in albuminuria (although not in advanced renal disease) in the group treated with an intensive therapy for glycemic control

- The **ACCORD** trial was a landmark in demonstrating that patients with **high cardiovascular risk**, when treated intensively with the aim to achieve HbA1c of approximately 6 %, presented an **increased risk of death**

- HbA1c goals for patients with a history of **severe hypoglycemia**, **limited life expectancy**, patients with **microvascular or macrovascular** complications in advanced stages, and patients with multiple comorbidities.

- The recommendation of less strict **HbA1c goals (around 8 %)** for these groups aims to reduce the morbidity and mortality

- **Nutritional recommendations for diabetic patients with CKD**

Table 1 Dietary plan macronutrient composition for DKD in the non-dialysis stage. Source: adapted from the Brazilian Diabetes Society (2014)

Macronutrients	Recommended intake/day
Total carbohydrates	45–60 % of TEI (total energy intake)
Saccharose	Up to 10 %
Fructose	Not recommended its addition to food
Dietary fibers	Minimum of 20 g/day or 14 g/1000 kcal
Total fat	Up to 30 % of TEI
Saturated fatty acids (SFA)	<7 % of TEI
Trans fatty acids (TFA)	≤2 g
Polyunsaturated fatty acids (PUFAs)	Up to 10 % of TEI
Monounsaturated fatty acids (MUFA)	Supplemented individually
Cholesterol	<200 mg/day
Proteins	0.8–1.0 g/kg/day in the early stages of disease and <0.8 g/kg/day in the final phases

- **Pharmacological treatment: non-insulin antidiabetic agents**

Table 2 Recommendations for the use of noninsulin antidiabetic agents in CKD

Antidiabetic Agents	Recommendations in CKD
Metformin	With creatinine clearance 30–45 mL/min/1.73 m^2, halve the dose and suspend the drug when the creatinine clearance is <30 mL/min/1.73 m^2
Sulfonylureas	Use drugs with a short duration of action and suspend the drugs when the creatinine clearance is <45 mL/min/1.73 m^2
Glinides	These can be used in patients with CKD, although with care when the creatinine clearance is <30 mL/min/1.73 m^2
Glitazones (pioglitazone)	Their use is associated with water and salt retention, which limits their use in CKD
Alpha-glucosidase inhibitors (acarbose)	Their use should be avoided in CKD, due to risk of drug accumulation and consequent hepatotoxicity
Sodium-glucose cotransporter type 2 inhibitors	Their use is not indicated with a creatinine clearance <30 mL/min/1.73 m^2
Peptide-1 receptor agonists similar to glucagon (GLP-1 RA)	Little knowledge in CKD. Gastrointestinal effects are exacerbated in patients with CKD. Use with caution with a creatinine clearance 45–60 mL/min/1.73 m^2 and avoid its use in patients with a creatinine clearance <45 mL/min/1.73 m^2
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Low risk of hypoglycemia. These can be used in CKD. With a creatinine clearance <50 mL/min/1.73 m^2, dosage adjustments should be made for vildagliptin, sitagliptin, and saxagliptin. The dose of linagliptin does not require adjustment in CKD

- Pharmacological treatment of DM in CKD: **insulin therapy**

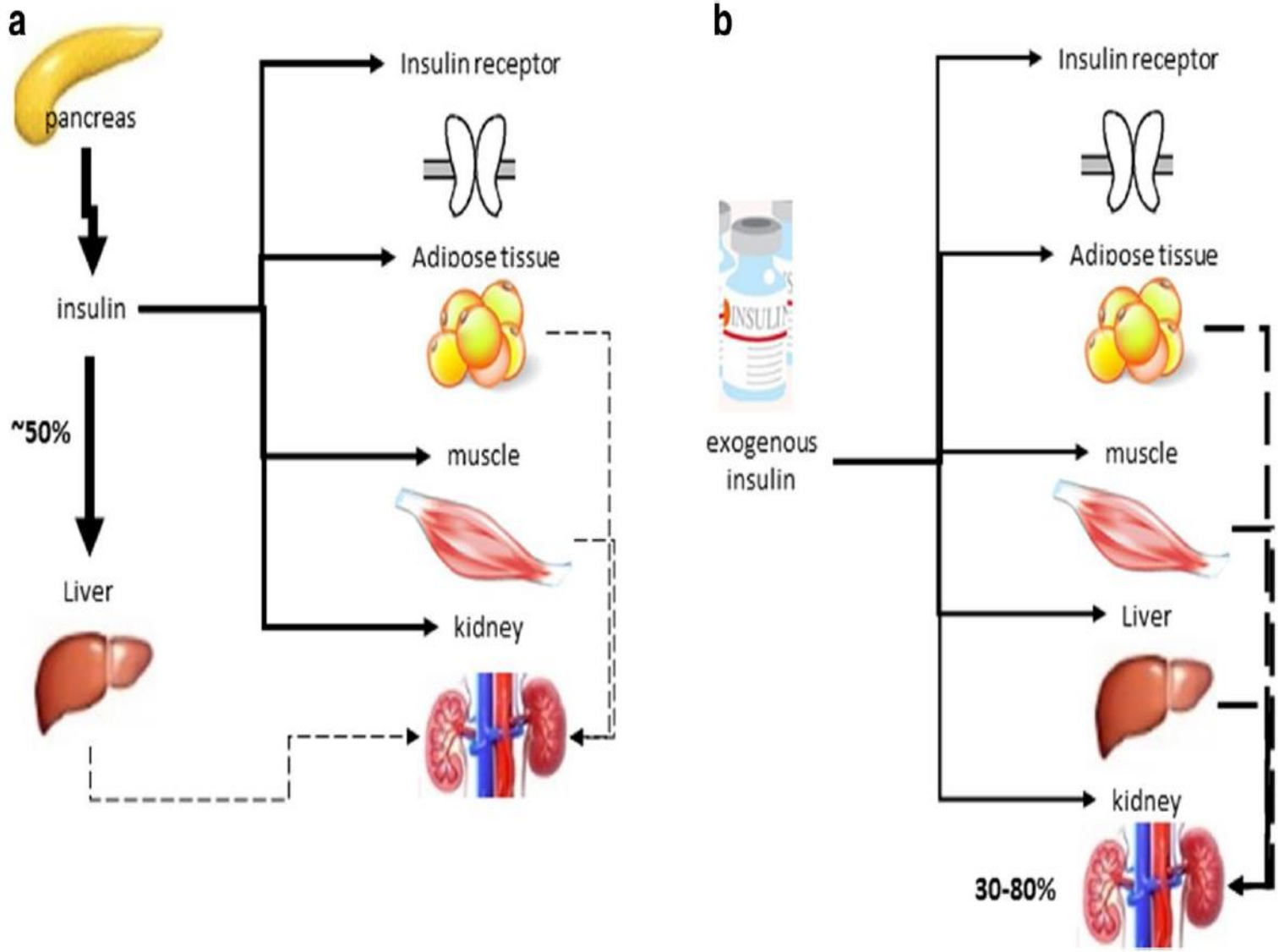

Fig. 3 Schematic presentation of the clearance of insulin. **a** endogenous insulin and **b** exogenous insulin. Adapted from Iglesias and Díez [130]

- a reduction of the dose of insulin when GFR is between **10–50** mL/min, **around25 %** of total daily dose and **50 % for a GFR <10** mL/min, regardless of the type of insulin used .

Table 3 Insulin pharmacokinetic profiles

Insulin type	Onset	Peak	Duration of actior
Rapid-acting profile			
Regular	30 min	2–4 h	5–7 h
Short-acting profile			
Lispro Aspart Glulisine	5–15 min	60–90 min	3–4 h
intermediate-acting profile			
NPH*	2 h	6–10 h	13–20 h
Long-acting profile			
Glargin	~2 h	Flat	20–24 h
Detemir	~2 h	Less-pronounced peak	6–24 h
Ultra-long-acting profile			
Degludec	20–40 min	Flat	~42 h

Table 1 Dose adjustment for insulin compounds and medications for diabetes in CKD

Medication class	CKD stages 3 and 4 and predialysis stag
Insulin	
Glargine	No advised dose adjustment*
Detemir	No advised dose adjustment*
NPH	No advised dose adjustment*
Regular	No advised dose adjustment*
Aspart	No advised dose adjustment*
Lispro	No advised dose adjustment*
Glulisine	No advised dose adjustment*

First-generation sulfonylureas	
Acetohexamide**	Avoid use
Chlorpropamide	eGFR 50–80: reduce dose by 50 % eGFR <50: avoid use
Tolazamide	Avoid use
Tolbutamide	Avoid use

Second-generation sulfonylureas	
Glipizide	eGFR <30: use with caution
Glimepiride	eGFR <60: use with caution
	eGFR <30: avoid use
Glyburide	Avoid use
Gliclazide**	No dose adjustment
Glinides	
Repaglinide	No dose adjustment but may wish to use caution with eGFR <30
Nateglinide	eGFR <60: avoid use (but may consider use if patient is on hemodialysis)

Biguanides

Metformin***

Per FDA, do not use if serum Cr ≥ 1.5 mg/dL in men ≥ 1.4 mg/dL in women.

Consider

eGFR ≥45-59: use caution with dose and follow renal function closely (every 3–6 months)

eGFR ≥30-44: max dose 1000 mg/day or use 50 % dose reduction. Follow renal function every 3 months. Do not start as new therapy.

eGFR <30: avoid use

Thiazolidinediones	
Pioglitazone	No dose adjustment
Rosiglitazone	No dose adjustment
Alpha-glucosidase inhibitors	
Acarbose	serum Cr >2 mg/dl: avoid use
Miglitol	eGFR <25 or serum Cr >2 mg/dl: avoid use
DPP-4 inhibitor	
Sitagliptin	eGFR ≥50: 100 mg daily

Table 1 Dose adjustment for insulin compounds and medications for diabetes in CKD *(Continued)*

	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

SGLT2 inhibitors

Canagliflozin	eGFR 45 to < 60: max dose 100 mg once daily
	eGFR <45, avoid use
Dapagliflozin	eGFR < 60, avoid use
Empagliflozin	eGFR < 45, avoid use

Dopamine receptor agonist	
bromocriptine mesylate	No dose adjustment known but not studied: use with caution
Bile acid sequestrant	
Colesevelam	No dose adjustment known but limited data

GLP-1 Agonists	
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
Amylin analog	
Pramlintide	No dose adjustment known but not studied in ESRD

- **Medical therapy in dialysis and post-transplant patients**

- There are a few **oral agents** that can be used safely in patients on dialysis, particularly if the diabetes is fairly **mild**.

- Patients receiving hemodialysis (HD) can have different clearance rates of insulin

- Patients who are on peritoneal dialysis (PD) have exposure to **large** amounts of **glucose** in the dialysate that can lead to uncontrolled hyperglycemia.
- In patients receiving PD continuously, a standard **basal/bolus insulin** regimen is best.
- However, with **overnight PD using a cycler**, coverage of the increased glucose load may best be accomplished using a fixed mixture insulin combination, such as **70/30 or 75/25 insulins,** given at the onset of PD.

THANK YOU

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Diabetes and Pregnancy

-Preexisting Type 1 or Type 2

-**GDM**

- Complications:

- Abortion
- Fetal anomalies
- Preeclampsia
- Macrosomia
- Neonatal hypoglycemia
- Hyperbilirubinemia
- Neonatal respiratory distress syndrom

- Obesity
- Hypertension
- Type 2 DM in offspring

- Diabetic embryopathy,directly proportional to elevation in A1C during the first 10 week of pregnancy:

  anencephaly
  microcephaly
  congenital heart disease
  caudal regression
  renal anomalies

Preconception counseling:

Ideally A1C<6.5%

- Preconception care:

  rubella,syphils,hepatitis B,HIV

  Pap smear,cervical cultur,folic acid

  smoking cessation

  TFT,A1C,U/A,Cr,Alb/Cr ratio

  review of medication(ASE,ARB,Statins)

- Dilated eye examination:

  before pregnancy or in the first trimester

  then every trimester

- Glycemic targets in pregnancy:(type 1,2)

FBS	**≤ 95**	**mg/dl**	**(70-95)**
1 h pp	**≤140**	**mg/dl**	**(110-140)**
2 h pp	**≤120**	**mg/dl**	**(100-120)**

A1c < **6**%

(<7% if hypoglyemia is present)

Preeclampsia and Aspirin

- **low dose 81 mg**(60-150)

-End of first trimester until delivery

(2,3 trimester)

Blood pressure

110-135/85

Drug Contraindication:

- Statins
- ACEs
- ARBs
- Atenolol
- Diuretic

- Glucose metabolism in pregnancy:

  - **FBS** are lower,due to insulin-independent glucose uptake by the fetus and placenta

  -postprandial hyperglycemia and carbohydrate intolerance of Diabetogenic placenta hormones

Insulin physiology:

Early pregnancy is a time of enhanced **insulin sensitivity,lower glucose levels and lower insulin requirements**.

The situation rapidly reverses as **insulin resistance** during **second and early third trimester**.

levels off toward the **end of the third trimester**.

- Iranian Endocrine Society Guildline

first trimester

	N	GDM	DM
FBS	**<100**	100-125	≥126
	24-28 screening	lifestyle SMBG	Insulin

24-28 weeks **OGTT(75 g)**

	GDM	DM
FBS	92-125	≥126
1h	180	
2h	153-200	≥200

- Management of GDM:

  -Medical Nutrition Therapy

  -Physical Activity

  -Pharmacologic Therapy

FBS < 95

1 h <140

2 h <120

70-85 % GDM can control with lifestyle modification alone

Medical Nutrition Therapy:

carbohydrate	175 g (50%)
protein	71 g (20%)
fiber	28 g

Exercise:

moderate

30 minutes

5 dayes in week

Gliburide

-Neonatal Hypoglycemia

-Macrosomia

Metformin

-Lower risk neonatal hypoglycemia

-Less maternal weight gain

-Prematurity(slightly)

-Higher BMI and obesity in the offspring

-pco(DC)

Isulin:

-NPH , REG

-Detemir ,Glargine(<50%)

-Aspart,Lispro (>50%)

Post partum care:

4-12 week postpartum

(75-g OGTT)

THANK YOU