Selection of Glucose-Lowering Medications for Patients With Diabetic nephropathy

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INTRODUCTION

- Diabetes mellitus is the leading cause of chronic kidney disease (CKD) and a major public health issue worldwide.
- Approximately 20–30% of patients with type 2 diabetes mellitus (T2DM) have renal impairment, classified as moderate-to-severe CKD glomerular filtration rate (GFR) <60 mL/min/1.73m2).
- Unfortunately, the combination of diabetes and CKD is associated with increased morbidity and mortality, mainly due to increased cardiovascular risk

Glucose-Lowering Medications

- *Biguanide – Metformin*
- *Sulfonylureas*
- *Glinides*
- *Alpha-glucosidase inhibitors*
- ***Glitazones***
- *Dipeptidyl peptidase-4 inhibitors* (DPP-4 I)
- ***Incretin mimetics(GLP-1 receptor Analog)***
- ***Sodium-glucose cotransporter 2 inhibitors(SGLT2I)***
- ***Insulin therapy***

Biguanide - Metformin

- metformin is the initial pharmacological agent for type 2 diabetes treatment.
- It inhibits mitochondrial respiratory chain complex 1, activates the energy metabolism and AMPK, thereby regulating various metabolic systems to promote ATP synthesis and suppress ATP consumption, and inhibits gluconeogenesis in the liver
- This drug acts mainly by decreasing hepatic glucose production, increasing peripheral glucose uptake, improving glucose tolerance and lowering fasting and postprandial plasma glucose.

Biguanide - Metformin

- The use of metformin is still avoided in patients with CKD stages 3–5 with other associated risk factors for lactic acidosis.

- Its most serious adverse effect is the development of lactic acidosis, although this is a very rare occurrence

Sulfonylureas

- Sulfonylureas (SUs) are drugs that stimulate endogenous insulin secretion by pancreatic b cells
- These drugs may potentially cause hypoglycemia, especially in association with high doses;
- Hypoglycemic episodes may be severe in patients with renal failure, and the drugs are contraindicated from stage 3 of CKD (eGFR <60 mL/min).

Sulfonylureas

- They are divided into two groups: first-generation agents, which includes chlorpropamide, tolazamide, and tolbutamide, and second-generation agents, which includes glipizide, glimepiride, and glyburide.
- The first-generation sulfonylureas are known to have longer half-lives, higher risk of hypoglycemia, and slower onset of action, as compared to second-generation sulfonylureas.
- Hypoglycemia is the major side effect of all sulfonylureas, while minor side effects such as headache, dizziness, nausea, hypersensitivity reactions, and weight gain are also common

Sulfonylureas

- Gliclazide has inactive metabolites that are eliminated mainly in the urine (80%) and presents a lower risk of severe hypoglycemia than glibenclamide and glimepiride do.

- This drug can be considered in renal impairment if appropriate attention is paid to the dose.
- However, use should be avoided if the GFR falls to <40 mL/min

Sulfonylureas

- Sulfonylureas are contraindicated in patients with hepatic and renal diseases and are also contraindicated in pregnant patients due to the possible prolonged hypoglycemic effect to infants.
- Drugs that can prolong the effect of sulfonylureas such as aspirin, allopurinol, sulfonamides, and fibrates must be used with caution to avoid hypoglycemia.
- Sulfonylureas should be used with caution in subjects receiving beta blockers.

Glinides

- Both Repaglinide and Nateglinide belong to a class of glinides, which are Su-like agents that stimulate insulin secretion but are rapidly absorbed, with a short duration of action, thus contributing to reducing postprandial hyperglycemia.
- Repaglinide is considered a safe option until the GFR falls to <30 mL/min/1.73 m_2
- In advanced renal disease, treatment with Repaglinide should begin cautiously, with 0.5 mg daily, to avoid hypoglycemia.

Alpha-glucosidase inhibitors

- Alpha-glucosidase inhibitors reduce the rate of digestion and intestinal absorption of carbohydrates, resulting in mild reduction of glycated hemoglobin (A1C).
- Acarbose is metabolized nearly completely within the gastrointestinal tract, so less than 2% of an oral dose is recovered as the active drug or its metabolites in the urine.
- As a result, it delays the digestion of carbohydrates and disaccharides into absorbable monosaccharides, thereby dampening the postprandial blood glucose peak

Thiazolidinedione

- **Like biguanides, TZDs improve insulin action.**
- **TZDs facilitate increased glucose uptake in numerous tissues including adipose, muscle, and liver.**
- **Mechanisms of action include diminution of free fatty acid accumulation, reduction in inflammatory cytokines, rising adiponectin levels, and preservation of β-cell integrity and function, all leading to improvement of insulin resistance**.
- These medications may cause fluid retention and thus should be used with caution in patients with heart failure (HF) as well as in those with CKD and a significant decrease in the GFR

- **Thus, TZDs are not preferred as first-line.**

Dipeptidyl peptidase-4 inhibitors **(DPP-4 Inhibitor)**

• Dipeptidyl peptidase-4 (DPP-4) inhibitors prevent degradation of incretin hormones by DPP-4, enhancing glucose-dependent insulin secretion.

Dipeptidyl peptidase-4 inhibitors **(DPP-4 Inhibitor)**

- There are five available DPP-4 inhibitors, also known a‘‘gliptins’’ (sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin), and despite their common mechanism of action, these agents have structural heterogeneity that translates into different pharmacological properties and different metabolism and excretion pathways.

Dipeptidyl peptidase-4 inhibitors **(DPP-4 Inhibitor)**

- Sitagliptin is mostly eliminated unchanged in the urine and can be used with appropriate dose reduction in all chronic kidney stages.
- The usual dose of 100 mg once per day should be adjusted to 50 mg/day for patients with moderate renal impairment.
- In severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease (ESRD) requiring dialysis, the dose is further reduced to 25 mg once daily.

Dipeptidyl peptidase-4 inhibitors (DPP-4 Inhibitor)

- The three most commonly reported adverse reactions in clinical trials with gliptins were:
- nasopharyngitis,
- upper respiratory tract infection,
- and headache.

Acute pancreatitis was reported in a fraction of subjects taking sitagliptin or metformin and sitagliptin

Incretin mimetics **(GLP1)**

- Incretin mimetics include glucagon-like peptide 1 (GLP1) analogs and agonists (exenatide, lixisenatide and liraglutide),

which increase insulin secretion and suppress glucagon secretion in a glucose-dependent manner, with reduced risk of hypoglycemia.

- These mimetics also slow gastric emptying and suppress appetite via central nervous system modulations, resulting in a reduced body weight.
- However, the main side effects are nausea and vomiting.

Incretin mimetics **(GLP1)**

- its prescription in patients beyond mild-stage renal disease is limited and there are no recommendations that support its use in the moderate and severe stages

Incretin mimetics **(GLP1)**

- The glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide reduced the incidence of a composite renal endpoint (consisting of new onset of albuminuria.
-

Sodium-glucose cotransporter 2 inhibitors(SGLT2 inhibitors)

• The sodium-glucose cotransporter 2 (SGLT2) protein, expressed in the kidney proximal tubules, is able to reabsorb approximately 90% of glucose filtered through the glomeruli.

SGLT2 inhibitors

- SGLT2 inhibitors, By inhibiting the function of the glucose, these drugs inhibit glucose reabsorption in the renal tubules and increase urinary glucose excretion.
- In addition to blood glucose control through the hypoglycemic effect caused by urinary glucose excretion, there is also a reduction in hypoglycemia, weight loss, and blood pressure.
- Furthermore, these drugs have varied effects, including improving lipid profiles, and lowering of uric acid levels
- These drugs have also been reported to reduce the risk of cardiovascular events

Sodium-glucose cotransporter 2 inhibitors

- This therapeutic class has been approved for the treatment of patients with T2DM with an eGFR of >45 mL/min/1.73 m_2

- To date, however, just canagliflozin has been evaluated, showing safety and efficacy in a subset of patients with stage 3 CKD

Sodium-glucose cotransporter 2 inhibitors

- Urinary tract infections leading to urosepsis and pyelonephritis, as well as genital mycosis, may occur with SGLT2 inhibitors.
- SGLT2 inhibitors may rarely cause ketoacidosis.

- Patients should stop taking their SGLT2 inhibitor and seek medical attention immediately if they have symptoms of ketoacidosis (frank nausea or vomiting, or even non-specific features like tiredness or abdominal discomfort).

UP TODATE

- The use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, such as canagliflozin and empagliflozin, in patients with type 2 diabetes reduced the risk of kidney disease progression and of renal endpoints in some trials

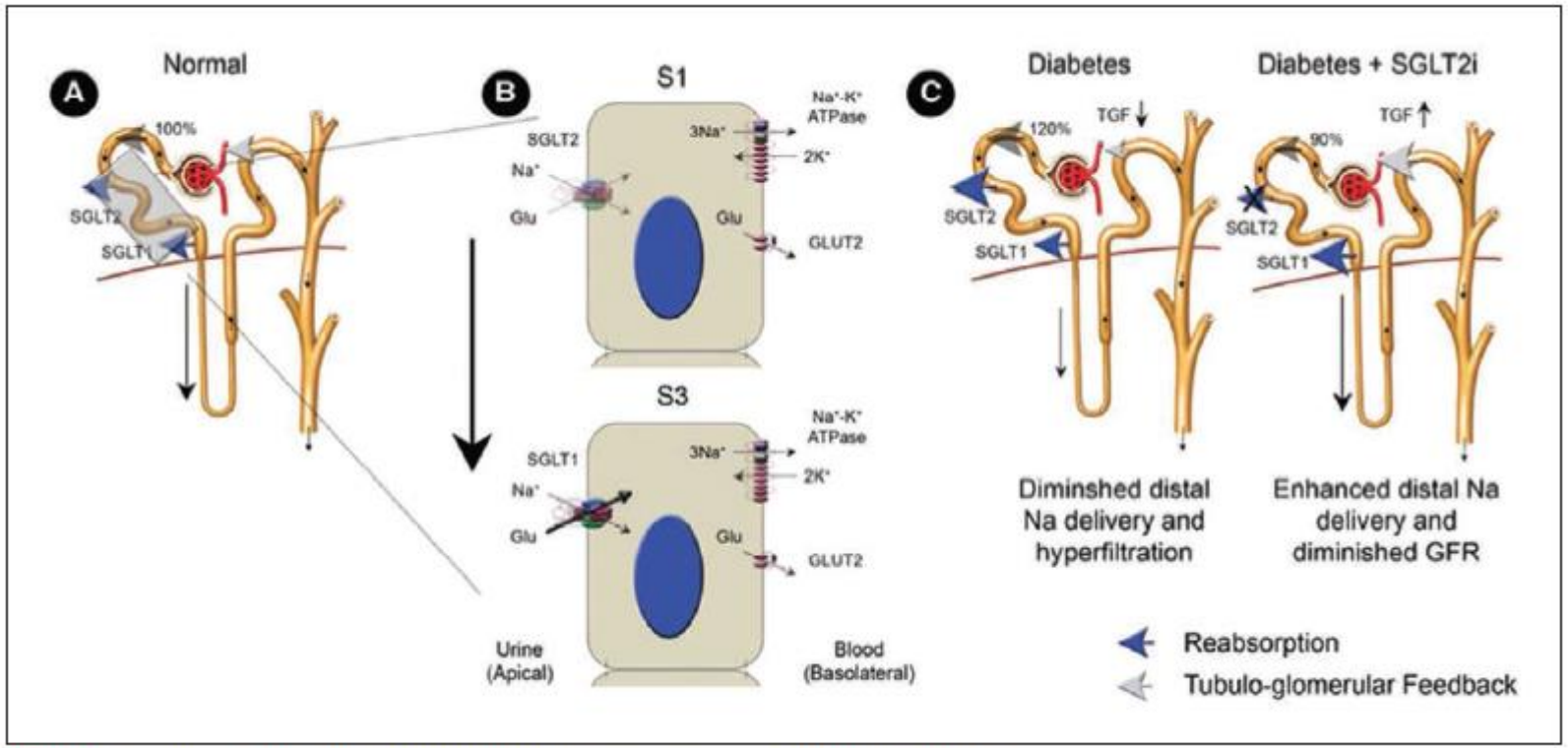

Figure 2. Mechanism of action of the SGLT (sodium glucose cotransporter) 2 inhibitors (SGLT2is)

Insulin therapy

- The kidney also plays an important role in insulin clearance from the systemic circulation by distinct pathways.
- The first route involves glomerular filtration and subsequent

absorption of insulin by proximal tubular cells through endocytosis

Insulin therapy

- Few studies have examined the pharmacokinetics of longacting insulin in diabetic patients with CKD.
- Although patients with impaired kidney function have lower insulin requirements, no dose adjustment is required if the GFR is >45mL/min
- Therefore, certain authors have suggested an insulin reduction to 75% of the total daily dose when the GFR is between 10 and 50 mL/min and to 50% for a GFR of <10 mL/min, independent of the insulin type being used.

CONCLUSIONS AND FUTURE DIRECTIONS

- SGLT2is and GLP-1 RAs represent antihyperglycemic therapies shown to reduce CVD and CKD risks in patients with T2D.
- In addition, SGLT2is have shown benefit in patients with HF independently of diabetes status, which opens up exciting possibilities for the use of these therapies in patients at risk for or with established cardiovascular or kidney disease without T2D.

TABLE 2 Pharmacologic Treatment Intensification Strategies Beyond Basal Insulin

Generic (Brand)	Favorable Effects	Unfavorable Effects/Cautions	Clinical Pearls for Drug Selection and Management Beyond Basal Insulin
Metformin (Glucophage)	• High efficacy • Low hypoglycemia risk • Weight neutral/modest loss • Low cost	• Long-term use associated with vitamin B-12 deficiency (monitor if peripheral neuropathy, anemia) • Contraindicated when eGFR < 30 • Rare/serious safety concerns: lactic acidosis	• Should be continued, if tolerated and not contraindicated • May require basal insulin dose reduction upon initiation • Consider metformin XR if previous GI intolerance to metformin IR
Thiazolidinediones Pioglitazone (Actos) Rosiglitazone (Avandia)	• High efficacy • Low hypoglycemia risk • Low cost • Benefit in NASH	• Weight gain • Fluid retention/edema (among those with heart failure) • Bone fractures (among postmenopausal females and elderly males) • Bladder cancer (pioglitazone) • Increased LDL-C (rosiglitazone)	• May require basal insulin dose reduction upon initiation • May cause weight gain when used in combination with insulin
Sulfonylureas Glipizide (Glucotrol) Glimepiride (Amaryl) Glyburide (Diabeta)	• High efficacy • Low cost	• High risk of hypoglycemia • Weight gain	• May cause weight gain when used in combination with insulin • Consider discontinuing when initiating combination injectable therapy

GLP-1 receptor agonists Liraglutide (Victoza) Exenatide ER (Bydureon) Dulaglutide (Trulicity) Semaglutide injection (Ozempic) Semaglutide oral (Rybelsus) Lixisenatide (Adlyxin)	• High efficacy • Low hypoglycemia risk • Weight loss (semaglutide> liraglutide>dulaglutide> exenatide>lixisenatide) • CV benefits (liraglutide>dulaglutide> semaglutide injection) • Renal benefits seen with liraglutide (LEADER) and injectable semaglutide (SUSTAIN-6)	• High cost • Avoid in setting of gastroparesis • GI intolerance (nausea, vomiting, diarrhea) • Rare/Serious safety concerns: MEN2 or thyroid C-cell tumors, acute pancreatitis, worsening of diabetic retinopathy complications (semaglutide oral and injection)	• Consider prior to basal insulin in most patients. • May require a lower insulin dose when initiating a GLP-1 receptor agonist • Shorter-acting agents have greater PPG reduction vs. longer-acting agents
SGLT2 inhibitors Canagliflozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance) Ertugliflozin (Steglatro)	• Intermediate efficacy • Low hypoglycemia risk • Weight loss • CV benefits (empagliflozin and canagliflozin) • Renal benefits seen with canagliflozin in CREDENCE; ongoing trials with dapagliflozin (DAPA-CKD) and empagliflozin (EMPA-KIDNEY) • Modest decrease in blood pressure	• High cost • Genitourinary infections • Volume depletion/hypotension • Rare/Serious safety concerns: amputation risk (canagliflzin and ertugliflozin), eDKA, bone fractures (canagliflozin), urinary tract infections, Fournier's gangrene	• May require basal insulin dose reduction upon initiation
DPP-4 inhibitors Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Tradjenta) Alogliptin (Nesina)	• Intermediate efficacy • Low hypoglycemia risk • Weight neutral	• High cost • Joint pain • Potential risk for heart failure exacerbation (saxagliptin, alogliptin) • Rare/serious safety concerns: acute pancreatitis, joint pain	• Consider discontinuing DPP-4 inhibitor when initiating a GLP-1 receptor agonist

Table 1

Pharmacological agents for glycemic control.

Class of antidiabetic medication (route of administration)	Representative agents	Mechanism of action	T1/2 and metabolism	HbA1C reduction (%)	Risk of hypoglycem
Biguanide (o)	Metformin	Insulin sensitizer Numerous effects on inhibition of hepatic glucose production	5 h; unmetabolized, renal excretion	1–2	None

Table 1

Pharmacological agents for glycemic control.

Dipeptidyl peptidase 4 (DPP-IV) inhibitor (o)	Sitagliptin Saxagliptin Vidagliptin Linagliptin Alogliptin	Inhibition of degradation of GLP	Excreted by kidneys (except linagliptin) (needs dose reduction in renal failure)	0.5–0.8	Low

Table 1

Pharmacological agents for glycemic control.

Sodium-glucose cotransporter (SGLT2) inhibitor (o)	Canagliflozin Dapagliflozin Empagliflozin	Glucosuria due to blocking (90%) of glucose reabsorption in renal PCT; insulin-independent mechanism of action	Low

GLP-1 agonists (p)	Liraglutide Exenatide Dulaglutide	Activate GLP1 receptor Increased insulin secretion, decreased glucagon, delayed gastric emptying, increased satiety	24 h 4–6 h (short acting) 7 days (long acting, extended release) 7 days	0.5–1.5	No [risk if used in combinatior with sulfonylurea (SU)]

SU (o)	Glimepiride Glipizide Glyburide	Insulin secretion	1–2	Prominent (severe in renal failure
TZD (o)	Rosiglitazone Pioglitazone	True insulin sensitizer	0.5–1.4	

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Lifestyle changes
Appropriate weight reduction
Diet
Exercise
Physical activity

Initial pharmacotherapy
Metformin
Sometimes insulin

(most have to continue t/t to maintain normal or near-normal glyc

Metformin Monotherapy failure

HbA1C>7% (FPG>135-150 mg/dl, PP(after meal), 1
less rigorous control in elderly, other comorbid cor
reduced life expectancy (guidelines unclear, rely or
decision)

Rule out drug incompliance, weight gain, dietary inconsisten
medication, intercurrent illness, new medication that may inter
insulin release or action, therapeutic inertia, latent autoimmune
adult

HbA1C>8.5%

HbA1C near 7%

Add **insulin**
(may be used with oral agent, until evidence of insulinopenia or complete lack of insulin)

Basal insulin; add rapid-acting mealtime insulin if target HbA1C not reached in 3 months; supplemental insulin with therapy

HbA1C>8.5%

Intensify insulin after weaning off SU; continuing metformin may help in responsive patients by controlling hepatic glucose production and reducing the total insulin dose

Add short-ac
sulfonylurea (SU
glipizide)

Drag image to reposition.

r-normal glycemic levels

dl, PP(after meal), 134-144 mg/dl);
other comorbid conditions with
lines unclear, rely on clinical

y inconsistency, new
hat may interfere with
autoimmune diabetes in

Add short-acting
lfonylurea (SU) (e.g.,
glipizide)

Risk of hypoglycemia (high rise worker, pilot etc), or preference for delaying insulin; consider hypoglycemia unawareness (for example, on beta-blockers)

Sulfonylurea Monotherapy failure

Use any of these class of medication either as a two-drug regimen with metformin or three-drug regimen with metformin and sulfonylurea; if target HbA1C goal is not reached in 3 months with only oral medications, switch to insulin, with or without GLP-1 receptor agonists

Repaglinide (hepatic excretion, safely used in chronic renal disease; risk of hypoglycemia)

GLP1 agonist (if weight loss is needed; liraglutide favorable in post-MI and stroke patients) (expensive option)

SGLT2 inhibitor (Empagliflozin) (cardiovascular positive effects, insulin-independent action, may be used close to beta cell exhaustion)

DPP-IV inhibitors (gliptins) (oral medication, modest reduction in HbA1C and current limited clinical information on efficacy of glycemic control, weight neutral); may be used with metformin

Thiazolidinedione (pioglitazone) (risk of heart failure/MI, osteoporosis, cost, use with caution)

Table 1 - Relationship among therapeutic class, medication dose and creatinine clearance.

Class and Medication	Dose Adjustment Based on eGFR
Biguanide	
Metformin	USA prescribing information: contraindication for men with serum creatinine ⩾1.5 mg/dL and women with serum creatinine ⩾1.4 mg/dL UK guideline allows metformin in patients with eGFR >30 mL/min/1.73 m^2 KDIGO recommends metformin in patients with eGFR >45 mL/min/1.73 m^2
Sulfonylureas	
Glipizide	No dose adjustment required
Glimepiride	Initiate conservatively at 1 mg daily Avoid use if eGFR <60 mL/min/1.73 m^2
Gliclazide	Reduce dose if eGFR <30 mL/min/1.73 m^2. Not recommended if eGFR <15 mL/min/1.73 m^2
Glyburide or glibenclamide	Avoid use in patients with eGFR <60 mL/min/1.73 m^2
Meglitinides	
Repaglinide	Initial dose of 0.5 mg before meals when eGFR <30 mL/min/1.73 m^2
Nateglinide	Caution when used with eGFR <30 mL/min/1.73 m^2. Initiate with 60 mg before meals
a-Glucosidase inhibitors	
Acarbose	Avoid if eGFR <30 mL/min/1.73 m^2
Miglitol	Avoid if eGFR <30 mL/min/1.73 m^2
TZDs	
Pioglitazone	No dose adjustment required. Use with caution in patients with CKD and hypervolemia
GLP-1 receptor agonists	
Exenatide	Avoid if eGFR <30 mL/min/1.73 m^2. When eGFR between 30 and 50 mL/min/1.73 m^2 dose should not exceed 5 mcg
Lixisenatide	Avoid if eGFR <50 mL/min/1.73 m^2
Liraglutide	Avoid if eGFR <60 mL/min/1.73 m^2

DPP-4 inhibitors	Sitagliptin and saxagliptin dose adjustment required based on eGFR
Sitagliptin	100 mg daily if eGFR <50 mL/min/1.73 m^2
	50 mg daily if eGFR 30–50 mL/min/1.73 m^2
	25 mg daily if eGFR <30 mL/min/1.73 m^2
Saxagliptin	5 mg daily if eGFR <50 mL/min/1.73 m^2
	2.5 mg daily if eGFR <50 mL/min/1.73 m^2
Alogliptin	1.25 mg per day when eGFR 30–60 mL/min/1.73 m^2, and for those patients with eGFR <30 mL/min/1.73 m^2 or hemodialysis, the dose should not exceed 6.25 mg/day
Linagliptin	No dose adjustment required
SGLT2 inhibitors	
Canagliflozin	No dose adjustment required if eGFR <60 mL/min/1.73 m^2
	100 mg daily if eGFR 45–59 mL/min/1.73 m^2
Dapagliflozin	Avoid use if eGFR <60 mL/min/1.73 m^2, and discontinue use if eGFR <45 mL/min/1.73 m^2

در ایران چه ترکیباتی داریم؟

Liraglutide-GLP-1 Agonist

نام تجاری
قلم تزریق ویکتوزا 6 میلی گرم/میلی لیتر 3 میلی لیتر [نوونورد دیسک پارس]
قلم تزریق ساکسندا 6میلی گرم/میلی لیتر 3میلی لیتر [نوونورد دیسک پارس]
قلم تزریق ملیتاید 18 میلی گرم/3 میلی لیتر [داروسازی سینا ژن]

sitagliptin

قرص سیتاویکس 50 میلی گرم [داروسازی اسوه]
قرص زیپتین 50 میلی گرم [داروسازی عبیدی]
قرص زیپتین 25 میلی گرم [داروسازی عبیدی]
قرص سیتاویکس 25 میلی گرم [داروسازی اسوه]
قرص زیپتین 100 میلی گرم [داروسازی عبیدی]
قرص ژانوویا 50 میلی گرم (جانوویا) [بهستان دارو]
قرص ژانوویا 25 میلی گرم (جانوویا) [بهستان دارو]
قرص ژانوپتین 100 میلی گرم [داروسازی سبحان دارو]
قرص ژانوپتین 25 میلی گرم [داروسازی سبحان دارو]
قرص ژانوپتین 50 میلی گرم [داروسازی سبحان دارو]

linagliptin

Sitagliptin +metformin

Linagliptin+metformin

نام تجاری
قرص ملیجنت-ام 2.5/1000 میلی گرم [داروسازی الحاوی]
قرص ملیجنت-ام 2.5/500 میلی گرم [داروسازی الحاوی]
قرص لیروپریم 2.5/1000 میلی گرم [داروسازی عبیدی]
قرص لیروپریم 2.5/500 میلی گرم [داروسازی عبیدی]

Empagliflozin

نام تجاری
قرص جاردیپا 10 میلی گرم [داروسازی تهران شیمی]
قرص جاردیپا 25 میلی گرم [داروسازی تهران شیمی]
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قرص امپادیانس 10 میلی گرم [داروسازی الحاوی]
قرص پگلینو 10 میلی گرم [داروسازی نانو حیات دارو]
قرص امپادیانس 25 میلی گرم [داروسازی الحاوی]
قرص پگلینو 25 میلی گرم [داروسازی نانو حیات دارو]
قرص جاردیانس 10 میلی گرم [شفایاب گستر]
قرص جاردیانس 25 میلی گرم

Empagliflozin+Metformin

نام تجاری
قرص سینوریپا 5/500 میلی گرم [داروسازی عبیدی]
قرص سینوریپا 12.5/1000 میلی گرم [داروسازی عبیدی]
قرص سینوریپا 5/1000 میلی گرم [داروسازی عبیدی]
قرص سینوریپا 12.5/500 میلی گرم [داروسازی عبیدی]
قرص امپادیانس-ام 12.5/1000 میلی گرم [داروسازی الحاوی]
قرص امپادیانس-ام 5/1000 میلی گرم [داروسازی الحاوی]
قرص امپاور پلاس 12.5/1000 میلی گرم [داروسازی اکتوورکو]
قرص امپاور پلاس 5/500 میلی گرم [داروسازی اکتوورکو]
قرص امپاور پلاس 12.5/500 میلی گرم [داروسازی اکتوورکو]
قرص آهسته رهش پگلیمت 12.5/1000 میلی گرم

Empagliflozin+linagliptin

نام تجاری
قرص امپاجنت 10/5 میلی گرم [داروسازی الحاوی]
قرص امپاجنت 25/5 میلی گرم [داروسازی الحاوی]
قرص گلورنتا 10/5 میلی گرم [داروسازی عبیدی]
قرص گلورنتا 25/5 میلی گرم [داروسازی عبیدی]
قرص گلایزامبی 25/5 میلی گرم [BOEHRINGER INGELHEIM]
قرص جارلینو 25/5 میلی گرم [داروسازی واریان فارمد]
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Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management

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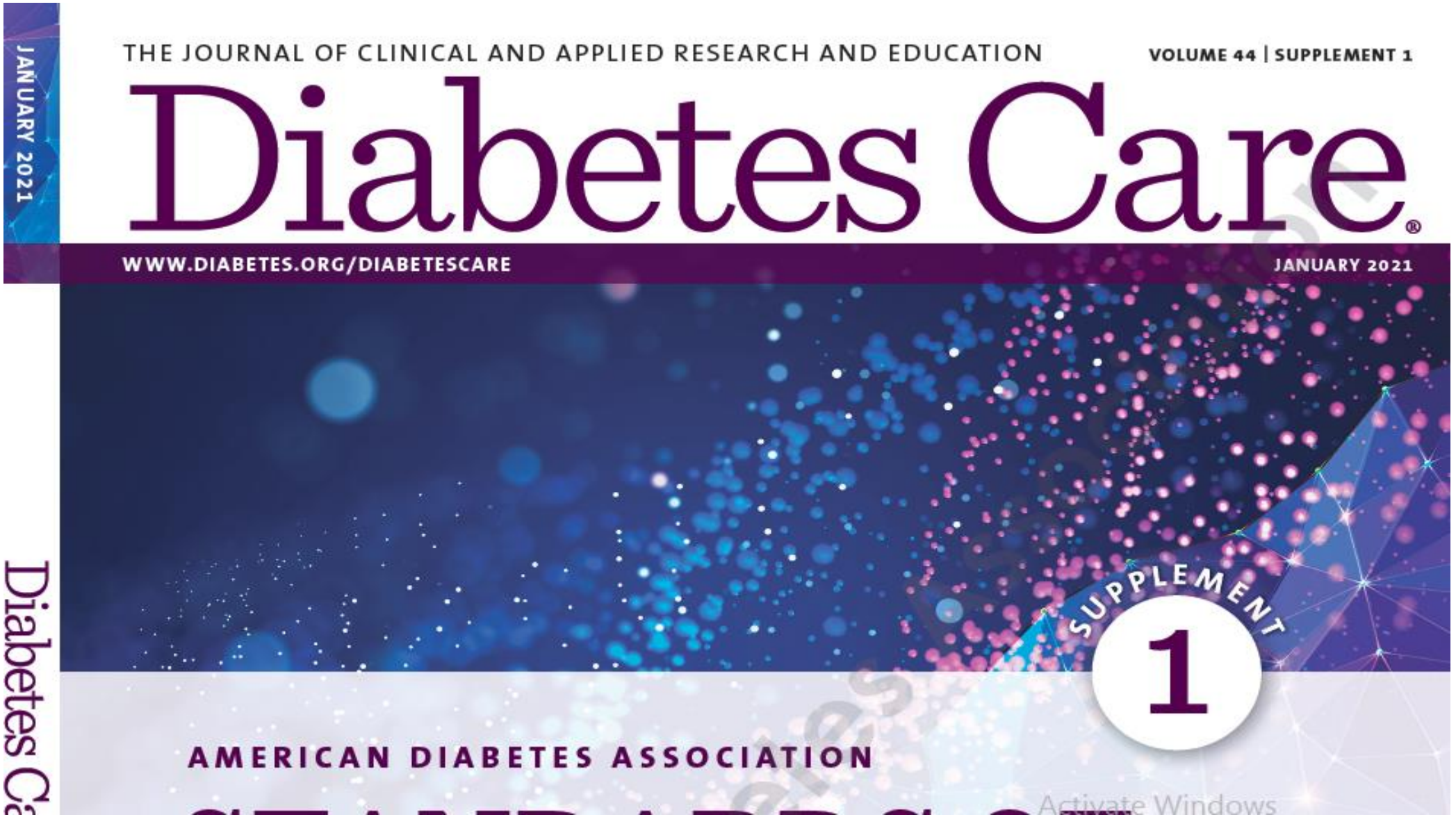
Type 2 diabetes mellitus (T2DM) is a global pandemic, as evident from the global cartographic picture of diabetes by the International Diabetes Federation (http://www.diabetesatlas.org/). Diabetes mellitus is a chronic, progressive, incompletely understood metabolic condition chiefly characterized by hyperglycemia. Impaired insulin secretion, resistance to tissue actions of insulin, or a combination of both are thought to be the commonest reasons contributing to the pathophysiology of T2DM, a spectrum of disease originally arising from tissue insulin resistance and gradually progressing to a state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AHA SCIENTIFIC STATEMENT

Cardiorenal Protection With the Newer Antidiabetic Agents in Patients With Diabetes and Chronic Kidney Disease

A Scientific Statement From the American Heart Association

ABSTRACT: Chronic kidney disease (CKD) with type 2 diabetes (T2D) is a major public health problem, resulting in significant cardiovascular and kidney adverse outcomes worldwide. Despite the widespread use of standard-of-care therapies for CKD with T2D over the past few decades, rates of progression to end-stage kidney disease remain high with no beneficial impact on its accompanying burden of cardiovascular disease. The advent of the newer classes of antihyperglycemic agents, including SGLT2 (sodium glucose cotransporter 2) inhibitors and GLP-1 (glucagon-like peptide-1) receptor agonists, has changed the landscape of therapeutic options for patients with CKD with T2D, with demonstration of significant reductions in cardiovascular adverse events and progression

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CLINICS

REVIEW

Management of diabetes mellitus in individuals with chronic kidney disease: therapeutic perspectives and glycemic control

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The purpose of this study was to evaluate the therapeutic options for diabetes treatment and their potential side effects, in addition to analyzing the risks and benefits of tight glycemic control in patients with diabetic kidney disease. For this review, a search was performed using several pre-defined keyword combinations and their equivalents: "diabetes kidney disease" and "renal failure" in combination with "diabetes treatment" and "oral antidiabetic drugs" or "oral hypoglycemic agents." The search was performed in PubMed, Endocrine Abstracts and the Cochrane Library from January 1980 up to January 2015. Diabetes treatment in patients with diabetic kidney disease is challenging, in part because of progression of renal failure-related changes in insulin signaling, glucose transport and metabolism, favoring both hyperglycemic peaks and hypoglycemia. Additionally, the decline in renal function impairs the clearance and metabolism of antidiabetic agents and insulin, frequently requiring reassessment of prescriptions. The management of hyperglycemia in patients with diabetic kidney disease is even more difficult, requiring adjustment of antidiabetic agents and insulin doses. The health team responsible for the follow-up of these patients should be vigilant and prepared to make such changes; however, unfortunately, there are few guidelines addressing the nuances of the management of this specific population.

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Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

Effect of anti-diabetic drugs in dialysis patients with diabetes: a nationwide retrospective cohort study

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Abstract

Background: Type 2 diabetes mellitus is common in patients undergoing dialysis. However, the association between anti-diabetic drug use and survival outcomes is rarely discussed. We aimed to investigate whether continued anti-diabetic medication use affects the survival of diabetic dialysis patients and whether different hypoglycemic drug use influences prognosis.

Methods: Using a nationwide database, we enrolled patients with incident end-stage renal disease under maintenance dialysis during 2011–2015 into the pre-existing diabetes dialysis (PDD), incident diabetes after dialysis (IDD), and non-diabetic dialysis (NDD) groups. The PDD group was further subclassified into patients who continued (PDD-M) and discontinued (PDD-NM) anti-diabetic drug use after dialysis.

Results: A total of 5249 dialysis patients were examined. The PDD-NM group displayed a significantly higher mortality rate than the IDD, PDD-M, and NDD groups (log-rank test $P < 0.001$). The PDD-M group had a significantly lower risk of death, regardless of insulin ($P < 0.001$) or oral hypoglycemic agent (OHA) ($P < 0.001$) use. Initial insulin administration or OHA had no statistically significant effect on overall mortality in the IDD group. But OHA use had better survival trends than insulin administration for the older ($P = 0.02$) and male subgroups ($P = 0.05$).

Conclusions: For dialysis patients with diabetes, continuous administration of anti-diabetic drugs after dialysis and choice of medication may affect outcomes.

Keywords: End-stage renal disease, Dialysis, Type 2 diabetes mellitus, Anti-diabetic drugs