In the name of God

Diabetes mellitus

Diagnostaic criteria

1) Sign & symptoms of diabetes + random plasma glucose ≥ 200 mg/dl

2) FPG ≥ 126 mg/dl

3) OGTT ≥ 200 mg/dl at 2 hr (75 g glucose for adult or 1.75 g/kg for a child)

4) HbA_{1c} > 6.5 %

	FPG	A1C	OGTT
Normal	<100	<5.7	<10
IGT	<126	5.7- 6.4	140-199
IFG	100-125		
Diabetes	≥126	≥6.5	≥200

Prediabetes

Plasma glucose levels in mg/dl

ADA goals for adult with DM

Glycemic goals

- HbA1c < 7% (normal: 4-6%)
- Preprandial plasma glucose: 70-130 mg/dl
- Postprandial plasma glucose: < 180 mg/dl

Lipids

- LDL< 100 mg/dl
- TG < 150 mg/ dl
- HDL: M > 40 , F > 50 mg/dl

Blood pressure

- <130/80 mmHg

American Diabetes Association.

Biochemical Index	ADA	AACE/ACE
Hemoglobin A_{1c}	<7% (<0.07; <53 mmol/mol Hb)[a]	≤6.5% (≤0.065; ≤48 mmol/mol Hb)
Preprandial plasma glucose	80-130 mg/dL (4.4-7.2 mmol/L)	<110 mg/dL (<6.1 mmol/L)
Postprandial plasma glucose	<180 mg/dL[b] (<10 mmol/L)	<140 mg/dL (<7.8 mmol/L)

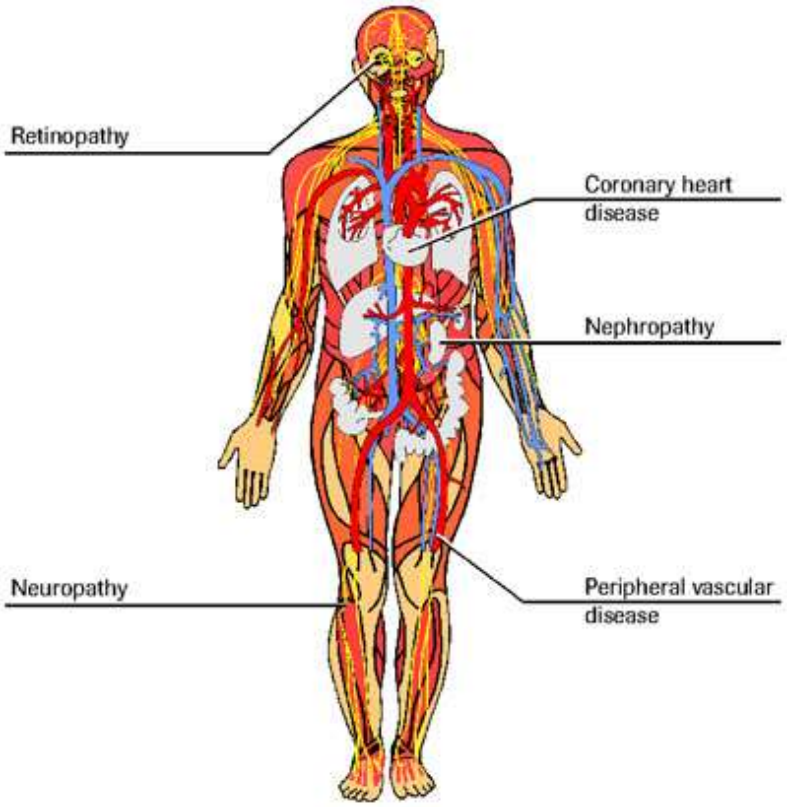
- AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ADA, American Diabetes Association

Long-term complications

- Account for most of the morbidity and mortality in diabetic population.

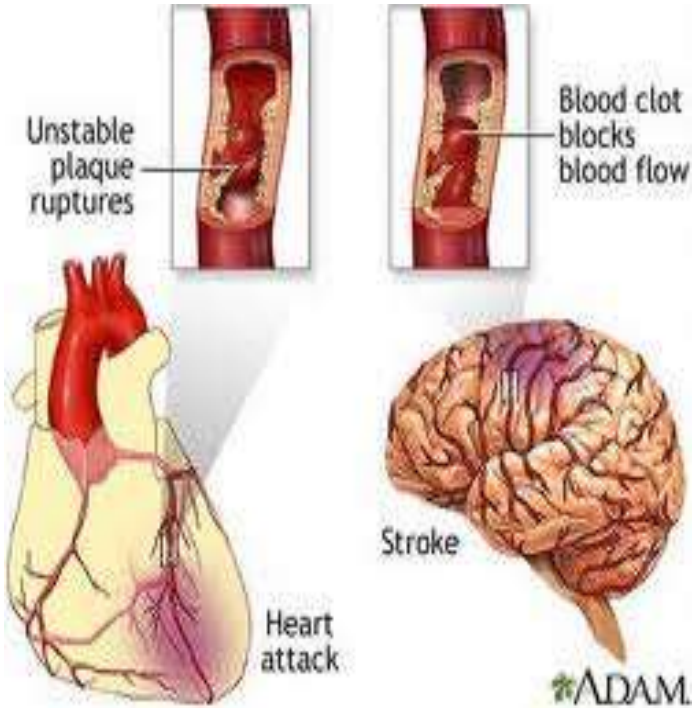
- *Microvascular complications*: retinopathy, nephropathy & neuropathy

- DM is a risk factor for *macrovascular complications*: peripheral vascular disease, CVD, stroke (specially type 2)



TREATMENT

Goals of therapy



- Reduce the risk for microvascular and macrovascular disease complications➔
  - ✓ Ameliorate Symptoms
  - ✓ Reduce Mortality
  - ✓ Improve Quality Of Life

- Near-normal glycemia (diet, exercise, drug, BP control)➔ reduce the risk of microvascular disease complications

- Elimination of other CV risk factors (obesity, HTN, antiplatelet therapy, tobacco use & hyperlipidemia)➔ reduce the development of macrovascular disease complications

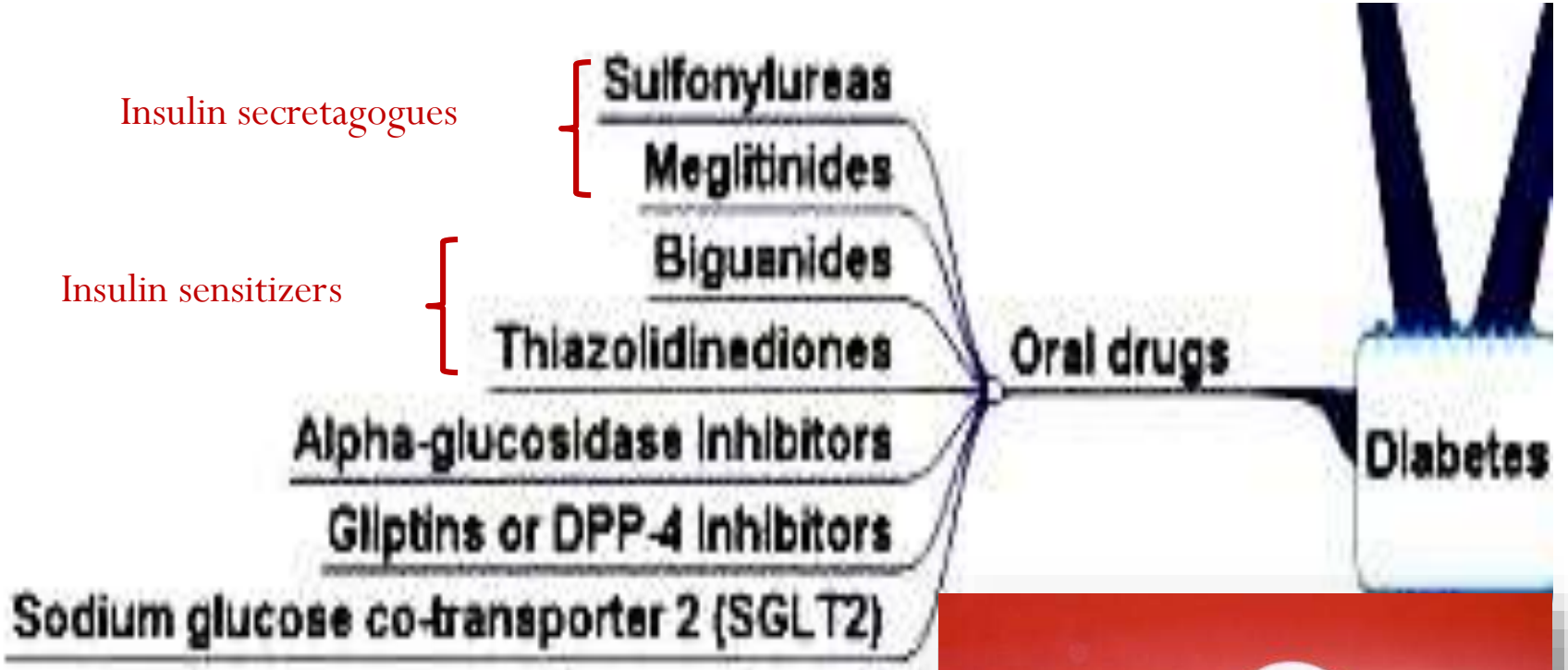
Medical nutrition therapy

- **Carbohydrates:** main determinant of insulin demand.
- **Fat:** < 30 % of total calories (saturated <7%)
- **Protein:** 15-20% (but in nephropathy: 0.8-1 g/kg/day)
- **Sodium:** < 2.3 g/day but < 2g/day in HF
- **Alcohol:** light to moderate intake ↓ risk of CVD
- **Exercise:** a key factor in the treatment (esp. DM2), at least 150 min/week

Insulin

- Diabetes
  - Insulin
    - Rapid acting
      - insulin lispro(Humalog),
      - insulin aspart(NovoLog)
      - insulin glulisine(Apidra)
    - Short-acting
      - Regular insulin
      - Humulin R
      - Novolin R
      - Rapidact insulin
      - regular (soluble) insulin
    - Intermediate-acting
      - NPH (Isophane) insulin
    - Long-acting
      - insulin glargine (Lantus)
      - insulin detemir (Levemir)
      - Ultra-lente insulins
    - Animal insulin
      - Beef insulin
      - Pork insulin

Pharmacotherapy



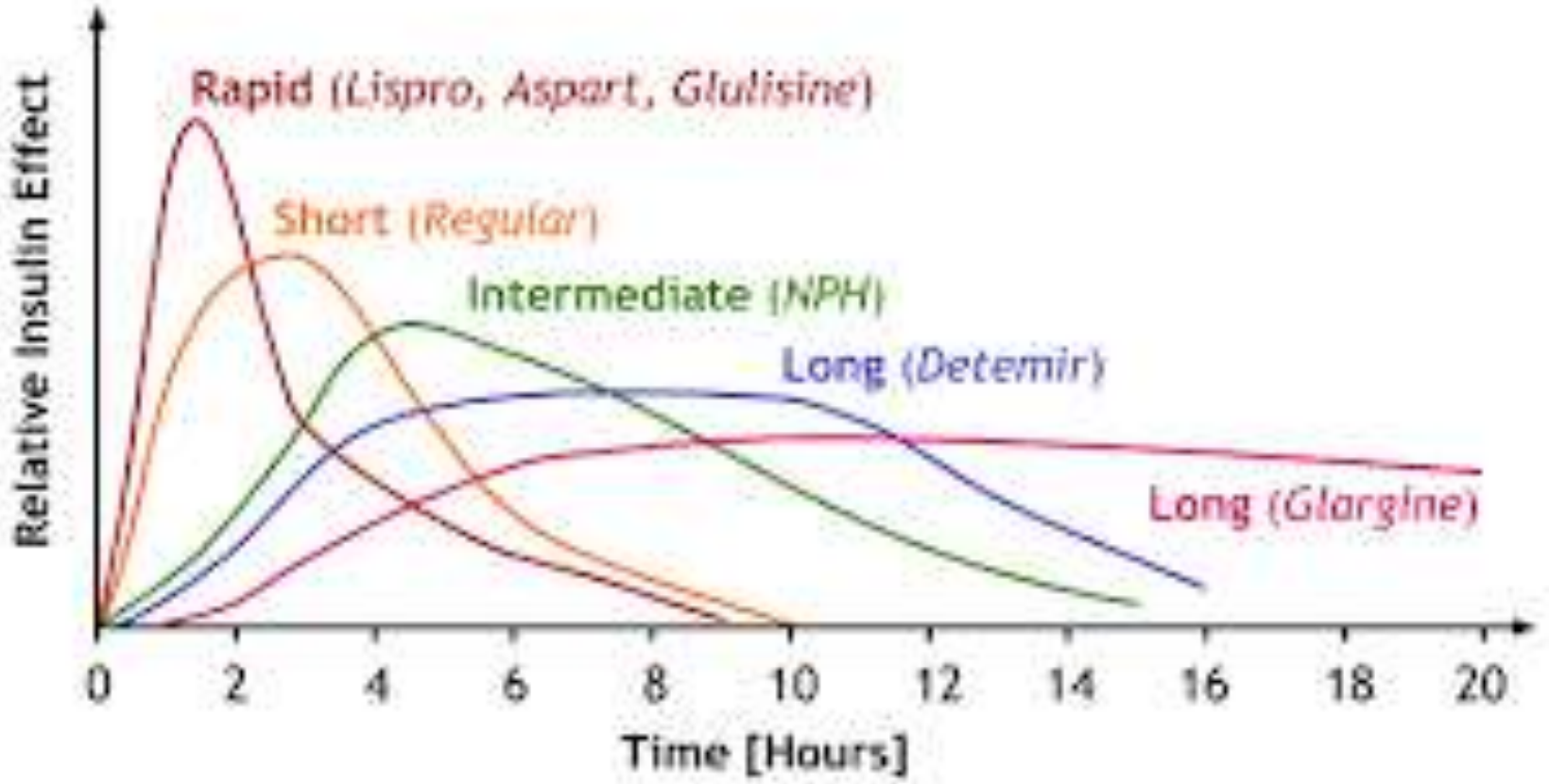
- Dopamine agonists
- Bile acid sequestrants

Indication

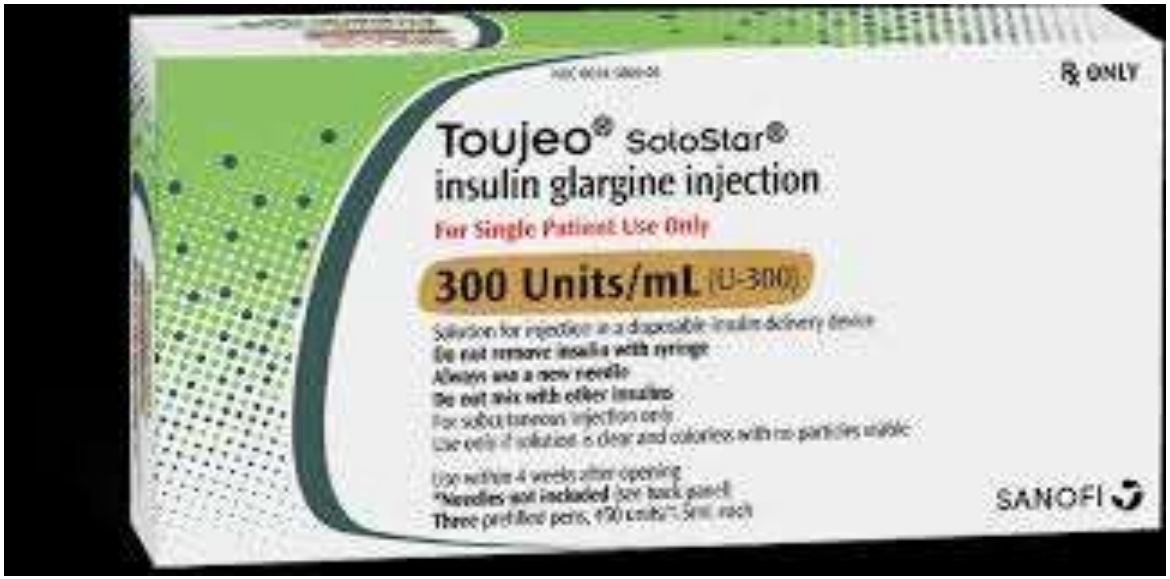
- Insulin is recommended in patients with:
- Extremely high FPG levels (>280 to 300 mg/dL) or HbA1c
- Patients with ketonuria or ketonemia
- Symptomatic patients (weight loss with polyuria, polydipsia, and/or nocturia)
- GDM
- If deemed appropriate by the clinician and patient

Insulin pharmacodynamic

Insulin	Name	Brand	Onset (hr)	Peak (hr)	Duration (hr)	pregnancy	Child (y)
Rapid acting	Lispro, Aspart, Glulisin	Humalog Novorapid NovoLog Apidra	5-15 min	30-90 min	< 5	B B C	> 3 > 2 > 4
Short acting	Regular	Humulin R	0.5-1	2-4	5-7	B	
Intermediate	NPH	Humulin N	2-4	4-12	12-18	B	
Long acting	Glargine Detemir Degludec	Lantus Toujeo (U-300) Levemir Tresiba (U-100 and U-200)	1.5 6 0.8-2 1	No peak Relatively Flat No peak	20-24 5.7-23.2 42	C C B C	≥ 6 ? ≥ 2 NO


Relative Insulin Effect
Rapid (Lispro, Aspart, Glulisine)
Short (Regular)
Intermediate (NPH)
Long (Detemir)
Long (Glargine)
0
2
4
6
8
10
12
14
16
18
20
Time [Hours]

GLARGINE (U-300)



LEVEMIR INSULIN

DEGLUDEC INSULIN

Compatibility of Insulin Mixtures[105]

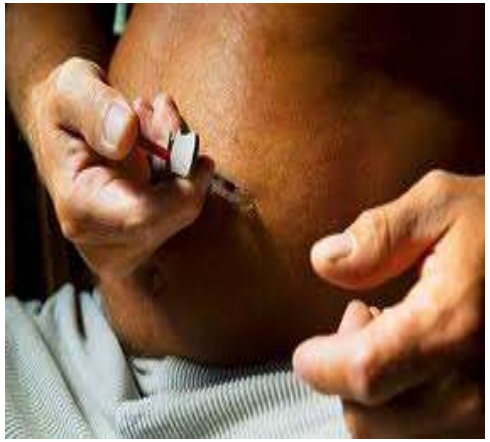
Mixture	Proportion	Comments
Regular + NPH	Any proportion	The pharmacodynamic profiles of regular and NPH insulin are unchanged when premixed and stored in vials or syringes for up to 3 months
Regular + normal saline	Any proportion	Use within 2–3 hours of preparation
Regular + insulin diluting solution	Any proportion	Stable indefinitely
Rapid-acting + NPH[70–72]	Any proportion	The absorption rate and peak action of the rapid-acting insulins are blunted; total bioavailability is unaltered. Rapid-acting insulin and NPH should be mixed just before use (within 15 minutes)
Insulin glargine and detemir[76,82]	Do not mix with other insulins	Pharmacodynamics could be modified

All have a neutral pH, except: glargine(PH=4)=> should not be administered IV or mixed with other insulin

Alteration in insulin kinetic

- Route of administration
- Thyroid function
- Renal failure lowers insulin clearance (exogenous insulin is cleared by kidney)
- Rate of absortion from injection site:

abdomen> arm> hip> thigh (less variation with lispro)



- Lipohypertrophy
- Insulin dose
- Insulin concentration
- Insulin mixtures
- Exercise
- Local massage
- Ambient temperature

Adverse Effects

- Most common:
  - Hypoglycemia
  - Weight gain (related to intensive insulin therapy, and can be somewhat minimized by physiologic replacement of insulin)

- Two forms of lipodystrophy:

1. **Lipohypertrophy**: caused by **many injections** into the same injection site(insulin's anabolic actions)→ a raised fat mass is present at the injection site with **resultant variable insulin absorption.**

2. **Lipoatrophy**: caused by **insulin antibodies**, with destruction of fat at the site of injection→ Injection away from the site with more purified insulin is recommended.

Hypoglycemia treatment

- ***Treatment:*** 10-20 g rapidly absorbed carbohydrate, may repeat in 15-20 min (15-15-15)

❑ 15 g carbohydrate =
- ½ cup of orange or apple juice
- 1 cup of fat-free milk
- 3 cubes of sugar

❑ In unconscious adult patient, severe:
- glucagon 1 mg SC,IM or IV
- 50 ml dextrose 50% IV

◉ Glucagon use would be appropriate in any situation in which the patient does not have or cannot have ready IV access for glucose administration

❑ The patient and close contacts should be informed that:

✓ It can take 10 to 15 minutes for the injection to start increasing glucose levels

✓ Patients often vomit during this time.

✓ Proper positioning to avoid aspiration should be emphasized

Insulin dosing

- The dose of insulin for any person must be individualized
- **Total daily dose(TDD):**

- ***Type 1 DM:***

Initial dose: 0.3-0.5 U/Kg

Honeymoon: 0.2-0.5 U/Kg

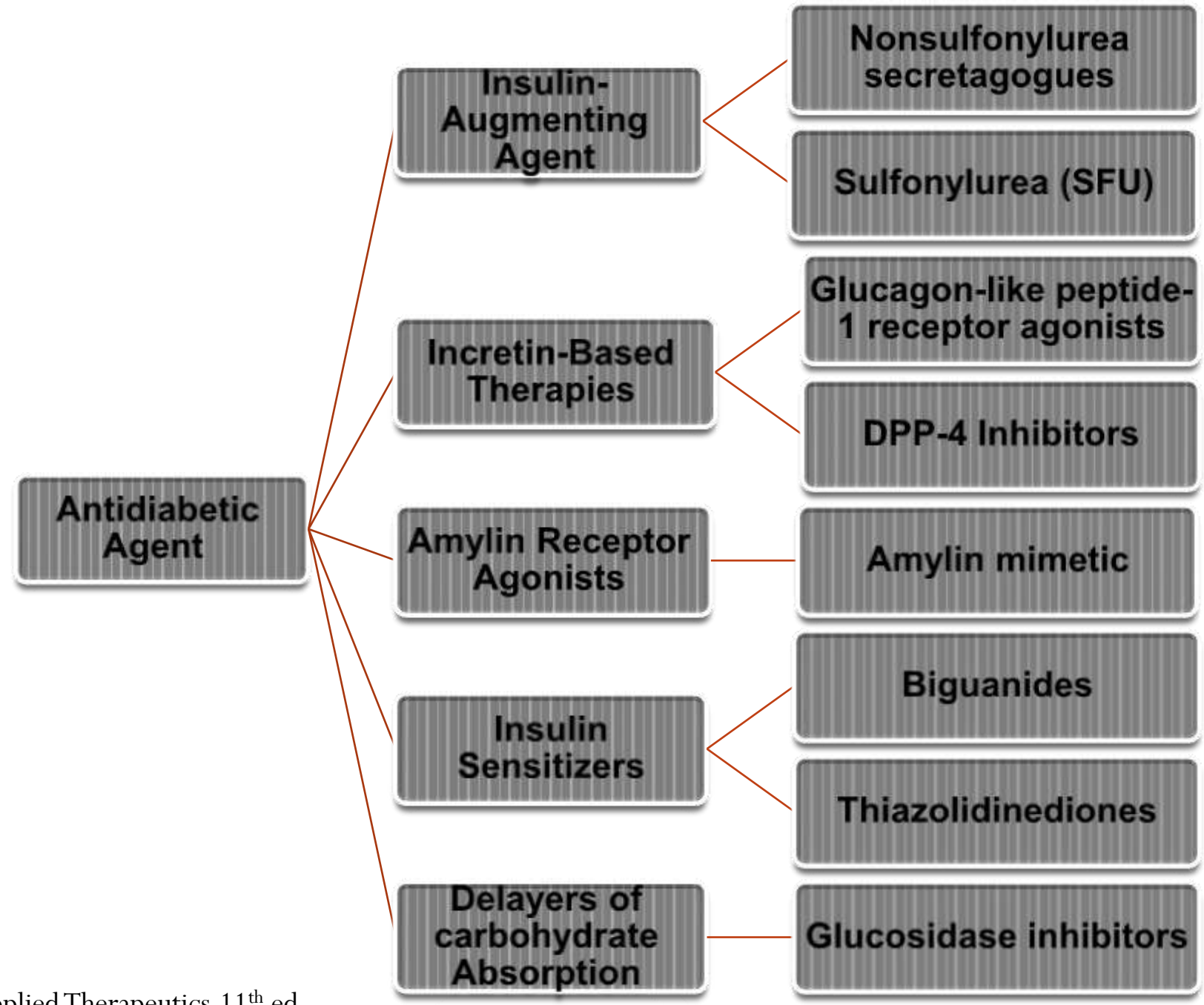
Ketosis, illnes, growth: 1-1.5 U/Kg

- ***Type 2 DM:***

With insulin resistance: 0.7-1.5 U/Kg

- 50% of TDD as basal insulin, and remaining 50% to meal coverage
- **Premeal requirement:** 500/TDD= grams carbohydrate covered by 1 U of insulin(500 for aspart & 450 for regular)

- **Correction factor:** 1700/TDD= point drops in blood glucose per U insulin (1700 for rapid act insulins & 1500 for regular)



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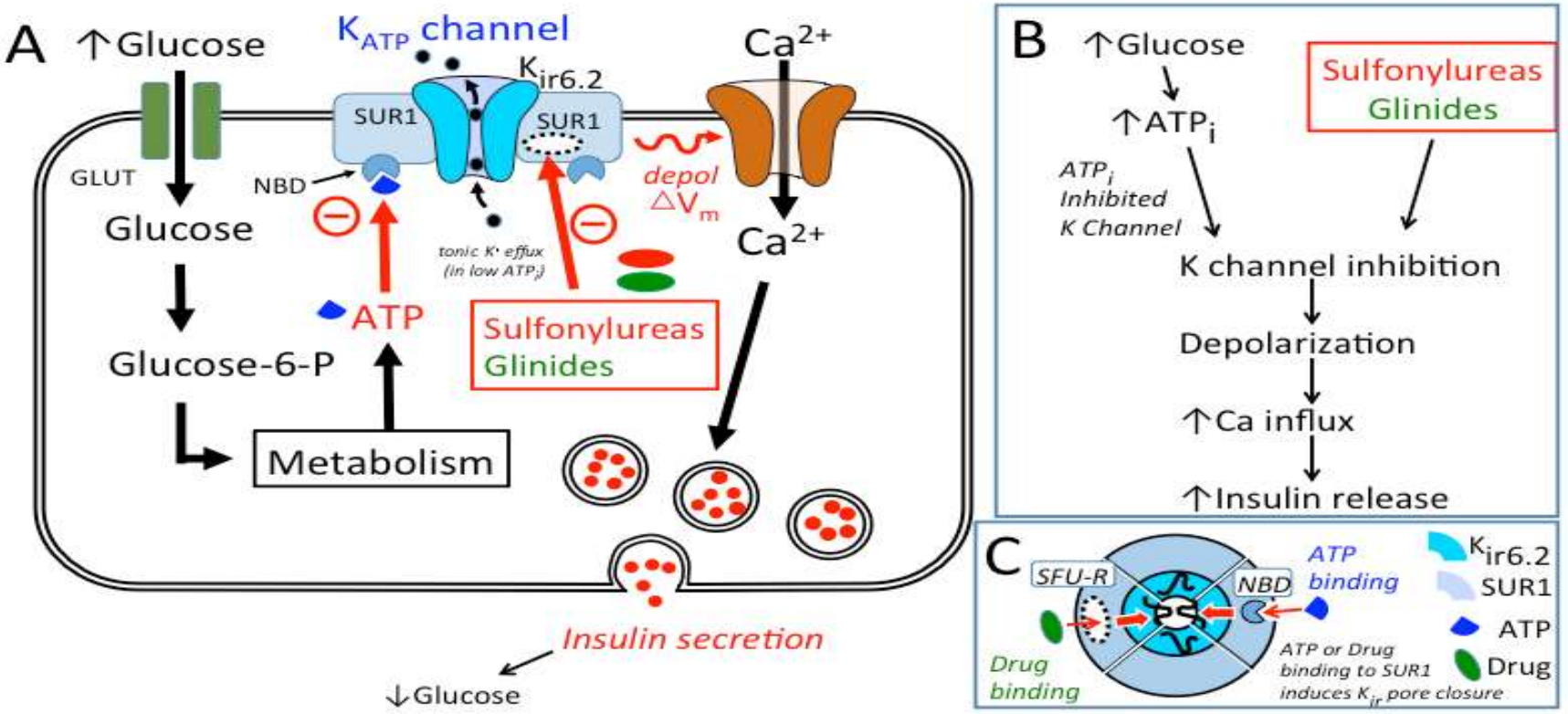
Class	Compound(s)
Biguanides	• Metformin
Sulfonylureas (2nd generation)	• Glyburide • Glipizide • Glimepiride
Meglitinides (glinides)	• Repaglinide • Nateglinide
Thiazolidinediones	• Pioglitazone • Rosiglitazone
α-Glucosidase inhibitors	• Acarbose • Miglitol
DPP-4 inhibitors	• Sitagliptin • Saxagliptin • Linagliptin • Alogliptin
Bile acid sequestrants	• Colesevelam
Dopamine-2 agonists	• Bromocriptine
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin • Empagliflozin
GLP-1 receptor agonists	• Exenatide • Lixisenatide • Liraglutide • Exenatide (extended release) • Albiglutide • Dulaglutide
Amylin mimetics	• Pramlintide

SULFONYLUREAS

Sulfonylureas

Mechanism of Action

- Stimulate insulin secretion from the pancreas
- Suppresses hepatic glucose production



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Sulfonylureas

- The three *first-generation* sulfonylureas:
  - ✓ Chlorpropamide
  - ✓ Tolazamide
  - ✓ Tolbutamide

Equally Effective In Equipotent Doses

- The three *second-generation* sulfonylureas:
  - ✓ Glipizide
  - ✓ Glyburide
  - ✓ Glimepiride

favorable side effect **profile & duration of activity**

that allows for *once or twice daily* dosing

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Sulfonylureas

Pharmacokinetics

- High pr.binding (90-100%)
- Rapid onset of effect
- **Chlorpropramide** has **the longest** serum half-life and duration of hypoglycemic activity
- All sulfonylureas are metabolized in the liver (CYP 2C9)

- **Glyburide :**
- **Duration of action: up to 24 hr ➔ allow QD dosing**
- **Metabolism :** hepatic via CYP2C9
- **Half-life elimination : 2-5 hr**
- **Elimination :**renal (50 %); biliary tract (50%)
- ***Food does not delay the rate or extent of absorption***

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Pharmacokinetics

- Agents with active metabolites or parent drug that are renally excreted ➔ dosage adjustment or use with caution in patients with compromised renal function

- The hypoglycemic potential is higher with chlorpropamide and glyburide

High risk for hypoglycemia

- elderly & renal insufficiency or advanced liver disease➔ start at a very low dose of a sulfonylurea with a short half-lif

Sulfonylureas

Efficacy

- ↓ **HbA1c 1.5%-1.7%**
- ↓ **FPG 50-70 mg/dl (depend on the baseline value)**

Contraindication

- **Type 1 diabetes**
- Pregnancy or breast-feeding **(except glyburide)**
- Documented hypersensitivity to sulfonylureas
- Severe hepatic or renal dysfunction
- Severe, acute intercurrent illness (e.g., infection, MI), surgery
- G6PD

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Sulfonylureas

Adverse Effects

- **Hypoglycemia** (particularly for long acting agents)
- **Weight gain**
- GI symptoms

- **SIDH:**Hyponatremia(Na < 129mEq/L)
- **(chlorpropamide, tolbutamide)➔ use to treat diabetes insipitus**
- Risk factors include age > 60 years, female gender, and concomitant use of thiazide diuretics

- **Rare:** Blood dyscrasias(hemolytic anemia), allergic dermatologic reactions, hepatotoxicity (cholestasis), and hypothyroidism

- Disulfiram reaction **(chlorpropamide)**

- **Mild duiretic effect (glipizide, glyburide, tolazamide, acetohexamide)**

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Drug intractions with sulfonylureas

Interaction	Drugs
Displacement from protein binding sites[a]	Warfarin, salicylates, phenylbutazone, sulfonamides
Alters hepatic metabolism (cytochrome P450)	Chloramphenicol, monoamine oxidase inhibitors, cimetidine, rifampin[b]
Altered renal excretion	Allopurinol, probenecid

Dipiro

Dosing and Administration

- **Glyburide:**
- Recommended starting dose: 5 mg/day (1.25 QD in elderly)
- Increase 1.25-2.5 every 1-2 weeks)
- Max dose: 20 mg/day (QD or BD)

- Lower dosages are recommended for:
- ✓ Elderly patients (daily dose> 10 mg should be avoided)
- ✓ Compromised renal or hepatic function.

GLINIDES

Glinides (Nonsulfonylurea Insulin Secretagogues)

Mechanism of Action

- Stimulate insulin secretion from the cells of the pancreas, similarly to sulfonylurea.
- Unlike SFU, they have a rapid onset & shorter duration of action.
- Require the presence of glucose to stimulate insulin secretion. As glucose levels diminish to normal, stimulated insulin secretion diminishes

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Glinides (Nonsulfonylurea Insulin Secretagogues)

Pharmacokinetic

- **Repaglinid:**
- **Onset of action** : ~ 0.5-1 hr
- **Half-life** :~1 hr , 1.5 hr
- **Absorption** : Rapid & complete
- **Pb** : >98% to albumin
- **Metabolism** :Hepatic via CYP3A4 & CYP2C8 & glucuronidation to inactive metabolites.
- **Excretion** : Feces (~90%,),Urine (~10%)
- **Moderate renal insufficiency does not appear to affect repaglinide, but moderate to severe hepatic impairment may prolong exposure**.

- **Nateglinide:**
- CYP2C9 (70%) & CYP3A4 (30%) to metabolites
- Urine (16% as unchanged drug, 75% metabolites),feces (10% metabolites)
- No dosage adjustment is needed in Moderate to sever renal insufficiency

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Nonsulfonylurea Insulin Secretagogues

Adverse Effects

- Mild hypoglycemia (less than sulfonylureas, because of the glucose-sensitive release of insulin)
- Weight gain (0.9-3 kg) (repaglinide > nateglinide)
- Elevated hepatic enzymes & hypersensivity reaction (Rare)

Contraindicatio n & Precaution

- **Contraindication** : **Type 1 diabetes**
- **Precaution** : Liver dysfunction, **Severe** renal insufficiency (Repaglinide➔ but it is safe at a reduced dose)
- **Nateglinide's** clearance **is not affected** in patients with moderate to severe renal insufficiency

Drug Interaction

- **Gemfibrozil** (a potent glucuronidation and CYP2C8 inhibitor), more than doubles the half-life of repaglinid
- **Trimethoprim**, a CYP2C8 inhibitor, increase repaglinide levels by 60%
- Rifampin
- Nateglinide : although no significant drug-drug interactions have been reported, but caution should be used with strong CYP2C9 and CYP3A4 inhibitors

Nonsulfonylurea Insulin Secretagogues (Glinides)

Efficacy

- **Repaglinide :**
- **↓ HbA1c 1.7 %**
- **↓ FPG 61 mg/dl**

Nateglinide :

HbA1c ↓ 0.7 %

FPG ↓ 13.6 mg/dl

Indication & Comments

- **Type 2 diabetes as monotherapy or in combination with metformin or TZDs**
- **The agents are usually added to therapy for patients with high PPG values**
- **Take only with meals** (up to 30 minutes prior)
- **If a meal is skipped, skip dose**

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Dosing and Administration

- The recommended starting dose (in HbA1c <8%):

Repaglinide: 0.5 mg with each meal, increased weekly to a total max: 16 mg/day (max effective dose: 2 mg with each meal)

**When used in patients who have failed sulfonylureas or in those with HbA1c > 8%, the initial dose is 1 to 2 mg with each meal*

Nateglinide: 60-120 mg prior to meals, and does not require titration

BIGUANIDES

Biguanides: **Metformin**

Mechanism of Action:

enhances **insulin sensitivity** of both **hepatic** and peripheral(muscle) tissues➔ ↓ Hepatic gluconeogenesis

↑glucose uptake by skeletal muscle & adipose tissue

↓Total cholesterol (5%-10%) & TG(10%-20%) & improvement of HDL

Weight loss

Pharmacokinetics

Onset of action : within days

Distribution : Vd : 645 ± 358 L (approximates body water)

Protein binding : Negligible

Bioavilability : 50% to 60%

Half-life elimination: plasma : 4-9hr (pharmacodynamically, effects last >24 hours)

Excretion: urine (90% as unchanged drug)

Metformin

Drug Interaction

1) Alcohol

2) Cimetidine (competes for renal tubular secretion)

3) Iodinated Material

(metformin should be withheld at time of, or before, & for 48hr after the procedure

Efficacy

↓ **HbA1c 1.5%-1.7%**

↓ **FPG 50-70 mg/dl**

(Genetic variation)

Indication & Comments

First line therapy for DM2

Monotherapy + lifestyle intervention

Monitoring SrCr & hepatic tests at baseline & then annually

For patients unable to achieve goals in monotherapy within 3 to 6 months, addition of insulin or another agent should be considered

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Metformin

Adverse Effects

1. GASTROINTESTINAL EFFECTS:

(transient)

Diarrhea (most common)

Nausea

Abdominal discomfort

Anorexia (loss of weight)

***Symptoms can be minimized by taking metformin with food & slowly titrating the dose**

2.LACTIC ACIDOSIS: (rare)

Clinically uncommon adverse effects:

Metallic taste,

interference with vitamin B12 absorption,

hypoglycemia during intense exercise

Contraindications

Renal Impairment

(GFRs < 60ml/min or elevated cr levels >1.4 mg/dl for female or >1.5 mg/dl for male)

Hepatic disease

CHF

History of lactic acidosis

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lactic acidosis

- Rare (3 cases per 100,000 patient-years)

- Increasing the risk of lactic acidosis by:

✓ Increased production of lactic acid:

Tissue hypoperfusion (CHF, hypoxic states, shock, or septicemia)

✓ Reduced removal of lactic acid in the liver:

severe liver disease or alcohol

- Clinical presentation of lactic acidosis is often nonspecific flu-like symptoms (weakness, malaise, myalgias, abdominal distress, and heavy, labored breathing), thus the diagnosis is usually made by laboratory confirmation.

Efficacy

- In preliminary findings, it may also **lower the risk of pancreatic, colon, and breast c**ancer in type 2 DM patients
- Partly because of this lack of hypoglycemia, metformin is recommended by the ADA to reduce the risk for developing diabetes in patients at high risk (IGT and IFG) because of its strong evidence base and long-term safety.
- Metformin **reduced macrovascular complications** in obese subjects
- Data showing a **reduction in all-cause mortality** and **vascular complications independent of glycemic control**.
- Metformin should be included in the therapy for all type 2 DM patients, if tolerated and not contraindicated

Dipiro

Renal insufficiency

- Elderly patients (reduced muscle mass & renal function):

1) In > 80 years: should have GFR (estimated by a 24-hour urine creatinine collection) If the GFR< 60 mL/min, metformin should not be given
2) Metformin should be titrated to the minimum effective dose and renal function should be monitored regularly

✓ Though not recommended to be clinically implemented, recent evidence has reported that metformin **may not accumulate in moderate to severe renal insufficiency, if a dose of 1500mg/day or less is used**

Dipiro

THIAZOLIDINEDIONES

Thiazolidinediones

TZDs enhance insulin sensitivity at **muscle**, liver, and fat tissues

- TZDs bind to and activate a nuclear receptor (peroxisome proliferator-activated receptor-γ [PPAR- γ]), which is expressed in many insulinsensitive tissues, including adipose (major site), skeletal muscle, and liver tissue.
- PPAR-γ regulates transcription of genes that influence glucose and lipid metabolism. For example, PPAR- γ stimulation increases the transcription of GLUT-4, a glucose transporter that stimulates glucose uptake. Reduced expression of GLUT-4 may contribute to the development of insulin resistance.

Thiazolidinedione's Pharmacokinetic

❖ **Action relies on gene transcription and protein production, the onset and duration of action are unrelated to the plasma half-life➔**
❖**Duration of action of >24 hr**
❖**Onset of action:** delayed, 1-3 w (**maximal effects 8-12 w)**
❖ **well absorbed with or without food**
❖ **Pr.b :** 99.8%

Rosiglitazone	*Pioglitazone*
Metabolism : hepatic(99%), CYP2C8 ; CYP2C9 (minor) **Half-life elimination :** 3-4 hr **Excretion :** urine (64%) & feces (23%) as metabolites	**Metabolism :** hepatic (99%), CYP2C8 & 3A4 to active & inactive met **Half-life**: parent drug: 3-7 hr; metabolite16-24 **Excretion :** urine (15-30 %) & feces as metabolites

✓ **No dose adjustment is necessary in patients with renal failure**
✓**Avoid in liver disease & HF**

Thiazolidinediones
Rosiglitazone & pioglitazone

Indication

✓**Unable to take or have failed metformin or sulfonylurea monotherapy** or who **have not responded to combination therapy with other oral antidiabetic agents**

✓ **Combined with insulin**

➢ **Individuals who are minimally responsive or unresponsive to TZD** :

1) **Not obese**

2) **Have lower levels of endogenous insulin**

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Thiazolidinediones

Drug Interaction

- Other glucose-lowering agents
- Pioglitazone induces CYP 3A4 (**estrogens & OCP**, cyclosporine, tacrolimus, statins)
- Rosiglitazone does not seem to affect any of the major CYP enzymes
- **Rifampin**
- **Gemfibrozil :** significant increase AUC of TZDs

Efficacy

- Monotherapy: ↓ **HbA_{1c} 0.8%–1.5%**
- Combination: ↓ **HbA_{1c} 0.6%–1.2%**
- **Reduce FPG levels by 60 to 70 mg/dL at maximal doses**
- Pioglitazone and to a lesser extent rosiglitazone : ↓TG
- Pioglitazone & Rosiglitazone : ↑ HDL (3 to 9 mg/dL)
- Rosiglitazone (not pioglitazone) increase LDL cholesterol (8 to 16%)
- Pioglitazone may not affect LDL

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Thiazolidinediones

Adverse Effects

- Hepatotoxicity (rare)
- Hematologic Effects (first 2-4 w)
- Dose-related weight gain
- **Cardiovascular Effects (MI risk & mortality with rosiglitazone only)**

✓**Can result pulmonary edema and/or HF**

- Hypersensitivity reactions (pruritus, urticaria, angioedema, anaphylactic, St.J)
- Increased risk of distal limb bone fractures and bone loss

Contraindications and Precautions

- Type 1 diabetes
- Patients with type 2 diabetes using insulin (with caution: edema & hypoglycemia)
- Myocardial ischemia (rosiglitazone only
- Preexisting hepatic disease & edema
- Patients with osteoporosis or at risk for bone fractures
- Symptomatic or severe CHF (NYHA classes III and IV) great caution with class I and II
- Patients with a current or previous history of bladder cancer

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Hepatotoxicity

- Troglitazone (first TZD approved) → idiosyncratic hepatotoxicity → removal
- Several case reports of hepatotoxicity with rosiglitazone or pioglitazone have been reported, but improvement in ALT was consistently noted when the drug was discontinued
- Prior to therapy, it is recommended that an ALT be checked, and then monitor periodically
- Patients with ALT levels >2.5 times → should not start TZDs
- **Discontinuation:**

1) ALT is >3 times
2) Rising serum bilirubin levels
3) Symptoms of hepatitis (e.g., fatigue, N/V, abdominal pain, and dark urine)

Dipiro

Adverse Effects

- Retention of fluid leads ➔

1. Peripheral vasodilation
2. Increase in renal sodium and water retention
3. A dilutional anemia:

➔ 10% increase in plasma volume ➔reduction in plasma hemoglobin (2-4%) does not require treatment

- **Edema** (commonly)

✓ When a TZD is used in combination with insulin, the incidence of edema (~15%) is increased

✓ Dose related➔ if not severe:

I. reduction in the dose or
II. use of diuretics (anecdotally triamterene-H, amiloride or spironolactone instead of loop diuretics)

will allow the continuation of therapy in the majority of patients

Adverse Effects

- Rarely, TZDs have been reported to worsen macular edema in the eye
- Weight gain, which is also dose related (both fluid retention and fat accumulation)➔substantial when use with insulin & SFU
- TZDs, besides stimulating fat cell differentiation, also reduce leptin levels➔ stimulate appetite and food intake
- Rarely, a patient will gain large amounts of weight in a **short period of time**➔ necessitate discontinuation of therapy.

Dipiro

Adverse Effects

- An increased fracture rate in the upper and lower limbs (women > men)
- These fractures are not osteoporitic and do not accur in spine or hip (are most in wrists, forearms, ankles, or feet)
- Pathophysiology is speculative (shunting of new cells to fat instead of osteocytes)
- Consider patient's risk factor for fracture (e.g. older female patient) before therapy

Dosing and Administration

- The recommended starting dosages:

Pioglitazone 15-30 mg once daily with or without food

Rosiglitazone 2-4 mg once daily (BD is more effective than QD)

- Dosages can be increased slowly based on therapeutic goals and side effects.

- The maximum dose and maximum effective dose of pioglitazone is 45 mg, and rosiglitazone is 8 mg once daily

GLUCOSIDASE INHIBITORS

Glucosidase Inhibitors

Mechanism of Action

1.reversibly inhibit glucosidases (maltase, isomaltase, sucrase, and glucoamylase) present in the mucosa of the small intestine

2. delaying the breakdown of sucrose and complex carbohydrates and glucose absorption

3. PPG are lowered when these agents are taken with a meal containing complex carbohydrates

Pharmacokinetics

Acarbose :

Bio.A :<2% as active drug
Metabolism : Exclusively **via GI tract**

Half-life elimination :~2 hr

Excretion : urine (34%),feces (51%)

Miglitol :

Absorption : saturable at high dose: 25mg: completely absorbed , 100mg: 50% to 70% absorbed

Metabolism : none

Half-life elimination : ~2 hr

Excretion : urine (as unchanged drug)

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Glucosidase Inhibitors

Advers Effects

GI Effects (common)

Flatulence

Diarrhea

Abdominal pain

Elevated LFT

Acarbose (300 mg/day)

Monitoring LFT every 3 months for the *first year* of therapy & periodically thereafter

Miglitol

has not affect hepatic function (no metabolite)

Contraindication & Precaution

Gastrointestinal Condition

short-bowel syndrome

Malabsorption

IBD

intestinal **obstruction**

Renal Impairment

Acarbose

(SrCr > 2mg/dl) has not been studied

Drug Interaction

Other glucose-lowering agent **(Treatment of dextrose)**

Digestive enzyme preparations & charcoal➔absorption may be diminished

↓ **Bioavailability of digoxin**

Miglitol → ↓ bioavailability of ranitidine & propranolol

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Glucosidase Inhibitors

Acarbose & Miglitol

Efficacy

- ↓ **HbA1c 0.5 to 1 % (**modest)
- ↓ **FPG 20-30 mg/dl (**relatively low)
- ↓ ***PPG*** **25-50 mg/dl**

Acarbose & Miglitol have no effect on weight or lipid profile

Indication

usually used as add-on therapy (limited effects on HbA_{1c} and side effect profile)

patients near target HbAlc levels with near-normal FPG levels, but high postprandial levels, might be candidates for therapy

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GI side effects

- By distal intestinal fermentation of undigested carbohydrate by the microflora → gas production(carbon dioxide [CO2] and methane).

→ initiate at a low dose and titrate slowly to reduce GI intolerance

- GI discomfort usually improves with continued therapy

- If a patient develops hypoglycemia within several hours of drug ingesting → oral glucose is advised (drug will inhibit the breakdown of more complex sugar molecules.)

- Milk, with lactose sugar → alternative (as acarbose only slightly (10%) inhibits lactase)

- Rarely, transient increase in serum aminotransferase levels have been reported with the highest doses (> 300 mg/day) of acarbose (appeared to be dose and weight related) → weight-based maximum doses

Dosing and Administration

- Dosing for both miglitol and acarbose are similar.

- Initiate with a very low dose (25 mg with one meal a day);

increase very gradually (1-2 months) to a
max: 50 mg TDS for patients ≤60 kg or
100 mg TDS for patients >60 kg

- Max response after 6 month

- Both should be taken with the first bite of the meal

Incretin-Based Therapies

Incretin-Based Therapies

- Incretins: insulinotropic hormones secreted from neuroendocrine cells in the small intestinal mucosa in response to carbohydrate ingestion and absorption

- two hormones with incretin effects:

glucose-dependent insulinotropic polypeptide (GIP)

glucagonlike peptide-1 (GLP-1)

- **GLP-1 also inhibits pancreatic α-cells (glucagon release)**
- Incretins are metabolized by dipeptidyl peptidase-4 (DDP-4) to inactive metabolites
- GLP-1 Receptor Agonists & Dipeptidyl Peptidase-4 Inhibitors

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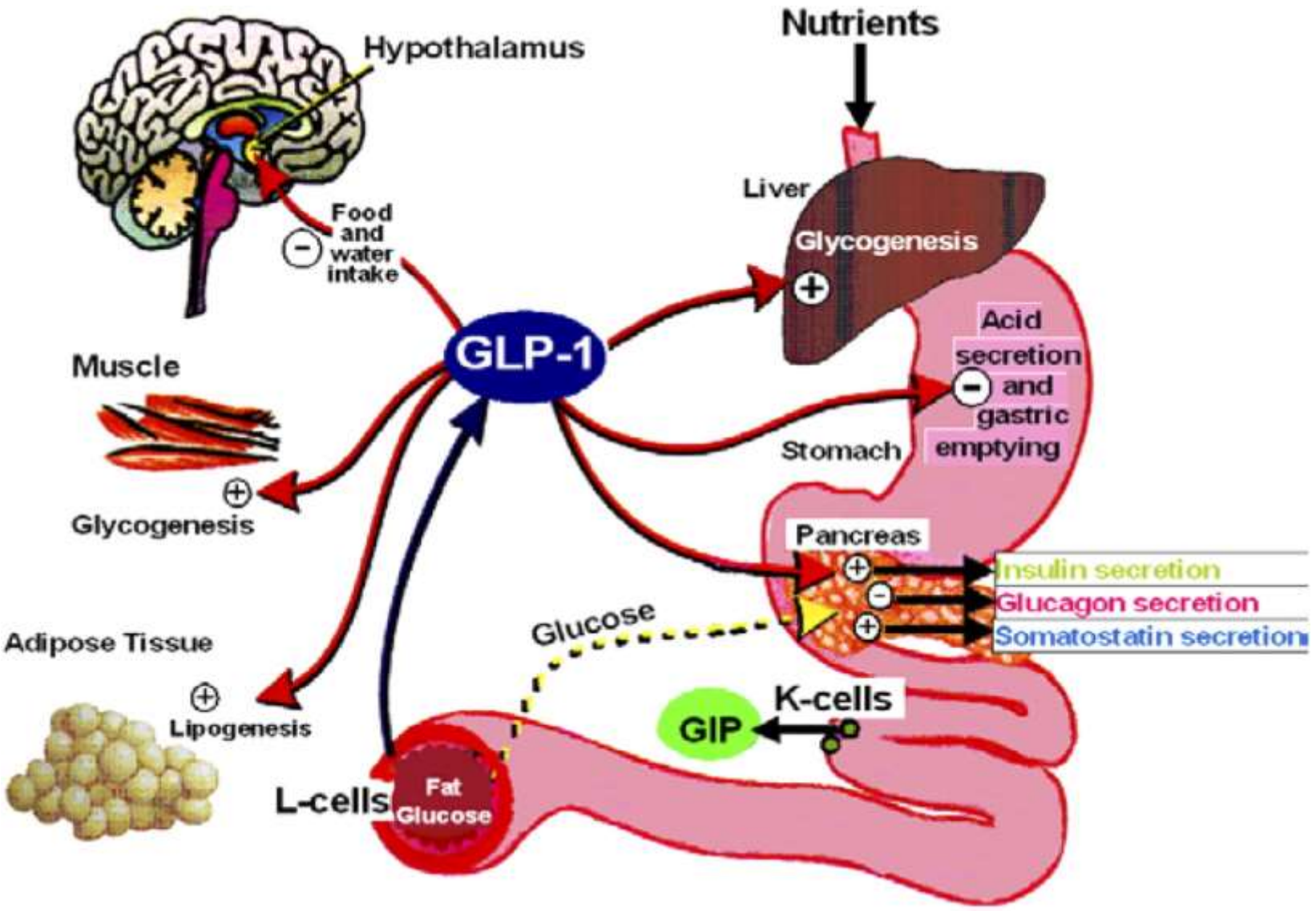
GLP-1 Mimetics/Analogs


Hypothalamus
Nutrients
Liver
Glycogenesis
Food and water intake
GLP-1
Acid secretion and gastric emptying
Stomach
Muscle
Glycogenesis
Pancreas
Insulin secretion
Glucagon secretion
Somatostatin secretion
Glucose
Adipose Tissue
Lipogenesis
K-cells
GIP
L-cells
Fat
Glucose

Exenatide

250µg/ml

Liraglutide

6mg/ml

GLP-1 Mimetics/Analogs

Exenatide :

- **Half-life elimination** : 2.4 hr➔ **BD**
- **Starting dose: 5 mcg injected SC ,twice daily within 60 minutes before morning and evening meals**
- **Excretion** : urine (majority of dose)
- It is not recommend in :
  - ✓ severe GI disease
  - ✓ severe renal impairment (CrCl <30 mL/minute)
  - ✓ end-stage renal failure, or those requiring hemodialysis.
- **Liraglutide:**
- **highly protein bound (>98%)**
- **half-life of about 10 to 14 hours➔ QD**

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GLP-1 Mimetics/Analogs

Adverse Effects :

- **GI side effects: common and dose dependent** (nausea (40%) , vomiting and/or diarrhea (15%)

- Decreased appetite➔ **Weight loss (1.5-5 kg)**

- Hypoglycemia (hypoglycemic oral agent or insulin)

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Glucagonlike Peptide-1 Receptor Agonists

Indication

- Type 2 diabetes (add-on agent) who have been unable to reach target goals on monotherapy or combination therapy with other oral agents and/or insulin

- type 2 diabetes who are obese and struggling with weight loss

Dipeptidyl Peptidase-4 Inhibitors

DPP-IV inhibitors

- Prolong the half-life of an endogenously produced glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).

- DPP-IV inhibitors reduce the inappropriately elevated glucagon postprandially and improve insulin response to a high glucose level

- These drugs do not alter gastric emptying or have significant satiety effects, & body weight

Sitagliptin
25,50,100mg

linagliptin
50,100mg

Dipeptidyl Peptidase-4 Inhibitors

Indication

- Sitagliptin, which is approved for monotherapy, is generally reserved for add-on (combination) therapy (with SFU, biguanides, TZDs, & insulin)
- However, it can be used as monotherapy for patients in whom the use of other oral agents is precluded (such as renal dysfunction for metformin or severe heart failure for the TZDs

Efficacy

- ↓**HbA1c 0.62 to 0.85 %**
- ↓**FPG 15 to 30 mg/dl**
- ↓**PPG 63 to 71 mg/dl**

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Dipeptidyl Peptidase-4 Inhibitors

Adverse Effects

- Increased risk of infection (nasopharyngitis,upper respiratory tract infction, sinusitis,UTI)
- Headache
- patients taking sitagliptin in combination with other antidiabetic agents that may cause **hypoglycemia**, the dose of the other agent (e.g., sulfonylurea) may need to be reduced.

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Dipeptidyl Peptidase-4 Inhibitors

Pharmacokinetic

- Sitagliptin may be initiated at 100 mg taken once daily with or without food
- **Excretion :** urine 87%
- Renal function should be assessed before initiation with sitagliptin therapy and periodically thereafter.
- moderate renal insufficiency (CrCl 30–50 mg/dL)➔ dose should be reduced to 50 mg once daily.
- severe renal insufficiency (CrCl <30 mg/dL) or end-stage renal failure requiring dialysis, the sitagliptin dose should be reduced to 25 mg once daily

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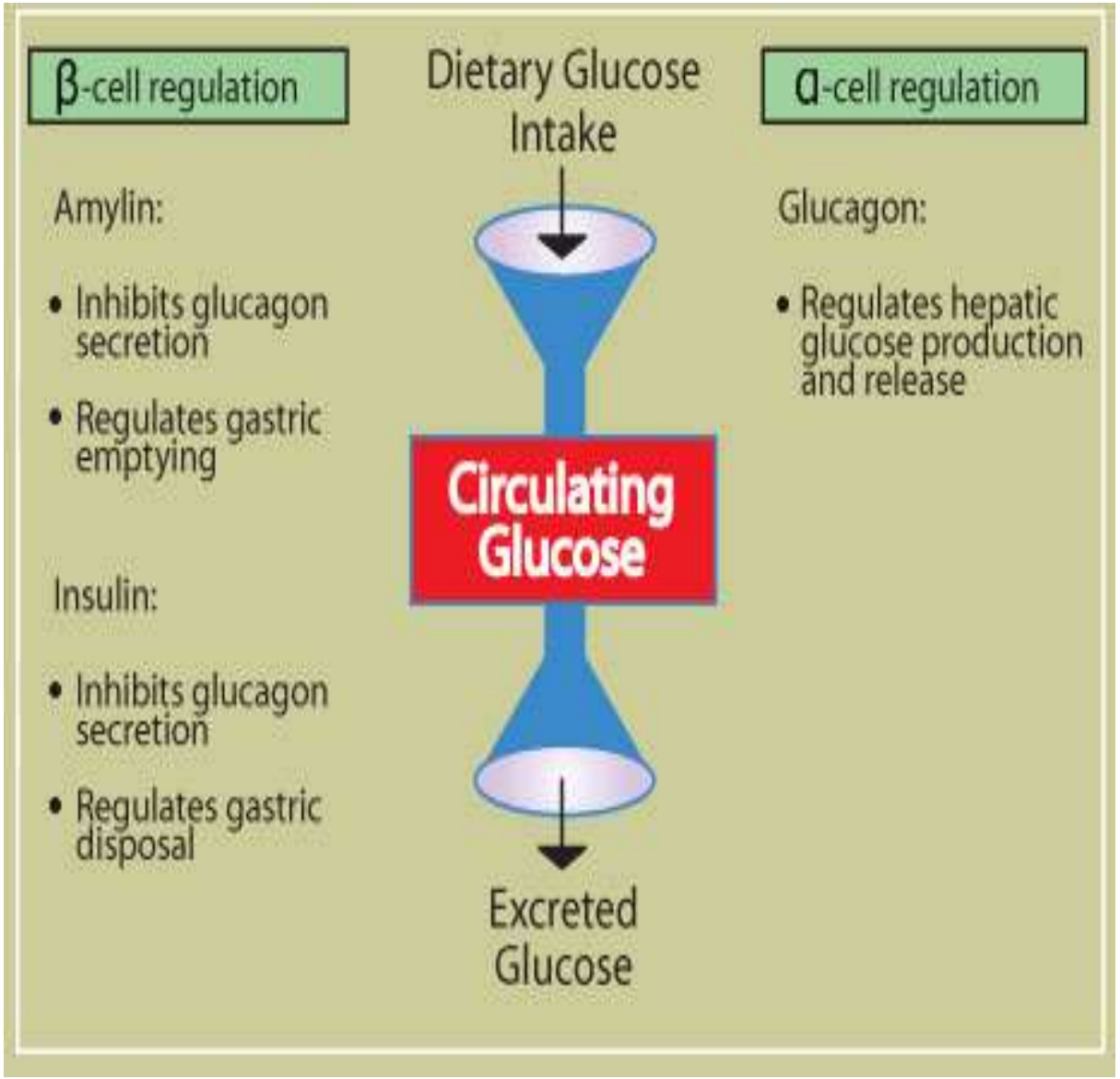
Amylin Receptor Agonists (Amylinomimetics)

Amylin Receptor Agonists (Amylinomimetics)

- Amylin, is a hormone found in the β-cells where it is co-manufactured, stored, and released with insulin in response to food intake

- Its actions seem to be centrally mediated & include slowing gastric emptying, suppressing glucagon secretion & modulating the regulation of appetite.

- **Pramlintide (Symlin)**


β-cell regulation
Amylin:
• Inhibits glucagon secretion
• Regulates gastric emptying
Insulin:
• Inhibits glucagon secretion
• Regulates gastric disposal
Dietary Glucose Intake
Circulating Glucose
Excreted Glucose
α-cell regulation
Glucagon:
• Regulates hepatic glucose production and release


Symlin
(pramlintide acetate)
0.6 mg/mL
5 mL Vial
SUBCUTANEOUS USE ONLY


SymlinPen 120
(pramlintide acetate)
pen-injector
For doses of 60 mcg and 120 mcg.
Two disposable multidose
pen-injectors pramlintide acetate
use only. Pen needles not included. Use 29, 30, or 31
Ask your healthcare provider which needle
SymlinPen 120
(pramlintide acetate)
120

Amylin Receptor Agonists

Pramlintide

Pharmacokinetic

Duration : 3hr

Pb : ~60%

Metabolism : primarily renal (active meta)

Bioavailability :~30 to 40 %

Half-life : ~48 min

Excretion : primarily urine

Pramlintide cannot be mixed with any type of insulin

It is injected SC into the abdomen or thigh immediately before every major meal

If a meal is skipped ,the pramlintide dose should be skipped

Adverse Effects

GI symptoms (transient up to 4-8 w) :

Nausea (up to 95%)

Vomiting (8-11%)

Anorexia(9-17%)

Abdominal pain (8%)

Amylin Receptor Agonists

Efficacy

1. Type 2 diabetes :

↓ **HbA1c 0.3 to 0.6 %**

↓ **Weight 0.5 to 4 kg**

2. Type 1 diabetes :

↓ **HbA1c 0.3 to 0.5 %**

↓ **Weight 0.3 to 1.8 kg**

Indication & Comments

1. Type 1 diabetes (add-on agent)who have failed to achieve target blood glucose goals on insulin therapy alone → initial dose 15 mcg

2. Obese Type 2 diabetes have failed to achieve target blood glucose levels with a regimen that includes a sulfonylurea or insulin → 60 mcg

Amylin Receptor Agonists

Pramlintide

CONTRAINDICATIONS AND PRECAUTIONS:

-Severe hypoglycemia can occur when it is used in combination with insulin and medications that can slow gastric emptying.

-Pramlintide has a black box warning for severe hypoglycemia, which can occur within 3 hours following an injection of pramlintide.

Caution individuals while driving, those who operate heavy machinery.

DRUG INTERACTION

-severe hypoglycemia can occur in patients who are concurrently taking an

oral hypoglycemic agent (e.g., sulfonylurea) or insulin

-Because pramlintide can delay the absorption of medications that are

administered concomitantly, medications that require rapid onset for effectiveness,

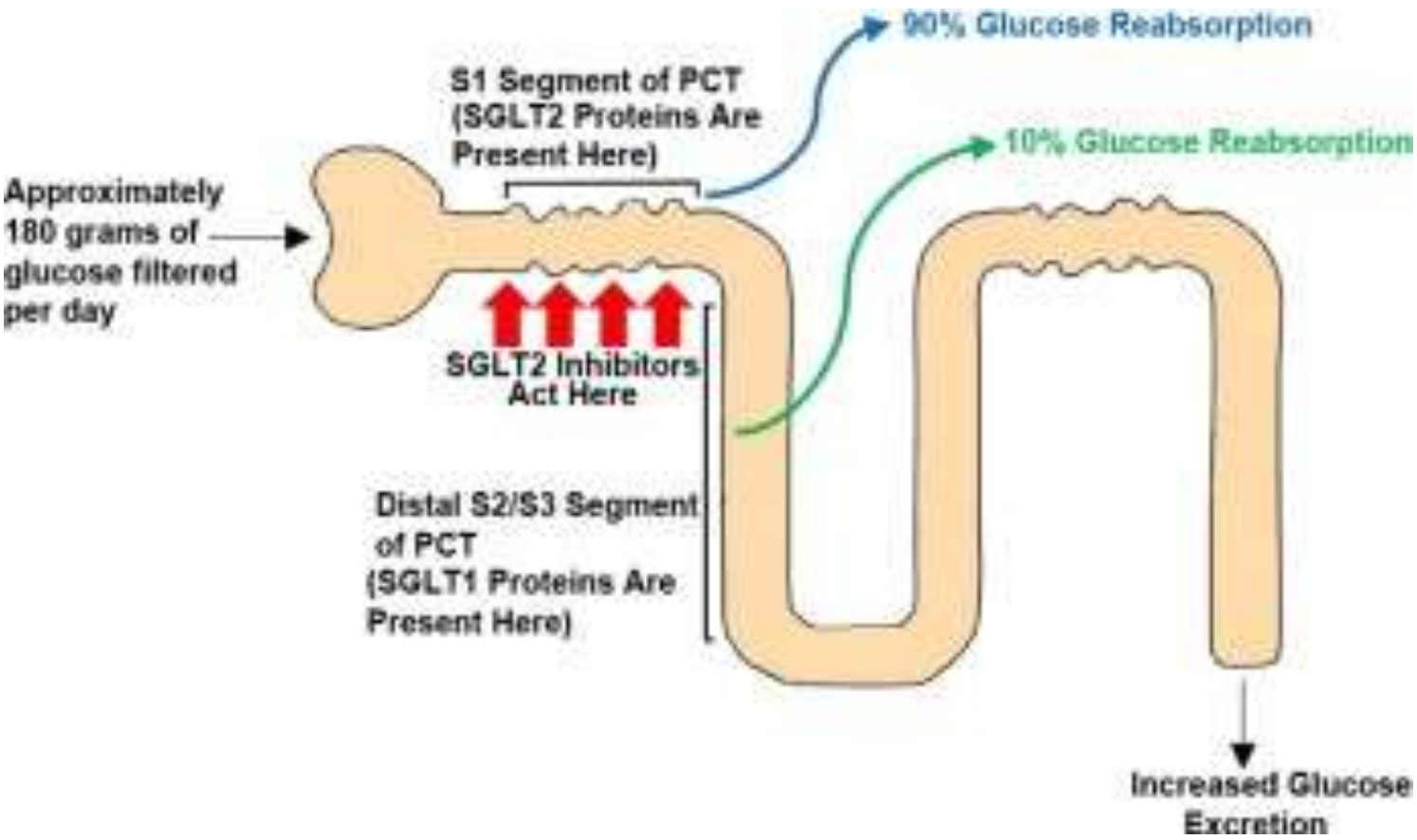
such as antibiotics, oral contraceptives, and analgesics, should be administered at least 2 hours after or 1 hour prior to the pramlintide injection

Sodium–Glucose Transporter 2 (SGLT2) Inhibitors

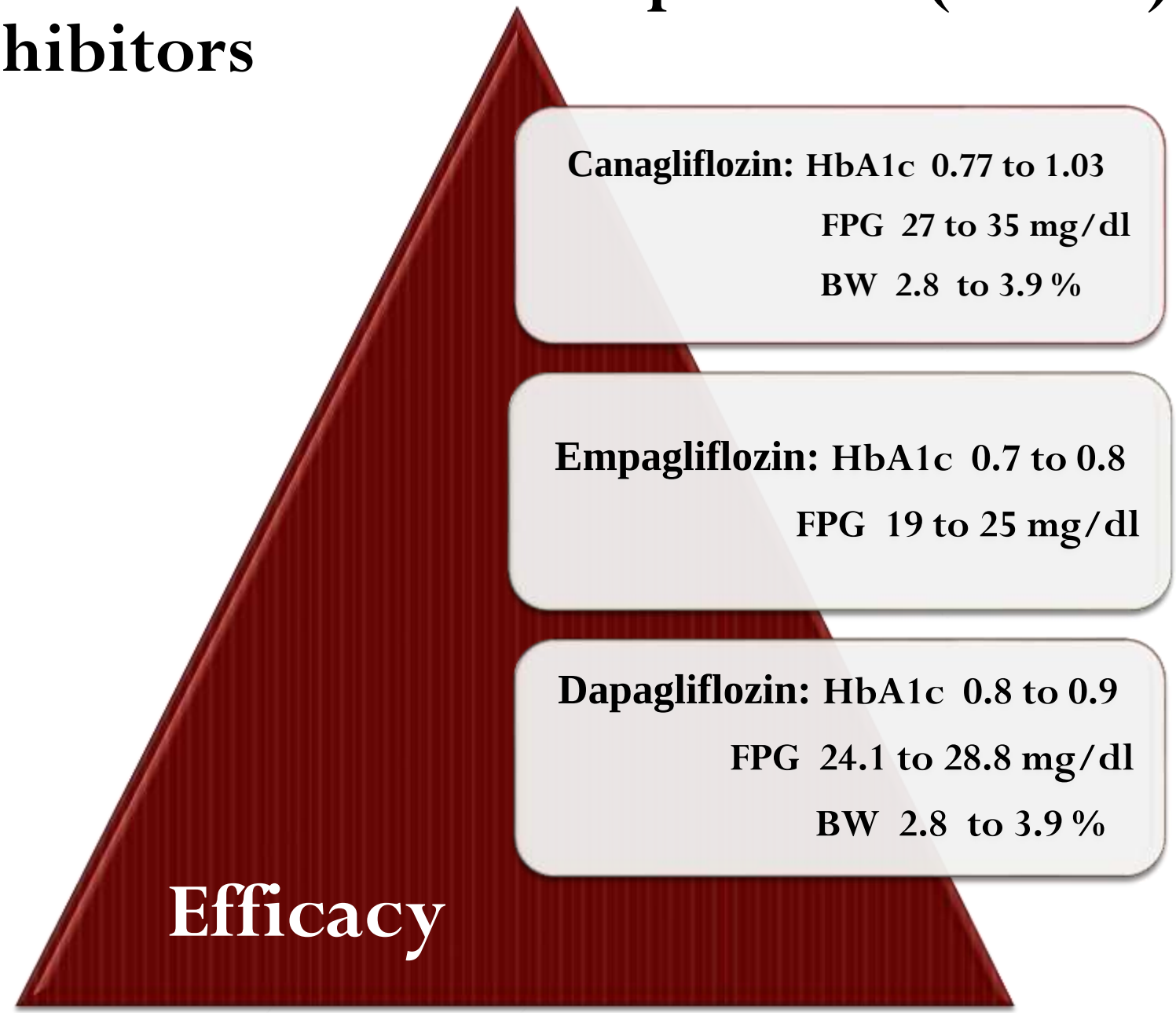
Sodium–Glucose Transporter 2 (SGLT2) Inhibitors

- Decreasing tubular reabsorption of glucose in the kidney, thereby increasing the excretion of urinary glucose
  - Canagliflozin
  - Dapagliflozin
  - Empagliflozin

- Because their mechanism of action is independent of insulin resistance or β-cell function, these medications **can be used in combination with all antidiabetic agent** classes, including insulin, for the treatment of Type 2 DM in addition to diet and exercise
- These agents have added benefits of **weight loss**, **increase in HDL**, and **decrease in blood pressure**; however, genital and urinary infections may be an adverse effect of these agents.


90% Glucose Reabsorption
S1 Segment of PCT
(SGLT2 Proteins Are
Present Here)
10% Glucose Reabsorption
Approximately
180 grams of
glucose filtered
per day
SGLT2 Inhibitors
Act Here
Distal S2/S3 Segment
of PCT
(SGLT1 Proteins Are
Present Here)
Increased Glucose
Excretion

Sodium–Glucose Transporter 2 (SGLT2) Inhibitors



Sodium–Glucose Transporter 2 (SGLT2) Inhibitors

Dosing

- **Canagliflozin**:100 mg once daily taken before the first meal of the day, max dose : 300 mg once if eGFR > 60ml/min, If eGFR of 45 to 60 mL/min max: 100 mg once daily and should be discontinued in patients with an eGFR <45 mL/min
- **Dapagliflozin**: Should be initiated at a dose of 5 mg once daily in the morning, with or without food.
- Monitor renal function prior to initiation and do not use in patients with an eGFR <60 mL/min.
- **Empagliflozin** should be initiated at a dose of 10 mg once daily in the morning, with or without food, and may be increased to 25 mg once daily.
- Do not initiate empagliflozin therapy in patients with an eGFR <45 mL/min and discontinue therapy if eGFR persistently falls below 45 mL/min

Adverse Effects

- Female genital mycotic infections,
- Increased urination, and
- Urinary tract infections

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Sodium–Glucose Transporter 2 (SGLT2) Inhibitors

Pharmacokinetic

- Empagliflozin: peak plasma concentrations at 1.5 hours.
- 86.2% bound to plasma proteins, and the agent is
- primarily metabolized by glucuronidation by UGT3B7, UGT1A3, UGT1A8, and UGT1A9.
- Approximately 41.2% of the drug was eliminated in feces (unchanged parent drug), whereas 54.4% was eliminated in urine (half is unchanged parent drug). The terminal half-life is approximately 12.4 hours

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Sodium–Glucose Transporter 2 (SGLT2) Inhibitors

CONTRAINDICATIONS AND PRECAUTIONS

- **Hypersensitivity** reactions
- ESRD, and dialysis.
- **Ineffective in patients with severe renal impairment** and would place these patients at increased risk for renal adverse effects.
- Renal function may be impaired with use of these agents.
- **Hypovolemia**
- Patients already taking antihypertensive medications.
- **Hypoglycemia** may occur when SGLT2 agents are used in combination with insulin and secretagogues;
- Serum concentrations of **LDL may be increased** with SGLT2 therapy,
- Dapagliflozin has shown an increase in **bladder cancer** patients with previous history of bladder cancer should not take dapagliflozin.

Applied Therapeutics. 11th ed & APhA ,Drug Information Handbook. 18th ed


Gloripa
Empagliflozin
25
Gloripa
Empagliflozin
10
30 Film-Coated Tablets


25 mg
EMPAVER 25
Empagliflozin
10 mg
EMPAVER 10
Empagliflozin


Empajent 25/5
Empagliflozin 25 / Linagliptin 5
Each F.C. tablet contains:
Empagliflozin 25 mg
Linagliptin 5 mg
30 F.C. Tablets


Glorenta® 25/5
Empagliflozin / Linagliptin
Glorenta® 10/5
Empagliflozin / Linagliptin
30 Film-Coated Tablets

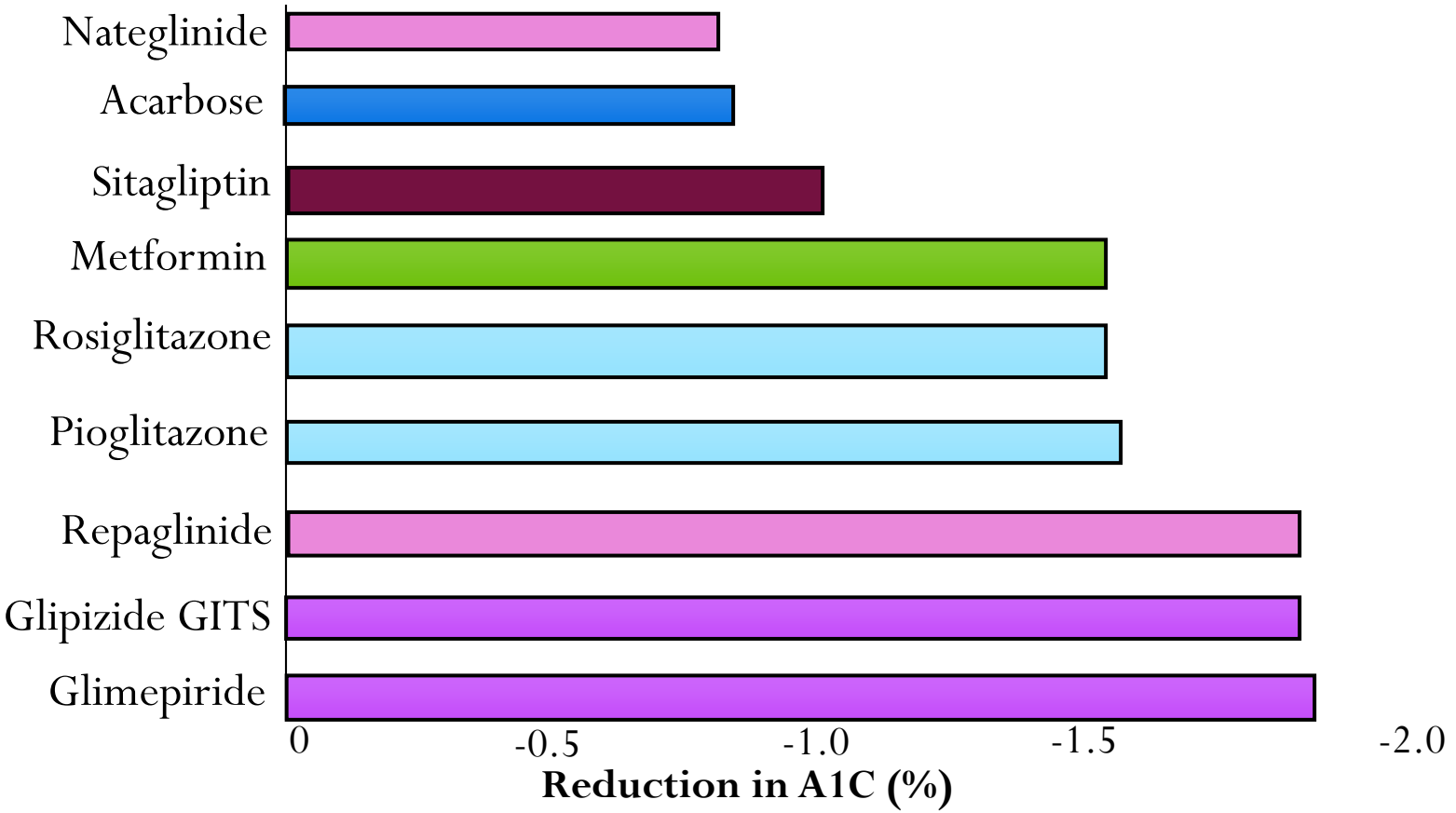

Synjardy
5 mg/850 mg
film-coated tablets
empagliflozin/
metformin hydrochloride
Synjardy
5 mg/1,000 mg
film-coated tablets
empagliflozin/
metformin hydrochloride
Synjardy
12.5 mg/850 mg
film-coated tablets
empagliflozin/
metformin hydrochloride
Synjardy
12.5 mg/1,000 mg
film-coated tablets
empagliflozin/
metformin hydrochloride


Synoripa 12.5/500
Synoripa 12.5/1000
Synoripa 5/1000
Synoripa 5/500

In May 2015, the FDA released a Drug Safety Communication warning that SGLT2 agents may cause ketoacidosis and patients should be warned to seek medical attention if they experience signs and symptoms of ketoacidosis including confusion, fatigue, difficulty breathing, abdominal pain, nausea, or vomiting.

The cases were not typical of DKA cases, because blood sugars were not highly elevated. In some of the cases, DKA may have been triggered by major illness.

Antihyperglycemic Monotherapy
Average Therapeutic Effect on A1C*



*Placebo-adjusted absolute percentage of A1C reduction. Different studies had different recruitment criteria, particularly baseline A1C

Kimmel B, Inzucchi SE. *Clin Diabetes.* 2005;23:64-76

Metabolic Effects of Noninsulin Antihyperglycemics

	Weight	LDL-C	HDL-C	Triglycerides
Secretagogues	↑	↔	↔	↔
Metformin	↓ or ↔	↓	↔	↓
α-Glucosidase inhibitors	↔	↔	↔	↔
TZDs	↑ ↑	↔ or ↑	↑ or ↔	↔ or ↓
Exenatide	↓	↓	↑	↓
Pramlintide	↓	↔	↔	↔
DPP-4 inhibitors	↔	↓ or ↔	↑ or ↔	↓ or ↔

Physicians' Desk Reference. 61st ed

Bile acid sequestrants

- Colesevelam is approved for the treatment of type 2 DM
- no absorption, distribution, or metabolism

- HbAlc reductions from baseline were 0.4% when a dose of 3.8 g/day was added to metformin, sulfonylurea, or insulin

- FBG was modestly reduced about 5-10 mg/L
- It may also reduce LDL_C
- TG increased in combination with sulfonylurea or insulin, but not with metformin
- It is weight neutral

Bile acid sequestrants

- The following are contraindications for use of colesevelam:
- Patients with triglyceride levels of more than 500 mg/dL
- Patients with a history of bowel obstruction
- Patients with a history of pancreatitis caused by hypertriglyceridemia
- Patients with of Type 1 diabetes or for the treatment of DKA

- Drug interaction
- Drugs with a known interaction with colesevelam (e.g., phenytoin, warfarin, levothyroxine, oral contraceptives) should be administered at least 4 hours before colesevelam.
- The bioavailability of glimepiride, glyburide, and glipizide may be affected by concomitant administration of colesevelam; therefore, these medications should be administered 4 hours prior to colesevelam
  - Dosing: six 625 mg tablets daily with meals

Bromocriptine

- Bromocriptine is currently approved for the treatment of type 2 DM
- Administration in the morning improves insulin sensitivity
- Reduce HbAlc by a modest 0.1-0.4% from baseline
- Dosing: 0.8 mg within 2 hr of waking in the morning.
- Dose may be increased weekly based on response by 0.8 mg increments to a MAX : 4.8 mg/daily
- Minimal effective dose: 1.6 mg daily

- Drug interaction
- Bromocriptine is highly protein bound, and when given concomitantly with other drugs that are highly protein bound, such as sulfonamides, salicylates, and probenecid, the unbound fraction of these other drugs may increase, altering their risk of adverse effects or their effectiveness.
- Bromocriptine is metabolized by CYP3A4; therefore, caution should be used when administering concomitant drugs that are CYP3A4 substrates, inducers or inhibitors.
- Neuroleptic agents with dopamine receptor agonist properties, such as olanzapine, clozapine, and ziprasidone, may reduce the effectiveness of both bromocriptine and the other drugs; therefore, concomitant use is not recommended


Diabetes
?