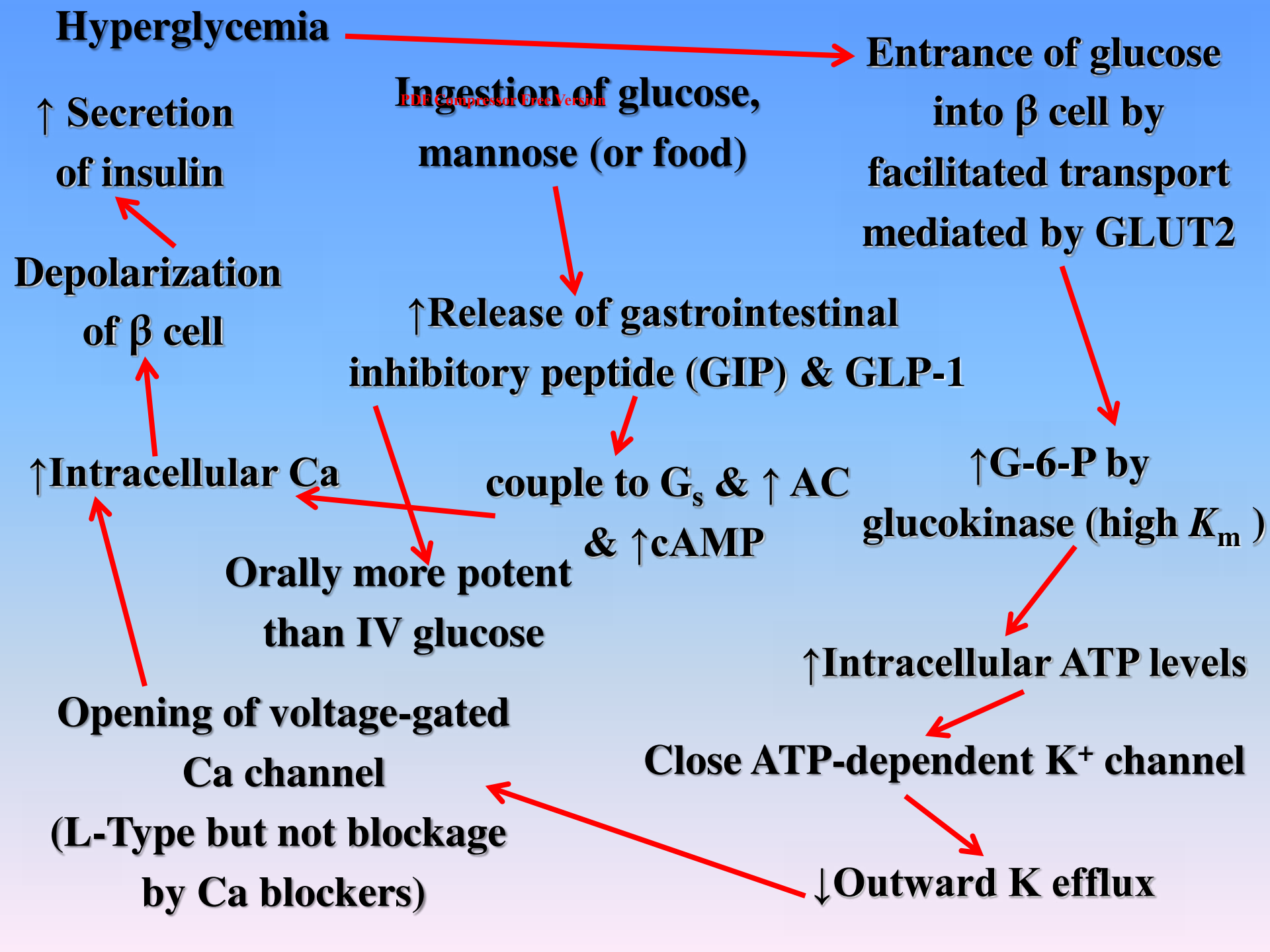
Antidiabetic and Hypoglycemic Agents

Insulin

- **Highly conserved of aa sequence in evolution but significant variations lead to differences in biological potency and immunogenicity.**
- **Human, bovine, and porcine: Equipotent.**
- **Hexameric in preparations used for therapy & monomer biologically active.**

Insulin Production

- Secreted in response to all insulin secretagogues.
- **4 cells in islet of Langerhans:** β (insulin), α (glucagon), δ (somatostatin) & PP or F (pancreatic polypeptide).
- Equimolar amounts of C peptide as a useful index of insulin secretion in distinguishing patients with factitious insulin injection and insulin-producing tumors.
- Blood supply in islet flows from β cell core to α and δ cells → Insulin inhibit glucagon release in a paracrine manner.


Hyperglycemia
Entrance of glucose into β cell by facilitated transport mediated by GLUT2
↑ Secretion of insulin
Ingestion of glucose, mannose (or food)

Depolarization of β cell
↑Release of gastrointestinal inhibitory peptide (GIP) & GLP-1
↑Intracellular Ca
couple to G_s & ↑ AC & ↑cAMP
↑G-6-P by glucokinase (high K_m)
Orally more potent than IV glucose
↑Intracellular ATP levels
Opening of voltage-gated Ca channel (L-Type but not blockage by Ca blockers)
Close ATP-dependent K^+ channel
↓Outward K efflux

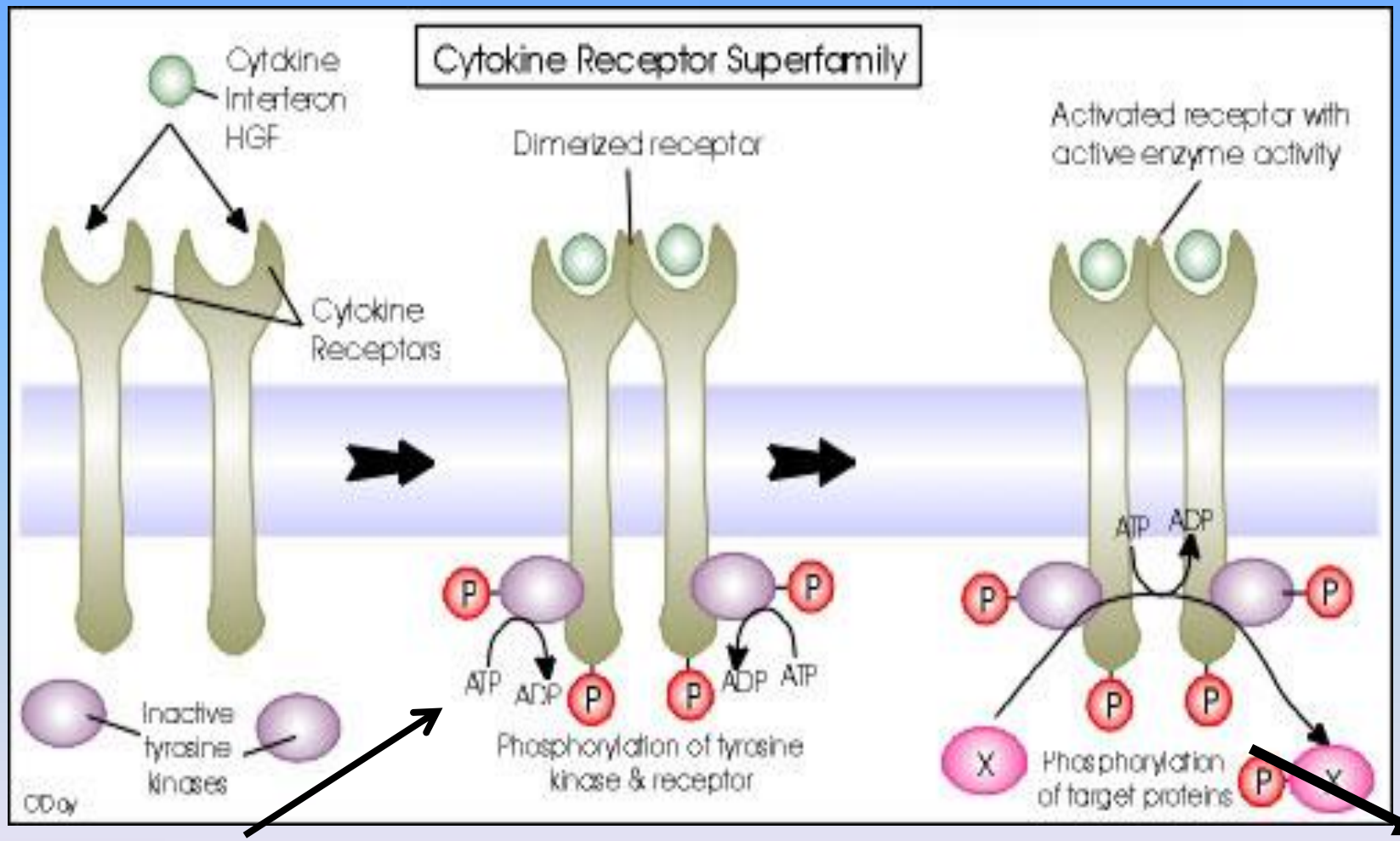
Stimulators of Insulin Secretion (Cont)

- **Biphasic insulin secretion: 1st phase reaches a peak after 1 to 2 minutes & short-lived; 2nd phase a delayed onset but a longer duration.**
- **Leucine, arginine, ketone bodies, activation of β 2 adrenergic receptor & sulfonylurea.**

Inhibitors of Insulin Secretion

- **Diazoxide, phenytoin, colchicin, vinblastin.**
- **Glucagon → ↑release of somatostatin → pass through the circulation to reach the α and β cells →↓ Secretion of insulin**
- **Any condition activating sympathetic branch such as hypoxia, hypoglycemia, exercise, hypothermia, surgery, or severe burns → Stimulation of α_2 adrenergic receptors →↓Secretion of insulin**

Receptors Activated by Soluble Tyrosine Kinases (Janus-Kinase-JAK)



Cross phosphorylation

Continue of action after dissociation of ligand from receptor

Physiological Effects of Insulin

- Primarily anabolic (conservative or constructive) - promotes conservation of energy and buildup of energy stores & ↓catabolic processes.
- ↑ Fatty acid uptake, ↑fatty acid synthesis , ↓lipolysis, ↑ storage of TG.
- ↓Hepatic concentration of carnitine →↓Production of ketone bodies.
- ↑ Amino acid uptake, ↓protein degradation in muscle and other tissues, ↑ storage & synthesis of protein.
- Activate glycogen synthase, inhibit glycogen phosphorylase & ↑storage of glycogen
- ↓ Gluconeogenesis.

Timescale Of Effects

- **Seconds or minutes:** **Activation of glucose and ion transport systems, covalent modification (*i.e.*, phosphorylation or dephosphorylation) of enzymes.**
- **A few hours:** **Protein synthesis and gene transcription.**
- **Days:** **Cell proliferation and differentiation.**

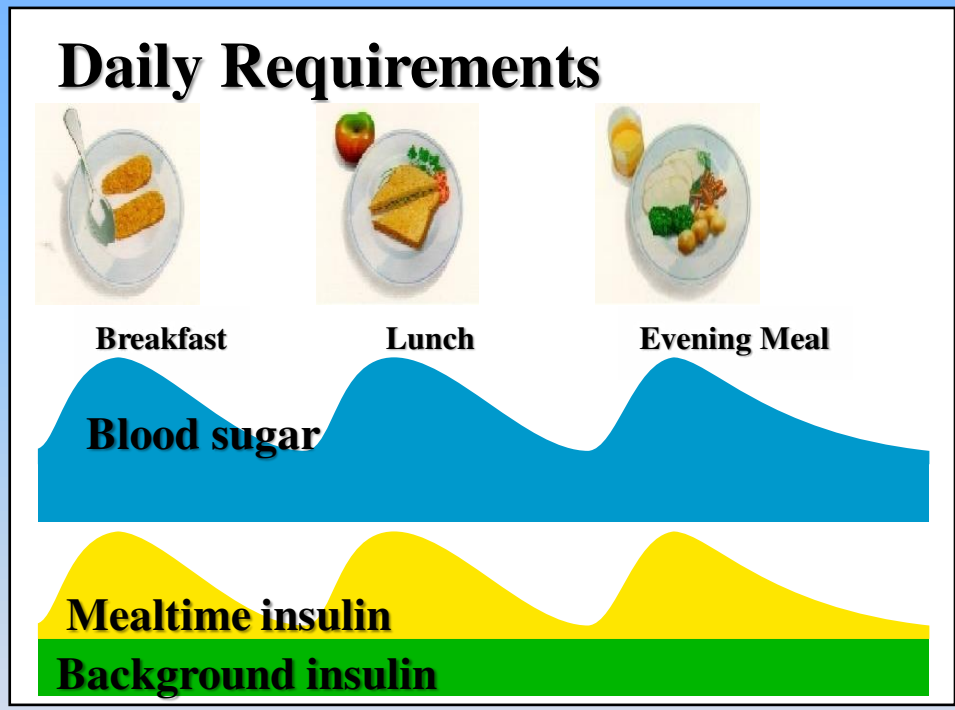
Regulation of Glucose Transport

- **By glucose transporters (GLUT):** 12 Membrane-spanning helical domains glycoproteins.
- Na^+-independent facilitated diffusion; a reversible effect, return to intracellular pool on removal of insulin.
- Faulty regulation of this process → Pathophysiology of type 2 DM
- **GLUT1:** All of tissues; especially RBC.
- **GLUT2:** Kidney, B-Cells, liver, gut, pancreas; regulation of insulin release, deficiency in NIDDM, ↓insulin secretion.
- **GLUT3:** Brain, placenta, kidney.
- **GLUT4:** Muscle, adipose; most important in decreasing of blood sugar.
- **GLUT5:** Gut, kidney, intestinal absorption of fructose.

Normal Insulin Profiles

- **Blood tests:**

1. FBS> 126 ml/dl (7 mM).
2. Oral Glucose
   Tolerance Test. BG> 200 mg/dl-2 hours after the ingestion of an oral glucose load.
3. Glycosylated Hemoglobin
   Assays.
4. Glycosylated Serum
   Proteins and Albumin.
5. Random BG> 200 mg/dl (11.1 mM)



HbA_{1c}		eAG	
%	mmol/mol[32]	mmol/L	mg/dL
5	31	5.4 (4.2–6.7)	97 (76–120)
6	42	7.0 (5.5–8.5)	126 (100–152)
7	53	8.6 (6.8–10.3)	154 (123–185)
8	64	10.2 (8.1–12.1)	183 (147–217)
9	75	11.8 (9.4–13.9)	212 (170–249)
10	86	13.4 (10.7–15.7)	240 (193–282)
11	97	14.9 (12.0–17.5)	269 (217–314)
12	108	16.5 (13.3–19.3)	298 (240–347)
13	119	18.1 (15–21)	326 (260–380)
14	130	19.7 (16–23)	355 (290–410)
15	140	21.3 (17–25)	384 (310–440)
16	151	22.9 (19–26)	413 (330–480)
17	162	24.5 (20–28)	441 (460–510)
18	173	26.1 (21–30)	470 (380–540)
19	184	27.7 (23–32)	499 (410–570)

Signs and Symptoms of DM

- **Hyperglycemia:**
- **≥ 200mg/dL in each time & no consider meal or in Glucose Tolerance Test**
- **≥ 126mg/dL FBS**
- **110 > FBS > 126mg/dL ;**
- **All indicators should be confirmed the following day.**
- **Blurred vision, fatigue, paresthesias, skin infections, glucosuria, polydipsia, polyuria, polyphagia, ketonuria , unexplained weight loss.**

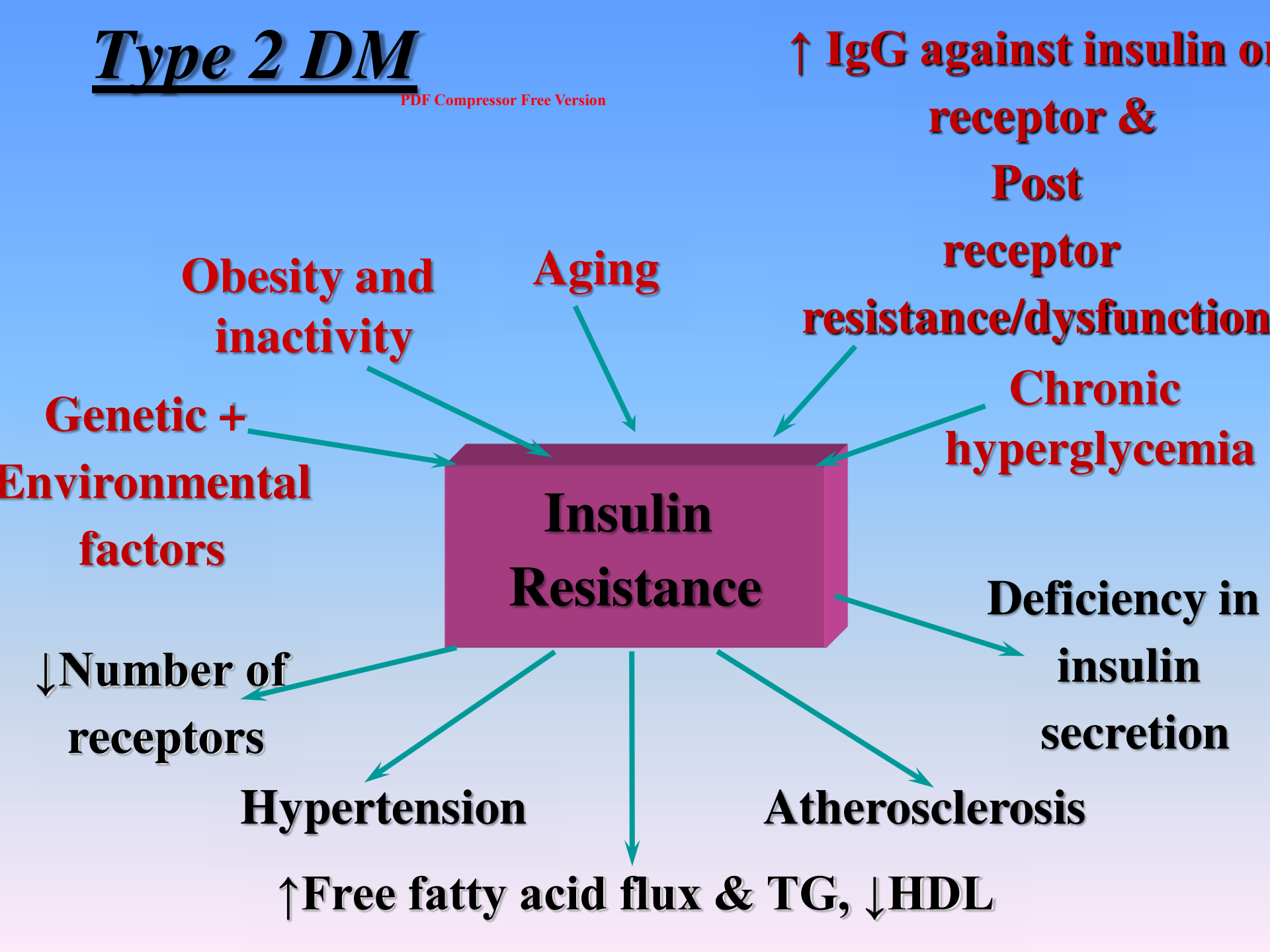
Diabetes Mellitus

- **Type 1 (IDDM) Insulin Dependent Diabetes Mellitus.**
- **Type 2 (NIDDM) Non-insulin Dependent Diabetes Mellitus.**
- **Type 3.**
- **Type 4.**

Type 1 DM

- < Age 30 & subdivide into autoimmune (1A) and idiopathic (1B) subtypes.
- Humoral and cell-mediated immune etiology.
- Auto-antibodies → Degeneration of beta cells, insulin, or enzymes in insulin synthesis.
- Genetic predisposition → ↑Sensitivity to viruses & diabeteogen Ab, mumps.
- Detection of > 1 form of Abs in healthy first-degree relatives of diabetic patients.
- Abs directed other endocrine tissues (adrenal, parathyroid, and thyroid) & ↑other autoimmune diseases.
- A multifactorial genetic linkage but only 10-15% of patients with a positive family history.

Type 2 DM



Type 3 Diabetes Mellitus

- **Nonpancreatic diseases, drug therapy, etc.**

Type 4 Diabetes Mellitus

- Gestational diabetes (GDM) as any abnormality in glucose levels noted for 1st time during pregnancy.
- GDM diagnosed in approximately 4% of all pregnancies in the USA.
- During pregnancy, the placenta and placental hormones create an insulin resistance that most pronounced in the last trimester.
- **Assessment:**

  - Starting at the first prenatal visit & high-risk women should be screened immediately.

  - Screening may be deferred in lower-risk women until the 24th to 28th week of gestation.

Long-Term Complications of Diabetes

- **Macrovascular disease:**
  - Hypertension.
  - Stroke.
  - Heart disease.
- **Microvascular disease:**
  - Capillary thickness.
  - Destruction of blood vessels.

- Nephropathy.
- Neuropathy.
- Amputations.
- Impotence.
- Gastroparesis.
- Retinopathy.

Insulin Therapy

- **Differences of SC insulin from its physiological secretion:**

  - No kinetics reproduce normal rapid rise and decline of insulin secretion in response to ingestion of nutrients.

  - Insulin diffusion into peripheral circulation instead of released into the portal circulation & elimination of direct effect on hepatic metabolic processes.
- **1 unit of insulin = Amount required to reduce the concentration of blood glucose in a fasting rabbit to 45 mg/dl (2.5 mM).**
- **All commercial preparations of insulin: Solution or suspension at a concentration of 100 units/ml= about 3.6 mg insulin per milliliter (0.6 mM).**
- **A more concentrated solution (500 units/ml) for patients resistant to the hormone.**

Insulin Dosage Regimens

- **Highly individualized:**
  - Diet & exercise.
  - Patient motivation & ability to comply.
  - Intermediate or long-acting with regular.
- **Frequency of Hypoglycemia episodes:**
  - Often occurs in middle of night.
- Before use store in fridge,
- In-use vials store in fridge (3 months).
- Out of fridge at max 25 C (4-6 weeks)

Daily Requirements

- **Insulin production by a normal, thin, healthy person:**

  - 18-40 Units/day or about 0.2-0.5 units/kg per day; ½ secreted in basal (0.5-1 units/h) & ½ in response to meals (to 6 units/h).

  - To 4-fold or more in nondiabetic, obese, and insulin-resistant individuals.

- **Successful regimens:** ↓Risk of micro & macrovascular complications.

- **Multiple daily injections:** Preprandial a short-acting (bolus) + long-acting at bedtime (basal).

TDI (Total Daily Insulin) Division

- 50% Before sleep as long-acting (Lantus/Glargine).
- 20% Before breakfast as short-acting.
- 13% Before launch as short-acting.
- 17% Before dinner as short-acting.

Insulin + Oral Hypoglycemic Agents

- **Progressive insulin deficiency in type 2 DM:** **↓50% β cell insulin secretory capacity for every 6 years → Difficult to achieve tight glycemic control (HbA_{1C} < 7.0%) with oral antihyperglycemic agents → Requirement of insulin + oral hypoglycemic agents.**

Correction of TDI

- TDI 10%.
- Rule of 1700.
- Corrected dose must administrated during BG determination or if repeated, add to previous dose of insulin.
- If usage of short-acting before meal: Determination of BG 2h after instead of before meal due to duration of insulin (3-4h).

The 1,700 Rule Of Tamborlane, & Davidson

- **1700/TDI= ISF.**
- **Insulin Sensitivity Factor (ISF): Decline of glucose level; mg/dl/ 1 IU of insulin.**
- **BG-Aim BG/ISF= Required Insulin**
- **Example:**

  - TDI= 50 IU, BG=300, Aim BG= 140 mg/dl.

  - 1700/50= 34(ISF).

  - 300-140= 160.

  - 160/34= 4.7≈ 5IU.

Insulin Delivery Systems

- **Syringes, inhalation, portable pen-sized injectors (cartridges + replaceable needles), insulin pumps.**
- **Experimental approaches: IP Delivery devices, implantable pellets, closed-loop artificial pancreas, pancreatic transplantation, oral (protection of insulin by encapsulation or incorporation into liposomes), segmental pancreatic transplantation (islet preparation and a novel glucocorticoid-free immunosuppressive regimen) and gene therapy (transcription factors regulate ß cell function used to transdifferentiate hepatocytes into a functional endocrine pancreas).**

Types of Insulin

- **According to duration:** Very fast onset, rapid onset, short-acting, intermediate-acting & long-acting.
- **Rapid onset, short-acting:** Alternative for dietary insulin
- **Intermediate-acting & long-acting:** Alternative for base level of insulin
- Natural, Regular (natural).
- **Modified- 4 types:**
  - Lispro, NPH, Lente & Ultralente.
- Human, Genetically engineered using either ,yeast or E.coli, fast & shorter duration than animal origins.
- **Animal:**
  - **Beef (3aa)**- Increased incidence of allergic problems.
  - **Pork (1aa)**- Less antigenic than beef.
- **Human insulin vs. porcine insulins:**

  - More hydrophobic nature → More rapid onset and shorter duration of action than do porcine insulin.

Rapid-Acting Insulin

- Lispro, aspart & glulysine.
- Absorbed 3 times rapidly & duration of action rarely more than 3-5 hours.
- Injected immediately before or after a meal, preferred insulin for use in continuous SC insulin infusion devices.
- Lowest variability of absorption ~5% (compared to 25% for regular insulin and 25-50% for intermediate and long-acting formulations).
- Mimic normal endogenous prandial insulin secretion.
- **Lispro:** Identical to human insulin except Proline at position B28 moved to B29, and lysine reverse.
- **Aspart:** Replacement of proline at B28 with aspartic acid.
- **Glulysine:** Glutamic acid replaces lysine at B29, and lysine replaces asparagine at B23.

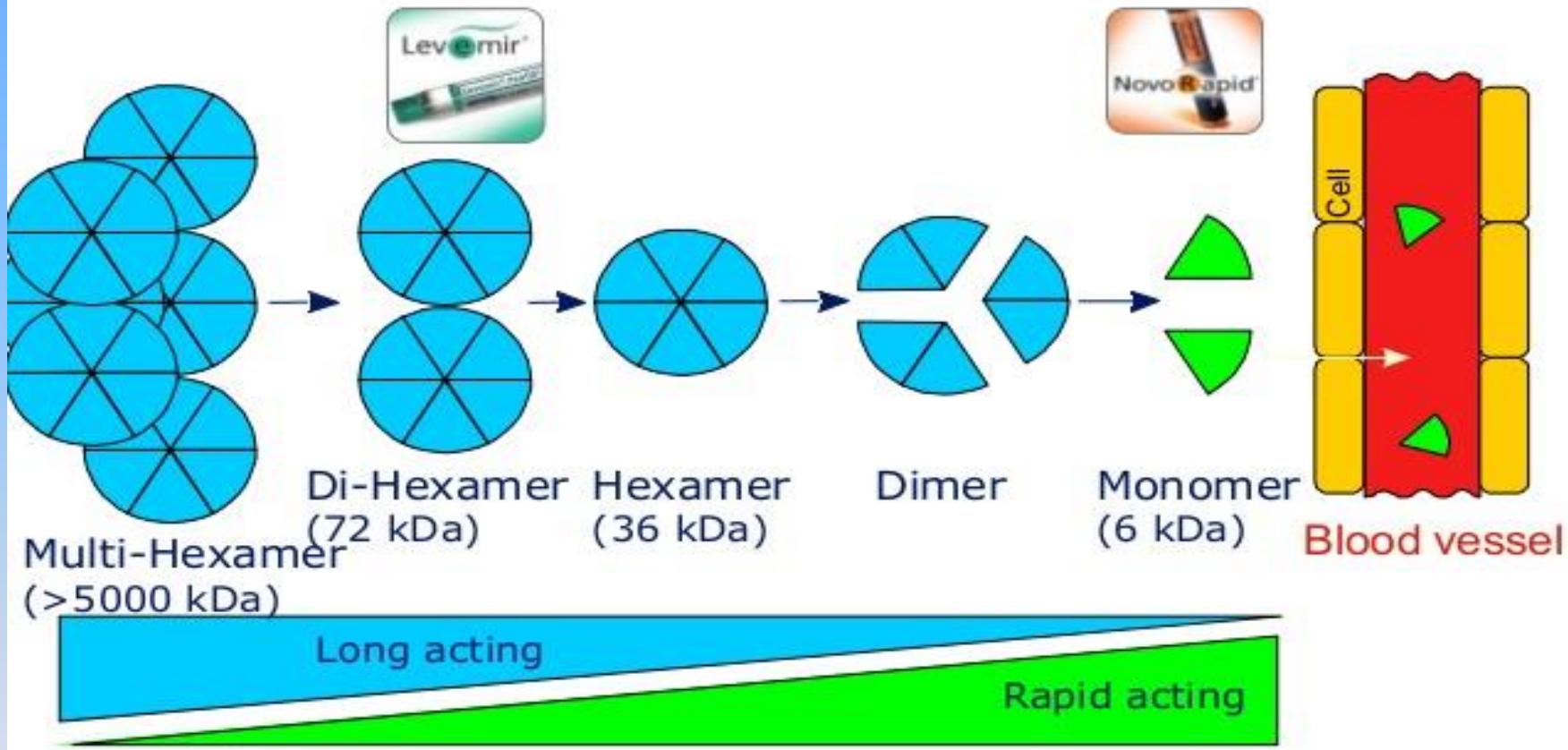
Inhaled Insulin

- ↑Absorption through the pulmonary mucosa postprandial glycemic control similar to short or rapid-acting SC.
- Onset, 30min; duration of action, 6-7 hours.
- 1mg inhaled= 2-3 IU of regular human insulin SC.
- ↑Patient satisfaction & prevalence of hypoglycemia no higher & may lower compared with regular (soluble) insulin.
- Not approved for asthma, bronchitis, emphysema, smokers, or those within 6 months of quitting smoking.
- Less than 30% of users achieve target BG after 6 months of therapy with inhaled human insulin.
- **Safety concerns:** Pulmonary fibrosis , reduced lung volume or oxygen diffusing capacity & excessive insulin antibody formation.

Short-Acting Insulins

- Solutions of regular, crystalline zinc (improve stability and shelf-life) dissolved usually in a buffer at neutral pH.
- Stabilize around zinc → Insulin hexamers → Too large and bulky to transported across the vascular endothelium into the bloodstream → Necessary to break down into dimers & monomers → Delayed onset & $\uparrow t_{p\ max}$ (Onset 30 minutes, Peak 1 - 3 hours, Duration up to 8 hours) → Mismatching of insulin availability with need → Should be injected 30 to 45 minutes before meals to minimize the mismatching.
- Useful for IV in the management of diabetic ketoacidosis.

Engineering insulin analogues



Intermediate-Acting Insulins

- **Either once a day before breakfast or twice a day, at bedtime in type 2 DM.**
- **Neutral Protamine Hagedorn (NPH) or isophane: Crystals in suspension (need re-suspending), cloudy of 6 molecule insulin + zinc + 1molecule protamine in a phosphate buffer → Degradation of protamine by proteolytic enzyme in SC → Gradual release of insulin.**
- **Onset1 $^{1}/_{2}$ hours, Peak 4 - 12 hours, Duration up to 24 hours.**

  - Interactions with the regular in a complex:

  - Not retard the action of regular insulin by NPH if mixed vigorously by the patient or available commercially as a mixture.

Long-Acting Insulins

- **Ultralente insulin**
- **Glargine**
- **detemir**

Ultralente (Extended Zinc Suspension) & Protamine Zinc Insulin Suspension

- **Low basal concentration of insulin throughout the day, no peak, given at bedtime.**
- **The long t1/2 → Several days required before achievement of C_{SS} of circulating insulin → Difficult to determine the optimal dosage → Once or twice daily according to FBS.**
- **Protamine zinc insulin today used rarely: Very unpredictable & prolonged course of action.**

Glargine (Lantus)

- Onset of action (1-1.5 hours), $t_{p\ max}$ (4-6 hours), duration (11-24 hours).
- Affinity to IGF-1 receptors slightly greater compared with human insulin.
- Equivalent efficacy any time during day & no difference in the frequency of hypoglycemic episodes.
- No influence site of administration & exercise on absorption kinetics.
- **To maintain solubility; pH of 4.0:**

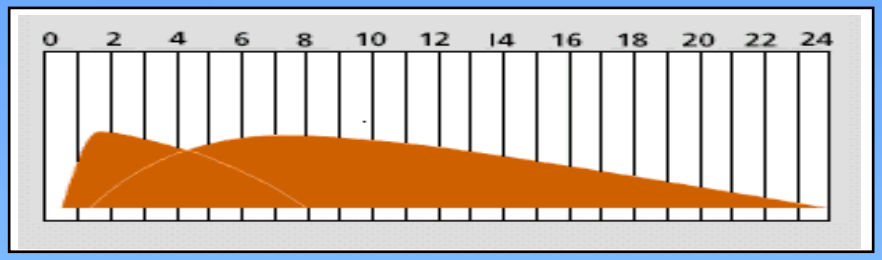
  - Stabilizes hexamer → prolonged, peakless & predictable SC absorption → Better once-daily coverage than ultralente or NPH insulin → Less hypoglycemia.

  - Acidic pH → Cannot mixed with short-acting insulin (regular insulin, aspart, lispro) formulated at a neutral pH.

Insulin Detemir (Levemir)

- **Myristic acid (C-14 fatty acid chain) + amino group of LysB29= a myristoylated or detemir.**
- **Administered BD, smoother time-action profile, ↓prevalence of hypoglycemia as compared with NPH.**
- **SC, binds to albumin via its fatty acid chain.**
- **Onset of action (1-2 hours), duration (>24 hours).**

Pre-mixed Insulin



- Lispro, aspart, and glulisine can be acutely mixed (ie, just before injection) with NPH insulin without affecting their rapid absorption
- Pre-mixed: NPL (neutral protamine lispro) & "NPA" (neutral protamine aspart) biphasic, ↓lispro solubility, ↑stability.
- Cloudy (needs re-suspending).
- 5 Different combinations (10, 20, 30, 40, 50);
- e.g. 30/70 Mixture = 30% fast acting + 70% intermediate acting
- Onset 30 minutes; Peak 2 - 8 hours, Duration up to 24 hours.
- **The benefit of premixed insulin:** Patients do not need to mix the two types of insulin thereby eliminating the risk of dosing errors.

What is NovoMix?

- A range of suspensions in cartridges (Penfill) and prefilled pens (FlexPen).
- Insulin aspart (100 units per millilitre) in 3 forms:

  - NovoMix 30: 30% soluble (rapid-acting) insulin aspart and 70% protamine-crystallised (intermediate-acting) insulin aspart.

  - NovoMix 50: 50% soluble and 50% protamine-crystallised insulin aspart.

  - NovoMix 70: 70% soluble and 30% protamine-crystallised insulin aspart.

Types of Pens

- **There are two pen systems: Durable and prefilled.**
- **Durable pen (Penfill) :**

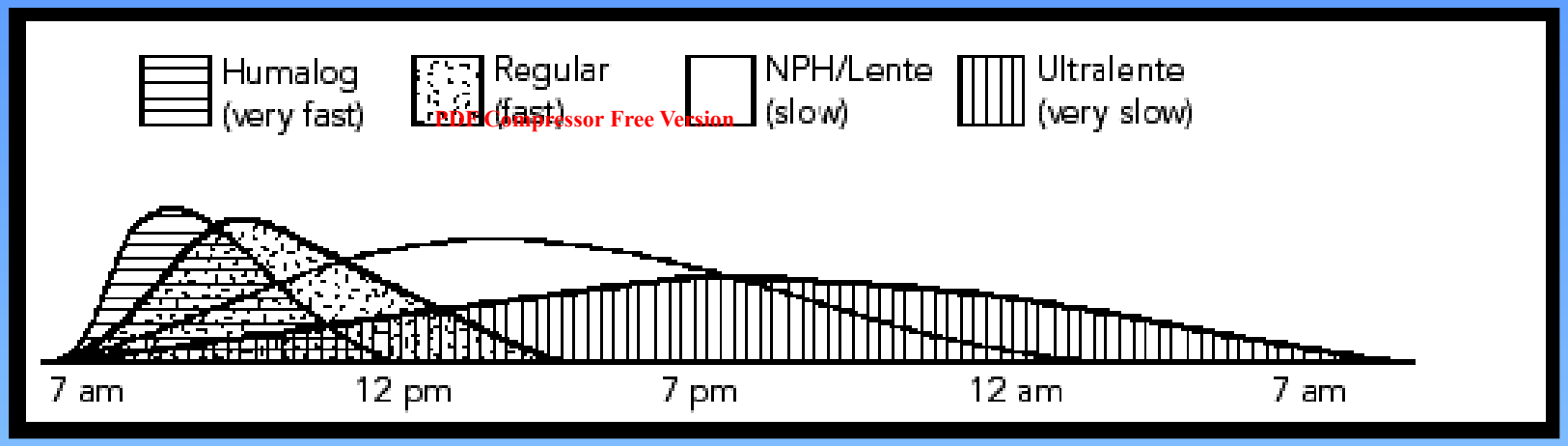
  - A replaceable insulin cartridge & disposed when the insulin cartridge is empty with the insertion of a new one in the pen.
- **Prefilled pen (FlexPen):**

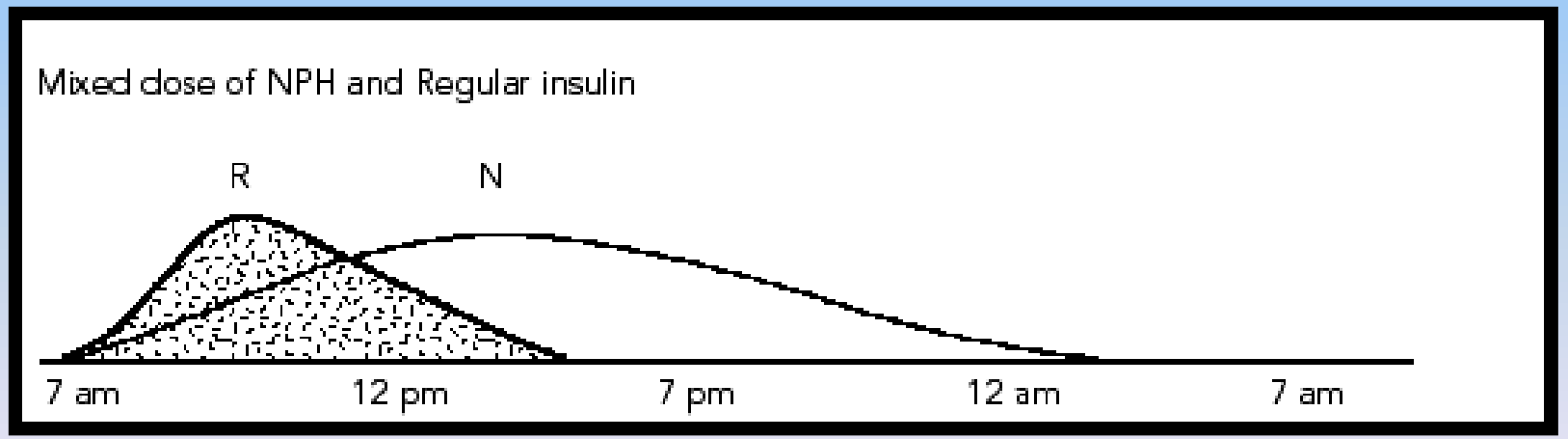
  - Entirely disposable when the insulin cartridge or reservoir is empty.
- **Most brands of insulin now available:**

  - NovoMix, NovoRapid and Levemir by Novo Nordisk.

  - Lantus and Apidra by Sanofi-Aventis Humulin.

  - Humalog by Eli Lilly and Company.





Insulin; Drug Interactions

- **What Rx enhances the effects of insulin (hypoglycemic effects) and how?**

  - Ethanol → Inhibition of gluconeogenesis.

  - Salicylates → ↑ß-cell sensitivity to glucose and potentiating insulin secretion.

  - Beta blockers → Block effects of catecholamines on glycogenolysis and gluconeogenesis, mask the sympathetically hypoglycemia.

- **What Rx stimulates alpha 2 receptors in the islets, therefore inhibits insulin release?** Clonidine.
- **What Rx increases gluconeogenesis?** Glucocorticoids.
- **Both hypoglycemia and hyperglycemia:** Pentamidine; destruction of ß-cell and release of insulin → Hypoglycemic → Continued use → Secondary hypoinsulinemia and hyperglycemia.

Insulin; Drug Interactions (Cont)

- **Cause hyperglycemia:**

  - Direct effects on peripheral tissues counter the actions of insulin: epinephrine, glucocorticoids, clozapine, olanzapine, antiretroviral of HIV-1 infection (protease inhibitors).

  - Inhibiting insulin secretion:

  - Directly: Phenytoin, clonidine, and Ca^{2+}-channel blockers.

  - Indirectly via depletion of K^+ → Hyperpol beta cells → Inhibit Ca++ influx : diuretics.

- **Two other Rxs that antagonize insulin effects?**

  - Beta 2 agonists, Ca++ channel blockers.

- بیمار زنی است که به مدت 25 سال به دیابت تیپ 1 مبتلاست. وی روزانه 4 تزریق دریافت می کند، انسولین لیسپرو پیش از هر وعده غذایی و انسولین گلارژین در موقع خواب. او می گوید که در اواسط بعدازظهر 2 تا 3 بار در هفته احساس عصبانیت، تعریق و گیجی می کند. گلوکز خون او در هنگام چنین احساسی 50-55 میلی گرم در دسی لیتر و میزان HgbA1c وی 7.1 درصد است. کدامیک از موارد زیر در ارتباط با رژیم انسولین مناسبتر است؟

الف) توجهی نکند .HgbA1cگلایسمیک مناسبی را نشان می دهد.

ب) رژیم انسولین خود را به دوبار در روز با انسولین 70/30 تغییر یابد.

ج) افزایش دوز انسولین گلارژین

د) کاهش دوز انسولین لیسپرو در موقع نهار

ه) کاهش دوز انسولین لیسپرو در موقع صبحانه

- کدامیک از عوامل زیر می تواند بر جذب انسولین تاثیر بگذارد؟ -

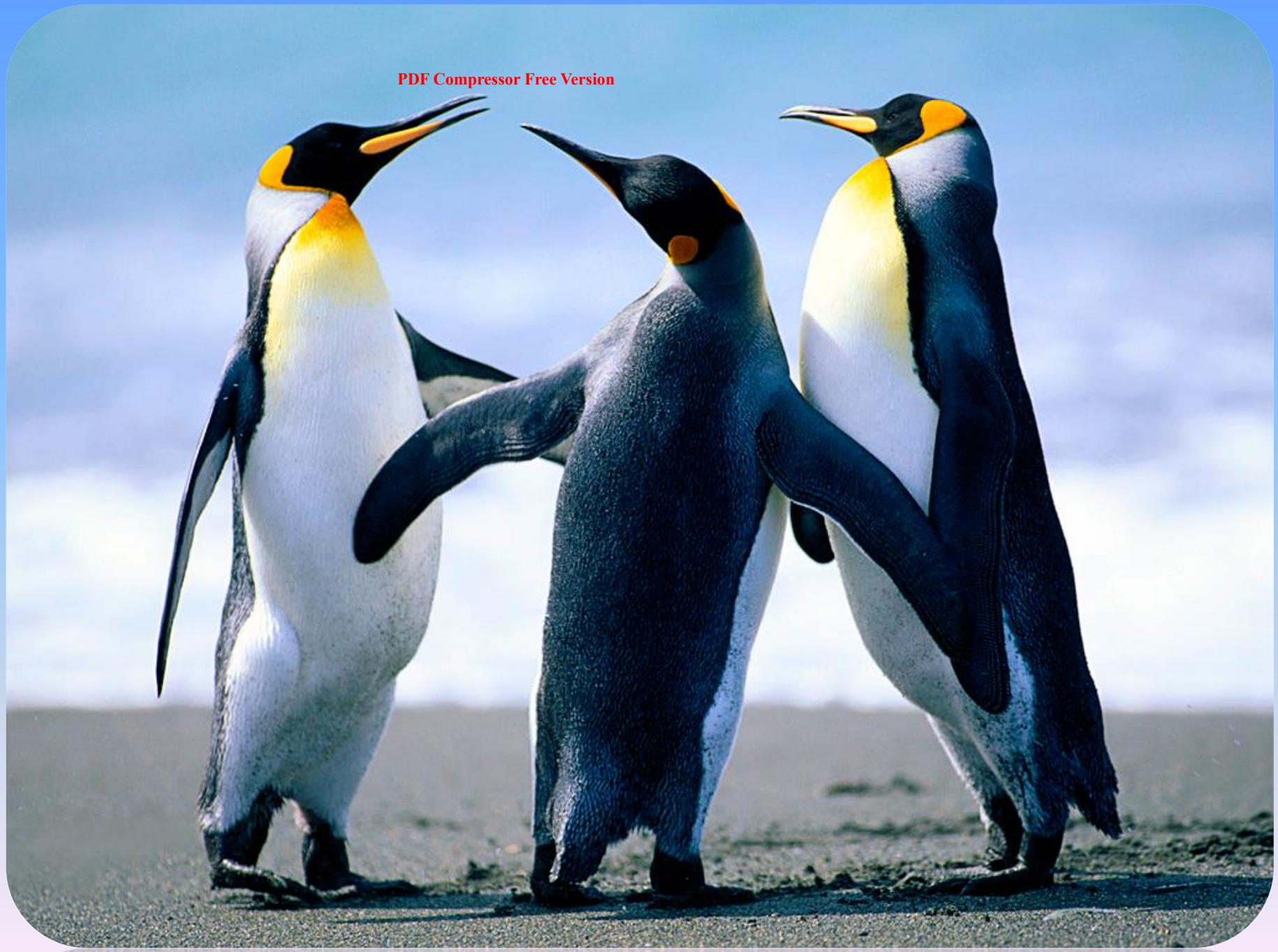
الف) ماساژ محل تزریق

ب) ورزش

ج) گرما

د) لیپوهیپوتروفی

ه) تمام موارد بالا



Oral Hypoglycemics

- **Insulin secretagogues: Sulfonylureas, meglitinides (benzoic acid derivatives), D-phenylalanine derivatives.**
- **Biguanides (metformin).**
- **Alpha-glucosidase inhibitors (Acarbose).**
- **Thiazolidinedione.s**

	%↓$HgbA_1$ C
Sulfonylureas	1.5-5
meglitinides	1.7
Amino acids derivative	0.5
Biguanides	1.5-2
Thiazolidinediones	0.6-1.5
α-Glucosidase Inhibitors	1-1.5

Sulfonylureas

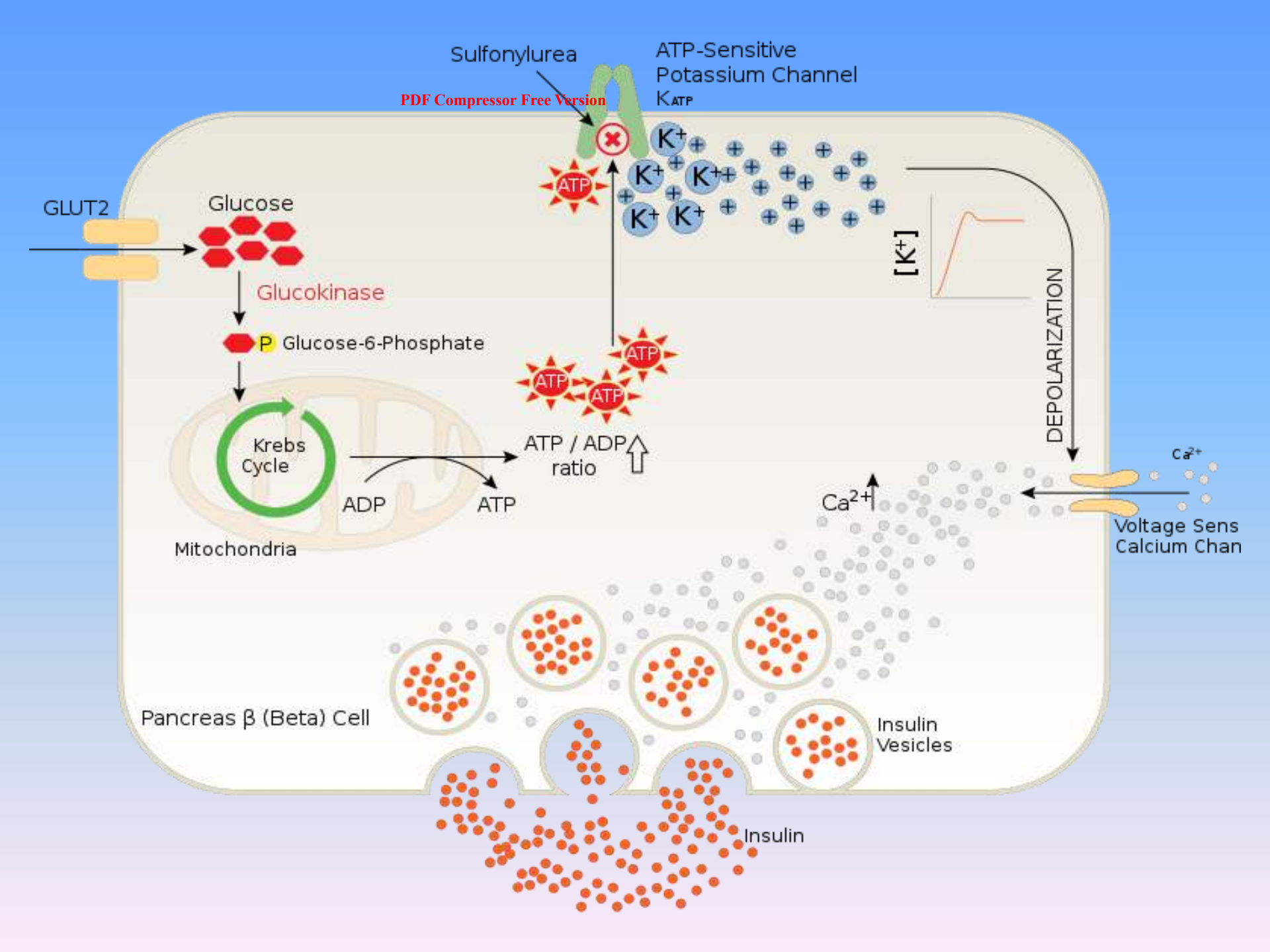
- **1st Generation:** Chlorpropamide (long lasting, 60 h; contraindicated in elderly), tolbutamide (less t ½, safest sulfonylurea in elderly).
- **2nd Generation:**

  - Glyburide (glibenclamide average maintenance dosage 5-10 mg/d, single morning, > 20 mg/d not recommended), glipizide, gliclazide, and glimepiride

  - 2nd Generation v potent (~100x>1st).
- Not effect in IDDM, absence of β cells; very weak response to sulfonylureas.
- Short-acting sulfonylureas given 30 minutes before meal to promote normalization of blood glucose; long-acting sulfonylureas may be given with meals.
- **Insulin + sulfonylureas:**

  - No evidence improvement in type 1 DM.

  - Significant improvements in metabolic control in type 2 DM; residual β-cell activity as prerequisite.


Sulfonylurea
ATP-Sensitive
Potassium Channel
KATP
PDF Compressor Free Version
GLUT2
Glucose
Glucokinase
P Glucose-6-Phosphate
Krebs
Cycle
ADP
ATP
ATP / ADP
ratio
Mitochondria
K+
ATP
[K+]
DEPOLARIZATION
Ca2+
Voltage Sens
Calcium Chan
Pancreas β (Beta) Cell
Insulin
Vesicles
Insulin

Sulfonylureas: Adverse Reactions

- **Hypoglycemia:**
  - An acute neurological emergency , a cerebrovascular accident, more common with long-acting agents, in elderly & in renal failure (more in glibenclamide & chlorpropamide & less in glipizide).
  - Sulfonamides, clofibrate, and salicylates (protein binding displacement) & ethanol → Hypoglycemia
- Hyponatraemia & water retention (potentiate ADH action); Chlorpropamide as therapeutic advantage in mild forms of central diabetes insipidus.
- Flushing (disulfiram-like); chlorpropamide.
- Agranulocytosis, aplastic and hemolytic anemias.
- **GI effects:** Nausea and vomiting, cholestatic jaundice.
- **Contraindications:** Hepatic or renal insufficiency (older preparations), type 1 DM, pregnancy. (teratogenic), lactation.
- **Glimepiride :** Greater cardiovascular benefits compared glyburide; reflex vasodilation to a subsequent ischemic episode preserved with glimepiride but reduced with glyburide.

Meglitinides; Repaglinide

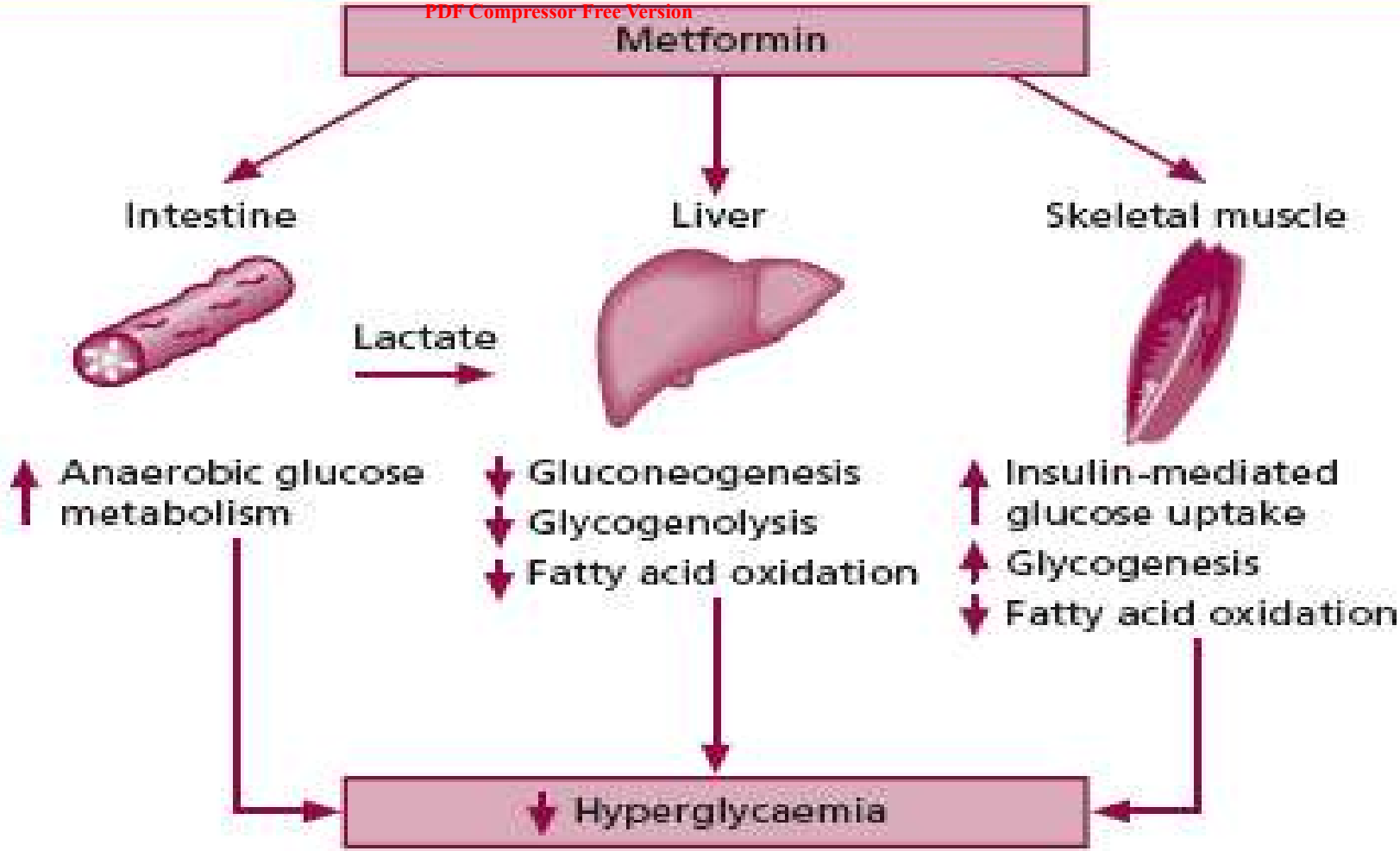
- **Fast-acting premeal therapy (t_{pmax} =1h) to limit postprandial hyperglycemia.**
- **Overlap with the sulfonylureas in their molecular sites of action; but have a weaker binding affinity and faster dissociation.**
- **As monotherapy or in combination with biguanides.**
- **No sulfur in its structure → May be used in sulfur or sulfonylurea allergy.**
- **Side effect: Hypoglycemia.**

D-phenylalanine Derivative; Nateglinide

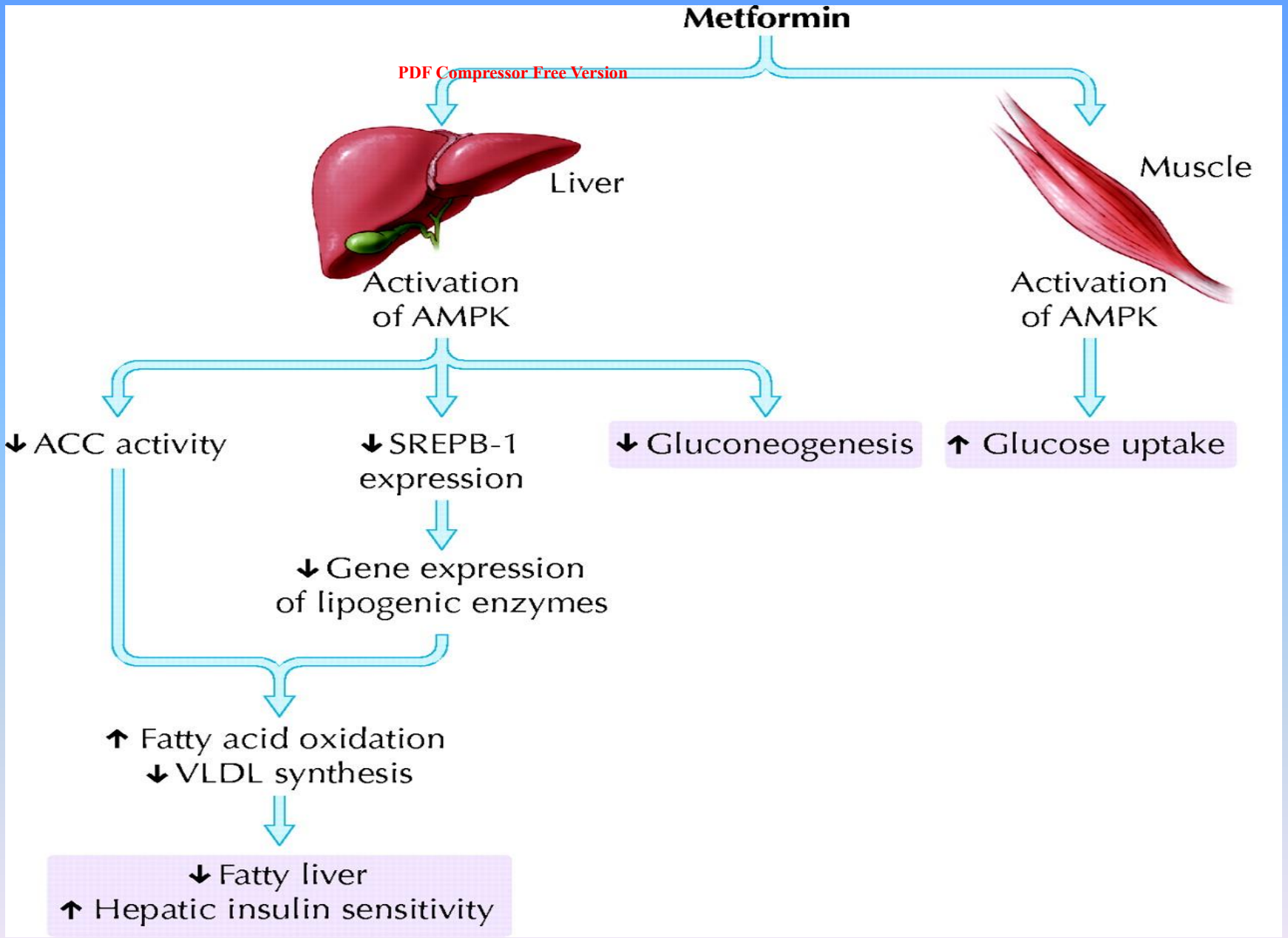
- Very rapid and transient release of insulin from ß cells through closure of the ATP-sensitive K^+ channel; (t_{pmax} >1h) .
- The lowest incidence of hypoglycemia of all the secretagogues.
- Safe in very reduced renal function but cautiously with hepatic insufficiency.
- Used in postprandial hyperglycemia & minimal effect on overnight or fasting glucose levels.

Biguanides (Metformin)

- Prescribed for ineffective insulin action, ie, insulin resistance syndrome.
- Not ↓blood sugar in normal persons after fasting, ↓blood sugar after meal (euglycemic).
- No depend on functioning pancreatic β cells.
- ↓Risk of macrovascular as well as microvascular disease; contrast to other therapies, which only modified microvascular morbidity.
- Efficacious in preventing the new onset of type 2 diabetes in middle-aged, obese persons with impaired glucose tolerance and fasting hyperglycemia; not prevent diabetes in older, leaner prediabetics.



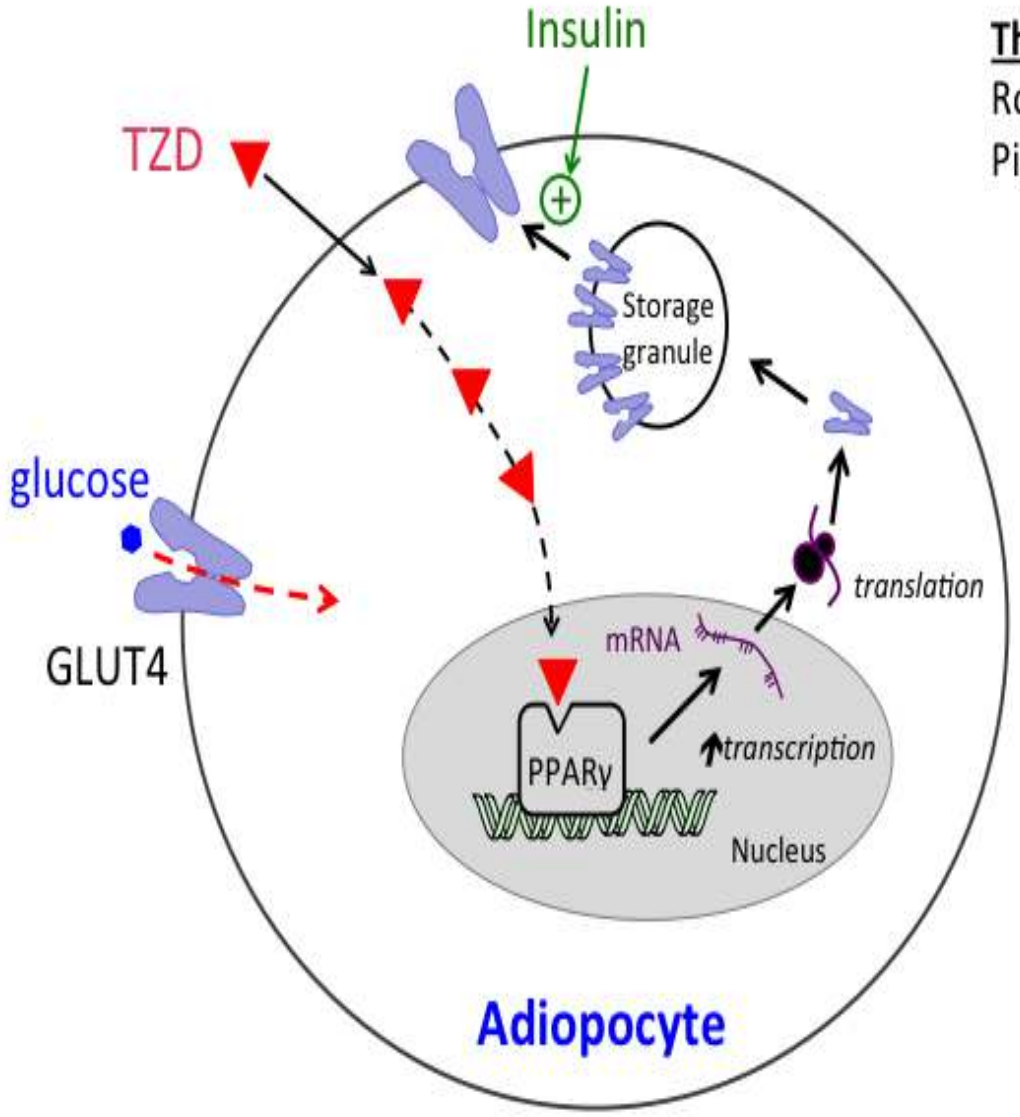
Adapted with permission from Bailey CJ, Feher MD, Therapies for Diabetes, Sherborne Gibbs, Birmingham UK, 2004



Metformin: Adverse Effects

- **Conversion to acetyl CoA, lactic acidosis production, inhibits pyruvate.**
- **Renal insufficiency or dehydration/renal hypoperfusion.**
- **The most common: GI (anorexia, nausea, vomiting, abdominal discomfort, diarrhea), up to 20% of patients, dose-related, occur at the onset of therapy & transient; minimized by increasing the dosage of the drug slowly and taking with meals.**
- **↓ Intestinal absorption of vitamin B_{12} and folate during long-term therapy.**
- **Must be stopped 24-48 h prior to procedure with IV contrast (i.e. angiogram) or use of IV contrast media for hypoxemia, dehydration, sepsis.**

Thiazolidinediones; Glitazones



Thiazolidinediones (TZDs):

Rosiglitazone - PPARγ

Pioglitazone - PPARγ > PPARα

PPARγ expression:

Adipose tissue

Skeletal muscle (↑in obesity)

Pancreatic β cells

Vascular endothelium

Macrophages

CNS

PPARα expression:

Liver

Heart

Skeletal muscle

Vascular wall

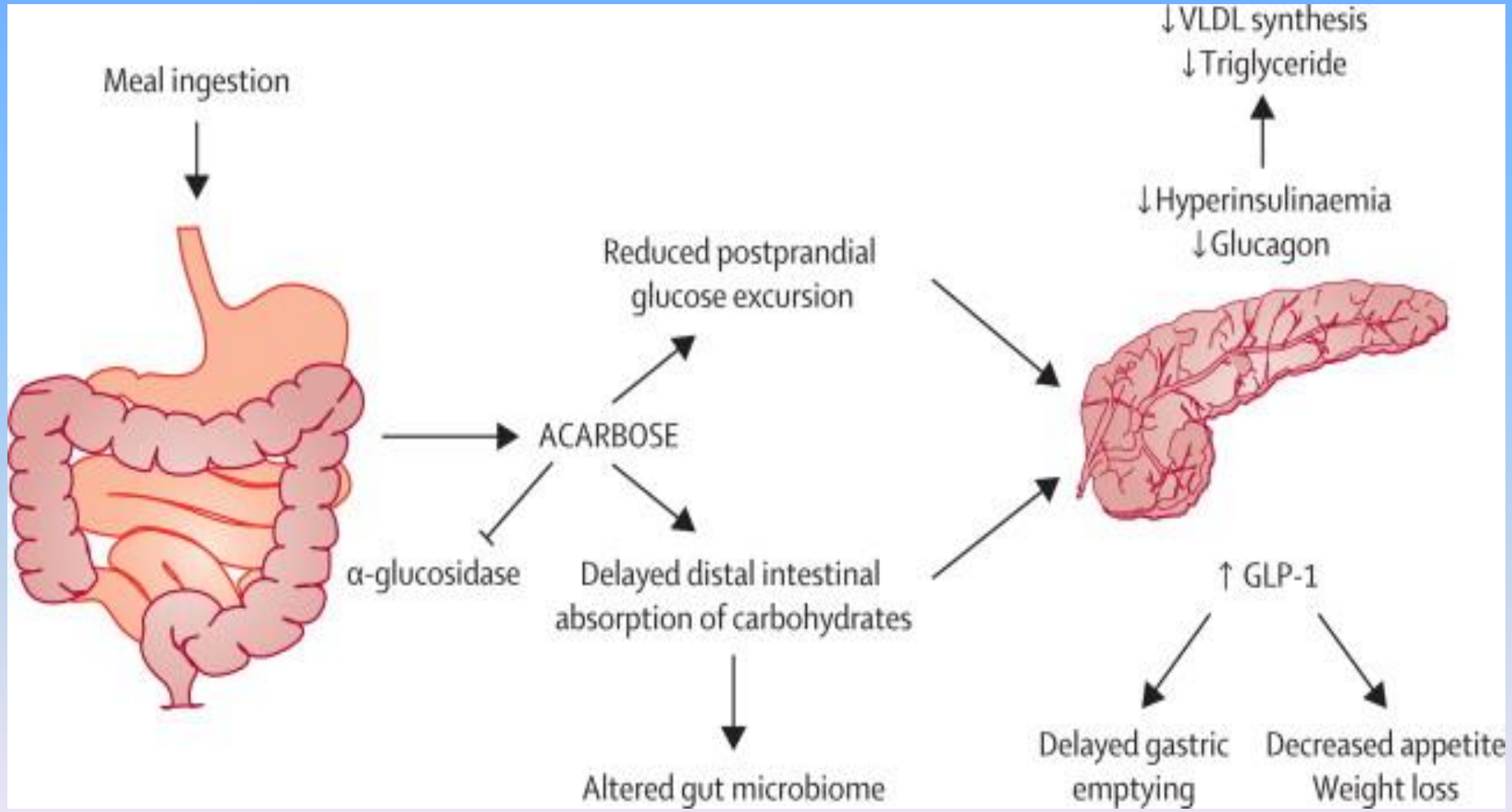
Precautions & Adverse Effects

- Fluid retention (more if combined with insulin), ↓renal sodium excretion, or direct ↑vascular permeability & weight gain.
- Hepatic toxicity; ALT > 2.5 ´ upper limit of normal.
- Withdrawal of troglitazone, higher hepatotoxicity due to tocopherol side chain.
- Concurrent diagnosis of heart failure & cardiac diastolic dysfunction.
- Hypoglycemia, anemia.
- **May increase fertility in women:**
  - Patient counseling about contraception.
  - Not be used during pregnancy.

Lyn Kinase Activators

- **Tolimidone: potentiate insulin signaling in a manner that is distinct from the glitazones.**
- **The positive results in a Phase 2a clinical study involving 130 diabetic subject.**

a-Glucosidase Inhibitors (Starch Blockers; Acarbose



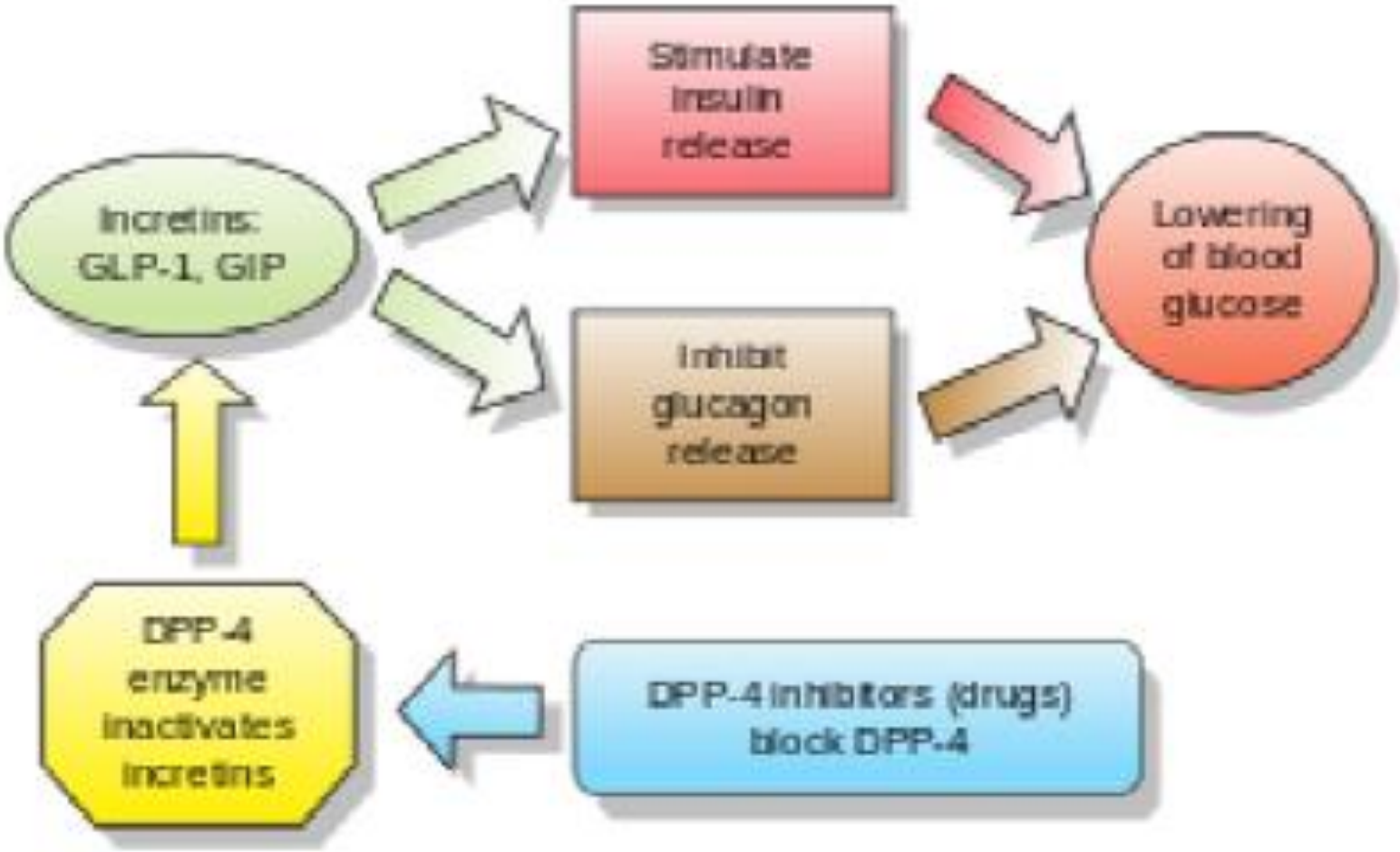
Acarbose; Adverse Effects

- **The effect of bacteria on unabsorbed carbohydrates:**

  - Abdominal cramps, diarrhea, flatulence.

  - Slowly titrating of dose (25 mg at the start of a meal for 4 to 8 weeks →↑At 4- to 8-week intervals to a maximum of 75 mg before each meal) →↓ GI side effects.
- **Weight loss; Beneficial in obese patients.**
- **Increased liver function tests.**
- **Contraindication: IBD or any intestinal condition worsened by gas and distention; in renal impairment.**
- **If insulin or an insulin secretagogue + acarbose → Hypoglycemia:**

  - Should be treated with glucose (dextrose) and not starch, or maltose sucrose, whose breakdown may be blocked.



Overview of insulin secretion

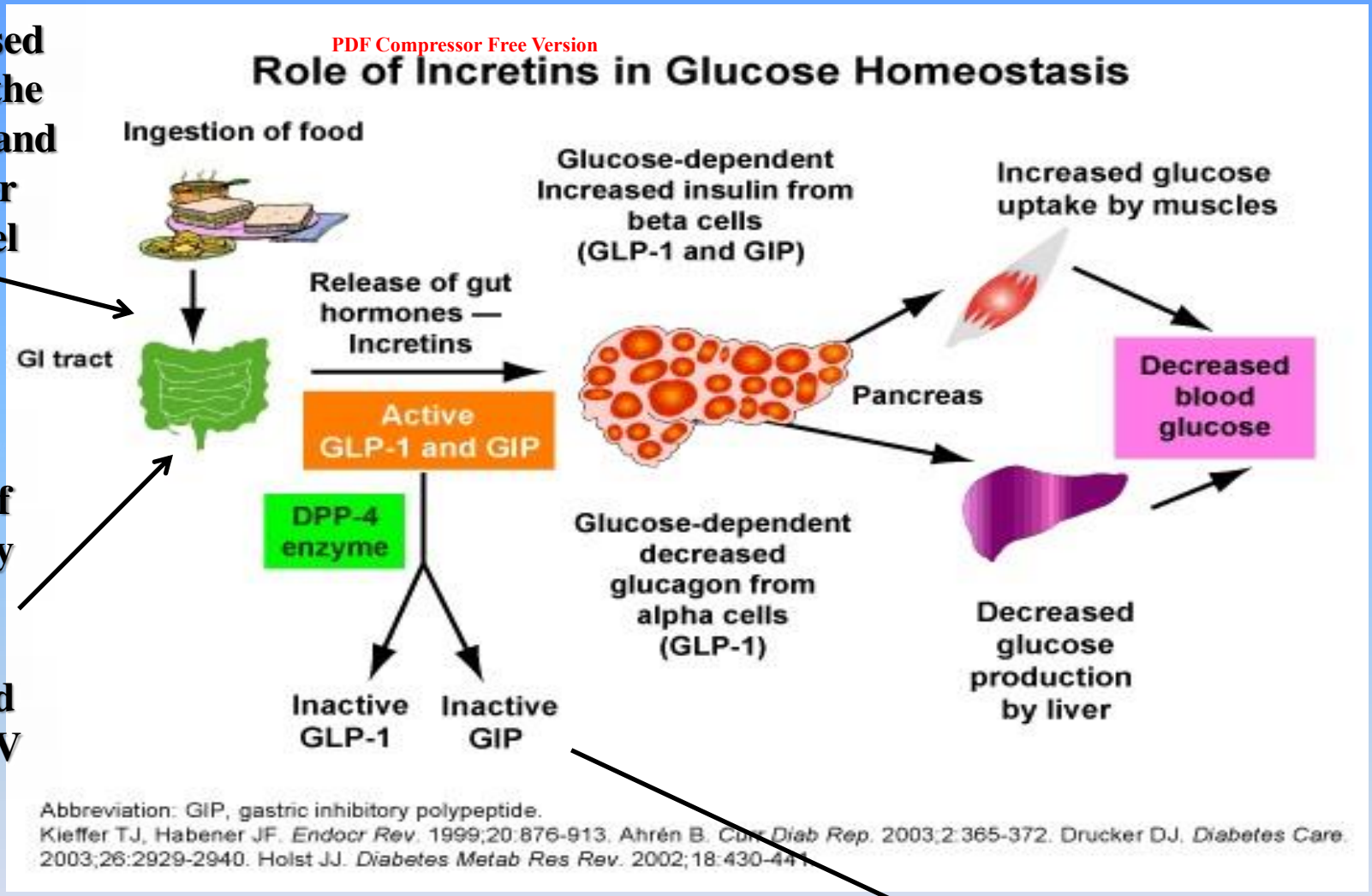
Islet Amyloid Polypeptide (IAPP, Amylin)

- Derived from islet amyloid deposits in pancreas; produced by pancreatic ß cells, packaged within ß -cell granules in a concentration 1-2% that of insulin.
- Co-secreted with insulin in a pulsatile manner and in response to physiologic secretory stimuli; 1 molecule for every 10 molecules of insulin.
- Modulate insulin release by acting as a negative feed back on insulin secretion.
- **At pharmacologic doses:** ↓Glucagon secretion, slows gastric emptying by a vagally medicated mechanism, and centrally decreases appetite.

Pramlintide

- **An injectable synthetic analog of amylin.**
- **↓Glucagon release, delays gastric emptying, CNS-mediated anorectic effects.**
- **Should be injected immediately before eating with dosage titration.**
- **Cannot be mixed with insulin.**
- **Side effects: Hypoglycemia & GI symptoms (nausea, vomiting, and anorexia).**

Released from the upper and lower bowel



Greater release of insulin by oral glucose compared with its IV

↓ glucagon secretion, slows gastric emptying & ↓appetite

Exendin-4 (Exenatide)

- **NN2211, liraglutide & exenatide.**
- **Exenatide: A synthetic analog of GLP-1 resistant to DPP-IV protease**
- **Side effects: Self-limiting nausea, hypoglycemia when used with oral insulin secretagogues.**

Sitagliptin & Vildagliptin

- **Inhibitor of dipeptidyl peptidase-4 (DPP-4) protease degrading incretin and other GLP-1-like molecules:** ↑Endogenous circulating GLP-1 levels.
- Orally once daily.

Glycosurics

- Sodium-glucose co-transporter 2 (SGLT2) inhibitors block the re-uptake of glucose in the renal tubules, promoting loss of glucose in the urine.
- Dapagliflozin
- Canagliflozin
- Empagliflozin
- **The side effects:** Mild weight loss, ketoacidosis, urinary tract infections, candidal vulvovaginitis, and hypoglycemia.

Combination Therapy In type 2 DM

- **Step 1:** Implement lifestyle change- caloric restriction, exercise, weight loss, ACE inhibitors.
- **Step 2:** Initiate therapy with one oral drug (depending on patient's body composition and degree of hyperglycemia); Lean patient (Sulfonylurea- because lean patients are insulin deficient); Obese patient (Metformin- because obese patients are insulin resistant).
- **Step 3:** Treat with two oral drugs; Sulfonylurea + Acarbose; Metformin + Acarbose.
- **Step 4:** Treat with drug + insulin bedtime replacement (no response to maximal oral therapy).
- **Step 5:** Treat with insulin alone.
- **Step 6:** Treat with insulin + Tzds.

Combination Therapy In type 1 DM

- **With pramlintide:** Leads to a significant reduction in early postprandial glucose.
- **With oral medications:**

  - No indication for combining insulin with insulin secretagogues (sulfonylureas, meglitinides, or D-phenylalanine derivatives).

  - If diets very high in starch benefit from a-glucosidase inhibitors.

  - Tzds for type 1, type 2 phenotype, or latent autoimmune diabetes mellitus of adulthood (LADA).

- بیمار خانمی 55 ساله است که از دو سال پیش به بیماری دیابت تیپ 2 مبتلا شده است. او از رژیم غذایی و برنامه ورزشی پیروی می کند.اما میزان HgbA1C او هم اکنون 8.5 درصد است. BMI بیمار 20.2 بوده و میزان کراتینین او 1.6mg/dL است. تست های عملکرد کبدی او نیز در حد طبیعی است. کدامیک از داروهای زیر مناسبترین درمان در شروع درمان به منظور کاهش HgbA1C به زیر 7 درصد است؟

الف) متفورمین-بی گوانید

ب) گلی پیزاید-سولفونیل اوره

ج) پیوگلی تازون-تیازولیدین دیون ها

د) آکاربوز-مهار کننده آلفا گلوکوزیداز

- بیمارآقایی است که به مدت 10سال به بیماری دیابت تیپ 2 مبتلا است. سایر مشکلات پزشکی او، دیس لیپیدیمی، فشار خون بالا و رتینوپاتی هستند. او انالاپریل، سیمواستاتین و متفورمین استفاده می کند. فشار خون او 70/120 میلیمتر جیوه، کلسترول LDL معادل 137 mg/dL و میزان HgbA1C او نیز 7.8 درصد است. او یک ونیم سال پیش معاینه شبکیه چشم را انجام داده است. وی از واکسن پنوموکوک استفاده نکرده و هیچ گاه تست ادراری انجام نداده است. کدامیک از استانداردهای مراقبتی زیر با رهنمودهای توصیه شده مطابقت دارد؟

الف) فشار خون

ب) معاینه چشم

ج) کلسترولLDL

د) HgbA1C

ه) واکسن پنوموکوک

و) آزمایش میکروآلبومینوریا

Thanks so much

for your attention