

Diabetes Mellitus

Chandan Shrestha, PhD

Pancreatic hormone

Cell Types	Approximate Percent of Islet Mass	Secretory Products
A cell (alpha)	20	Glucagon, proglucagon
B cell (beta)	75	Insulin, C-peptide, proinsulin, islet amyloid polypeptide (IAPP)
D cell (delta)	3–5	Somatostatin

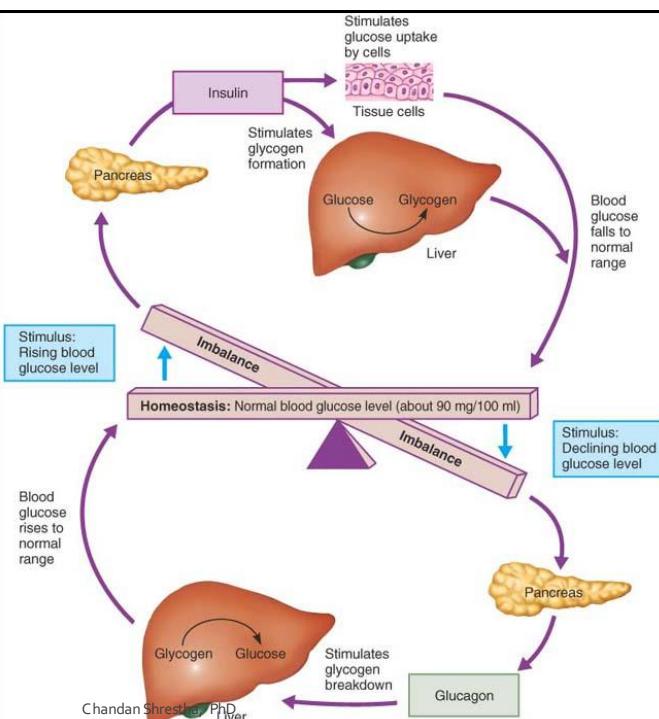
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Regulation of Blood Glucose level

When blood glucose levels are high, the pancreas releases the hypoglycaemic hormone insulin, which stimulates glucose uptake by cells and glycogen formation in the liver, so that blood glucose levels are lowered. When blood glucose levels are low, the pancreas releases the hyperglycaemic hormone glucagon, which stimulates glycogen breakdown and thereby increases the amount of blood glucose.

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Regulation of blood glucose levels by insulin and glucagon



Diabetes Mellitus

- Diabetes mellitus (DM) is a group of metabolic disorder of multiple etiology, characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both which lead to disturbance in carbohydrate, fat and protein metabolism.

Classification

- Type 1 DM
- Type 2 DM

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Type 1 Diabetes Mellitus

- Autoimmune destruction of β -cell, usually leading to absolute insulin deficiency.
- previously referred as the terms insulin-dependent diabetes, type I diabetes, or juvenile-onset diabetes .
- Type 1 diabetes accounts for only 5-10% of those with diabetes.
- Over 95% of persons with type 1 diabetes mellitus develop the disease before the age of 25, with an equal incidence in both sexes .
- An absolute requirement for insulin replacement therapy in affected patients may come and go

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Type 2 diabetes

- non insulin dependent diabetes, type II, or adult-onset.
- most common form of diabetes which accounts for about 90–95% of those with diabetes.
- heterogeneous disorder characterized by impaired insulin secretion, abnormal β -cell function, and increased resistance to insulin.
- highly associated with a positive family history, increased age, obesity, lack of exercise, and a history of GDM.

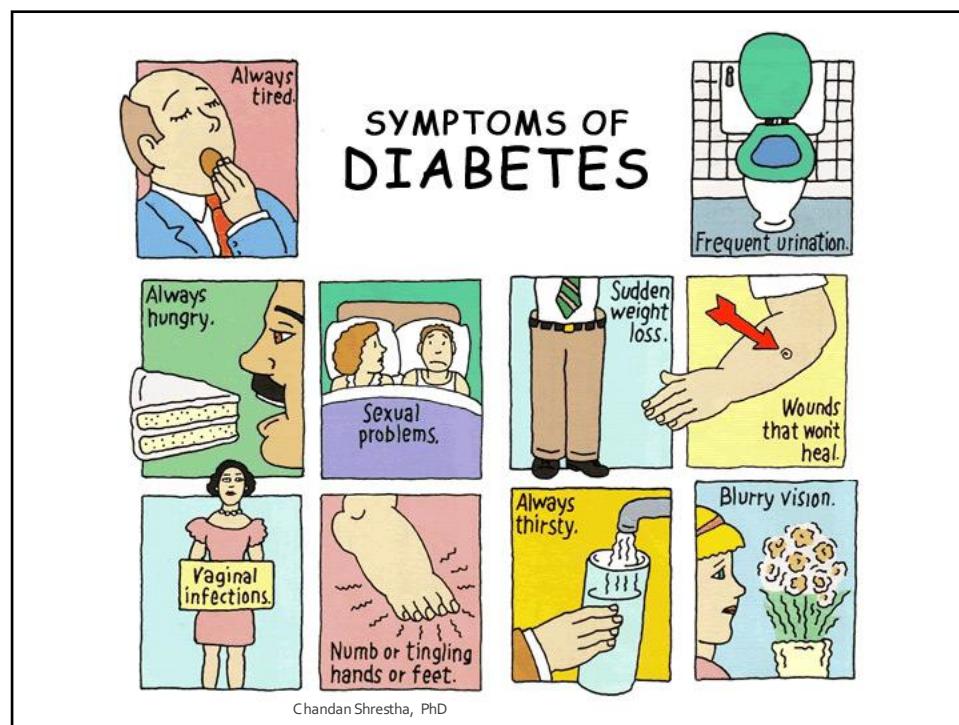
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1 Insulin resistance in peripheral tissues

LIVER
Increased production of glucose
Glucose
Decreased glucose uptake
ADIPOSE TISSUE MUSCLE

2 Inadequate insulin secretion from β cells

PANCREAS Insulin



Symptoms

- Diabetes → hyperglycemia → exceeds renal tubular ability to absorb glucose from ultrafiltrate → **glucosuria** → **polyuria** (osmotic diuresis) → (compensatory) **polydipsia**

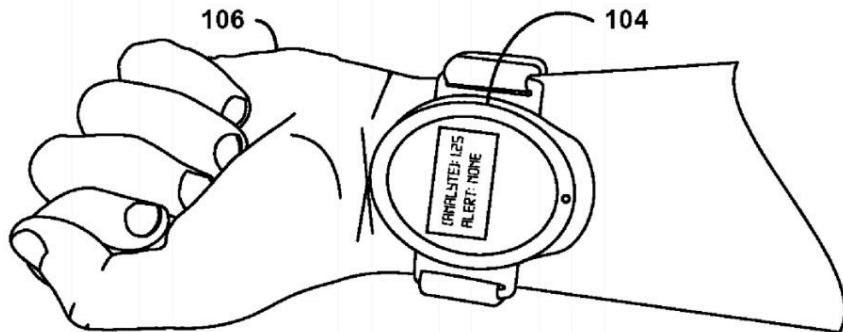
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Diagnostic Criteria

	Normo-glycemia	Pre-Diabetes	Diabetes
Fasting Plasma Glucose (FPG)	<100 mg/dl	100-125 mg/dl (Impaired Fasting Glucose)	FPG \geq 126 mg/dl
2-hour Plasma Glucose (post prandial)	<140 mg/dl	140-200 mg/dl (Impaired Glucose Tolerance)	\geq 200 mg/dl
Casual plasma glucose (random)	<120 mg/dl		\geq 200 mg/dl with symptoms

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Smart watch to take a small blood sample without the use of needles



Google's filed a patent for a watch that takes your blood without needles

Needle-free blood tests.

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Management of DM

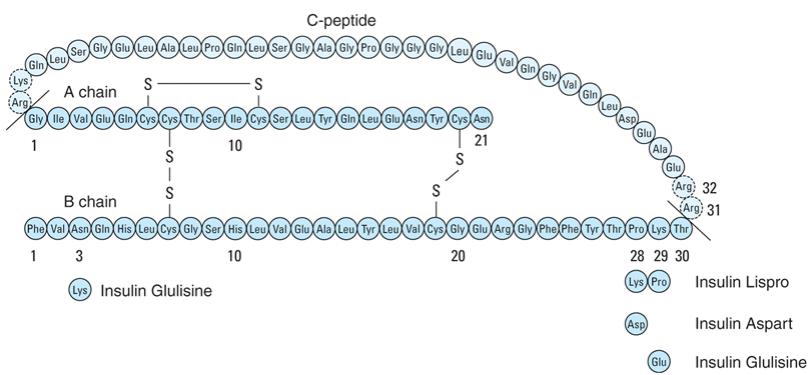
- Diet is the cornerstone of the management of diabetes, regardless of the severity of the symptoms or the type of diabetes.
- Exercise is also an important component in managing diabetes, particularly in obese individuals with NIDDM who may have a component of insulin resistance as a consequence of obesity.
- Type 1: Insulin therapy
- Type 2: OHA

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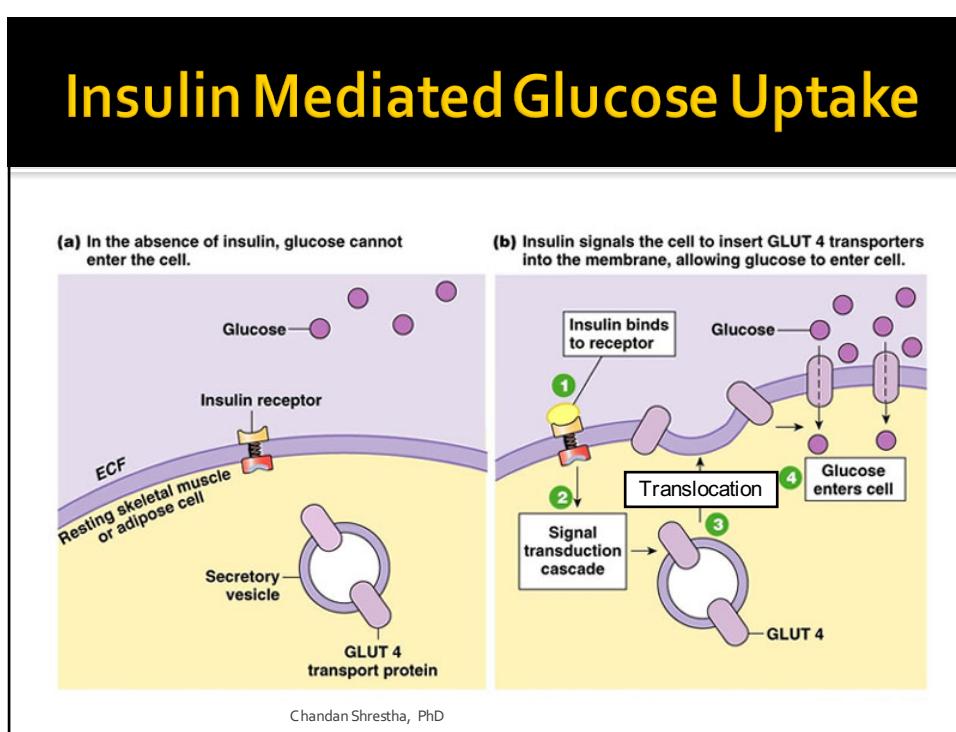
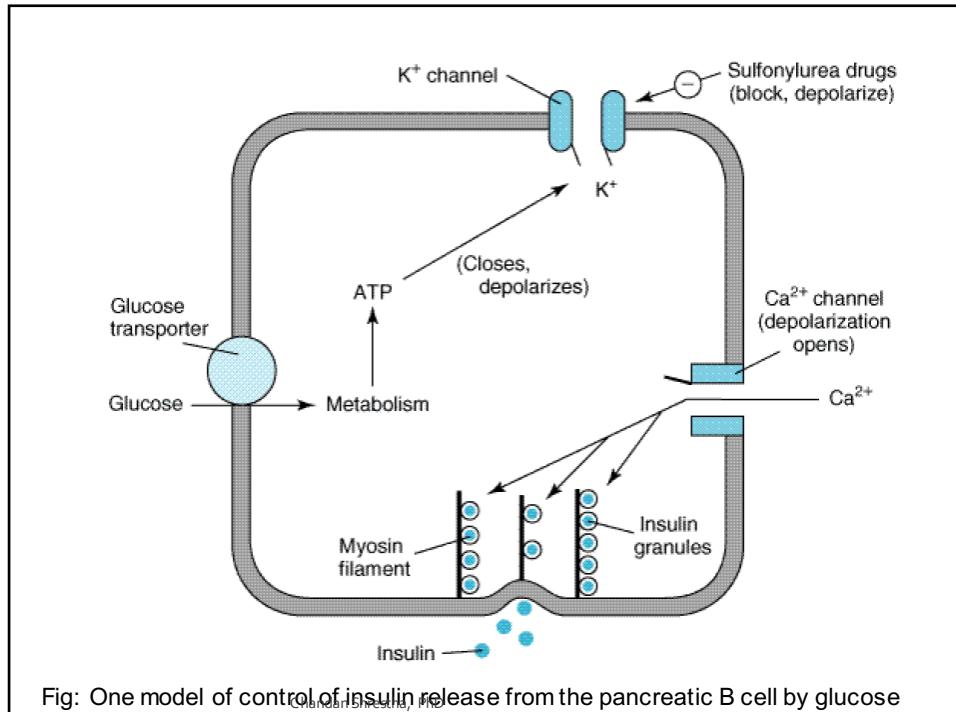
Insulin

- ✓ Insulin is a polypeptide hormone secreted by islets β cells.
- ✓ synthesized from its precursor (pro-insulin)
- ✓ Complex molecule: 51 amino acids
- ✓ Two chains of amino acids with 3 disulfide linkages
- ✓ Once insulin enters the circulation, its plasma half life is less than 4-5 minutes.
- ✓ When given orally, it is degraded in GIT. It therefore is generally administered by subcutaneous injection.

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ACTION of Insulin				
Types of Metabolism	Liver cells	Fat cells	Muscle	
Carbohydrate	↓Gluconeogenesis ↓Glycogenolysis ↑Glycolysis ↑Glycogenesis	↑Glucose uptake ↑Glycerol synthesis	↑Glucose uptake ↑Glycolysis ↓Glycogenolysis	
Fat	↑Lipogenesis ↓Lipolysis	↑Synthesis of triglycerides ↑Fatty acid synthesis ↓Lipolysis		-
Protein	↓Protein breakdown	-	↑Amino acid uptake ↑Protein synthesis	

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Insulin Preparation

Type	Appearance	Onset (hr)	Peak (hr)	Duration (hr)	Can be mixed with
<i>Rapid acting</i>					
Insulin lispro	Clear	0.2–0.4	1–2	3–5	Regular, NPH
Insulin aspart	Clear	0.2–0.4	1–1.5	3–5	Regular, NPH
Insulin glulisine	Clear	0.3–0.5	1–2	2–4	Regular, NPH
<i>Short acting</i>					
Regular (soluble) insulin	Clear	0.5–1	2–4	6–8	All preparations (except insulin glargine)
<i>Intermediate acting</i>					
Insulin zinc suspension or Lente*	Cloudy	1–2	8–10	20–24	Regular
Neutral protamine hagedorn (NPH) or isophane insulin	Cloudy	1–2	8–10	20–24	Regular
<i>Long acting</i>					
Protamine zinc insulin (PZI)	Cloudy	4–6	14–20	24–36	Regular
Insulin glargine	Clear	2–4	5–12	24	None

* Lente insulin is a 7:3 mixture of ultralente (crystalline) and semilente (amorphous) insulin zinc suspension. Ultralente (long-acting) and semilente (short-acting) are not separately marketed in India.

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Type of Insulin	Brand Name	Generic Name	Onset	Peak	Duration
Intermediate-acting	Humulin N	NPH (N)	1 to 3 hours	8 hours	12 to 16 hours
	Novolin N				
Long-acting	Levemir	Insulin detemir	1 hour	Peakless	20 to 26 hours
	Lantus	Insulin glargine			
Pre-mixed NPH (intermediate-acting) and regular (short-acting)	Humulin 70/30	70% NPH and 30% regular	30 to 60 minutes	Varies	10 to 16 hours
	Novolin 70/30				
Pre-mixed insulin lispro protamine suspension (intermediate-acting) and insulin lispro (rapid-acting)	Humalog Mix 75/25	75% insulin lispro protamine and 25% insulin lispro	10 to 15 minutes	Varies	10 to 16 hours
	Humalog Mix 50/50	50% insulin lispro protamine and 50% insulin lispro			
Pre-mixed insulin aspart protamine suspension (intermediate-acting) and insulin aspart (rapid-acting)	NovoLog Mix 70/30	70% insulin aspart protamine and 30% insulin aspart	5 to 15 minutes	Varies	10 to 16 hours

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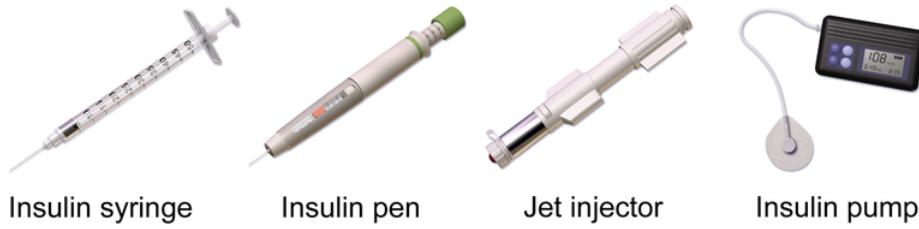
Insulin Inhaled	Brand/generic name	Onset in minutes	Peak	Duration	Administer
Ultra-Rapid insulin	Afrezza/ rDNA Human powder	12 -14 min.	≈1 hour	180 min.	Beginning of meal
Insulin (SubQ)	Brand/generic name	Onset in minutes	Peak effect	Duration	Administer
Rapid-acting (insulin analogs)	Novolog/insulin aspart	12 - 18 min.	1-3 hours	2 - 5 hours	5-10 min. before meal
	Humalog/ insulin lispro	15 - 30 min.	.5 - 2.5 hours	2 - 4 hours	<15 min. before meal
	Apidra/insulin glulisine	12 - 30 min.	1.6 - 2.8 hours	3 - 4 hours	15 min. before meal
Short-acting	• Humulin R/ regular insulin • Novolin R/ regular insulin	30 min.	2.5 - 5 hours	4 - 12 hours	30 min. before meal
Intermediate-acting	• Humulin N/insulin NPH • Novolin N/insulin NPH	1-3 hours	8 hours	12 to 16 hours	
	• Levemir/insulin detemir	3-4 hours	3-9 hours	5.7-24 Hrs	
Long-acting (insulin analogs)	• Lantus/insulin glargin	3-4 hours	No peak	≈ 24 Hrs	
Pre-mixed Insulins	Brand/generic name	Onset in minutes	Peak	Duration	Administer
	Novolin® 70/30 - Humulin® 70/30	30-60 min	2-12 hours	18 - 24 hours	30 min. between doses 30 min. before meals
	Novolog® Mix 70/30	10 - 20 min	1-4 hours	18 - 24 hours	10-20 min. between doses and before meals
	Humalog® Mix 75/25				

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Insulin Dispensing Methods

- Vial + syringe
- Pen
- Prefilled syringes
- Insulin pump

Insulin Delivery Devices



Insulin syringe

Insulin pen

Jet injector

Insulin pump

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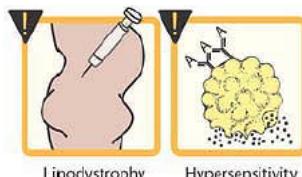
Therapeutic Uses of Insulin

- Type I diabetes
- Diabetic ketoacidosis
- Type II diabetes when pregnant
- Type II diabetes under stress
- Type II diabetes poorly controlled by diet and oral agents

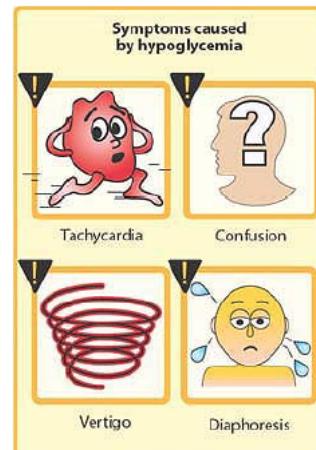
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Adverse effect

- hypoglycemia
- weight gain
- lipodystrophy (less common with human insulin)
- allergic reactions
- Insulin antibody Formation



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OHA (Oral Hypoglycemic Agent)

- These agents are useful in the treatment of patients who have Type 2 diabetes but who cannot be managed by diet alone.
- Patients with long-standing disease may require a combination of hypoglycemic drugs with or without insulin to control their hyperglycemia.

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OHA

- **Sulphonylureas**

First generation: Tobutamide, Chlorpropamide

Second generation: Glibenclamide (Glyburide), Glipizide, gliclazide, Glimepiride

- **Biguanides:** Metformin, Phenformin

- **Meglitinide analogues:** Repaglinide, Nateglinide

- **Thiazolidinediones:** Rosiglitazone, Pioglitazone

- **α -glucosidase Inhibitors:** Voglibose, Acarbose, Miglitol

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Newer Approaches

1. Incretin Mimetic: Exenatide

2. DPP4 Inhibitor: Sitagliptin

3. Synthetic Amylin Analogue: Pramlintide

4. SGLT 2 Inhibitor: Canagliflozin, Empagliflozin and Dapagliflozin

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Sulphonylureas (Glipizide, Glimepiride, Gliclazide)

Mechanism of action

1. Stimulate insulin secretion from β cell of pancreas.
- SUs bind to the SU receptor (SUR1), found on the surface of pancreatic β cells.
- This leads to a closure of voltage-dependent potassium adenosine triphosphate (K_{ATP}) channels, facilitating cell membrane depolarization, calcium entry into the cell, and insulin secretion.
2. Reduction in hepatic glucose production; and
3. Increase in peripheral insulin sensitivity.

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Sulphonylureas

Adverse effects:

Hypoglycemia, hypersensitivity, weight gain

Contraindications

Sulfa allergy

Early and late pregnancies

Hepatic and renal impairment (delay excretion of drug and can cause hypoglycemia)

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Drugs	Tablet size	Daily dose
Glipizide	5 and 10 mg	5-20 mg
Gliclazide	40 and 80 mg	40-240 mg
Glimepiride	1, 2 and 4 mg	1-6 mg

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Meglitinides: Replaglinide, Nateglinide

- Exert effects in a manner similar to SUs, by binding to the SUR of ATP sensitive potassium channels, thereby inducing depolarization of the β -cells and release of insulin.
- They have a rapid onset and a short duration of action
- Adverse effects include hypoglycemia and weight gain (comparatively lower than that with SU)

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Biguanides: Metformin

- Insulin sensitizer does not promotes insulin secretion.

MOA

- Biguanides sensitize the liver to insulin, which decreases hepatic glucose production by unknown mechanism
- Increases glucose uptake through the glucose transport system most likely in the muscle
- Decreases glucose absorption from the GI tract
- When given as monotherapy: no weight gain, no hypoglycemia.

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Metformin

Adverse effects

- GI effect: Anorexia, nausea, metallic taste, diarrhea, abdominal pain. (To minimize GI symptoms: take with meals)
- **Lactic acidosis (MALA: Metformin Associated Lactic acidosis)**
- contraindicated in patients with renal and hepatic disease, respiratory insufficiency, any hypoxic condition, severe infection, and alcohol abuse.

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Thiazolidinediones (TZD) or Glitazone: Rosiglitazone, Pioglitazone

- Insulin sensitizer does not promotes insulin secretion

MOA

- TZDs are ligands for a nuclear receptor known as peroxisome-proliferator-activated receptors (PPARs- γ), which are most highly expressed in adipocytes.
- When activated, the receptor binds with response elements on DNA, altering transcription of a variety of genes that regulate carbohydrate and lipid metabolism; resulting in increased insulin sensitivity in adipose tissue, skeletal muscle and liver.

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Thiazolidinediones (TZD) or Glitazone: Rosiglitazone, Pioglitazone

adverse events:

- *Most common* edema and fluid retention (weight gain).
- URT infection (rosiglitazone)
- Headache, Anemia
- Food and Drug Administration recommends periodic measurement of hepatic function
- rosiglitazone was associated with an increased risk of myocardial infarction and death from cardiovascular causes
- Women taking oral contraceptives and TZDs may become pregnant, because the latter have been shown to reduce plasma concentrations of the estrogen-containing contraceptives

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α -glucosidase inhibitors (Voglibose, Acarbose, Miglitol)

- MOA is unique, and this is the sole drug class not targeted at a specific pathophysiological defect of type 2 DM.
- inhibiting the intestinal enzyme (α -glucosidase) that cleaves polysaccharides into monosaccharides.
- AGIs delay intestinal carbohydrate absorption and limit the postprandial hyperglycaemia.
- The drug does not cause malabsorption.

adverse effects

- GI side effects (including bloating, abdominal discomfort, diarrhea, and flatulence)

OHA (Based on MOA)

- Drugs that primarily stimulates insulin secretion – Sulphonylureas, Meglitinides
- Drugs that alter insulin action – Biguanides, Thiazolidinedione
- Drugs that principally affect absorption of glucose – alpha glycosidase inhibitors

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Newer Approaches

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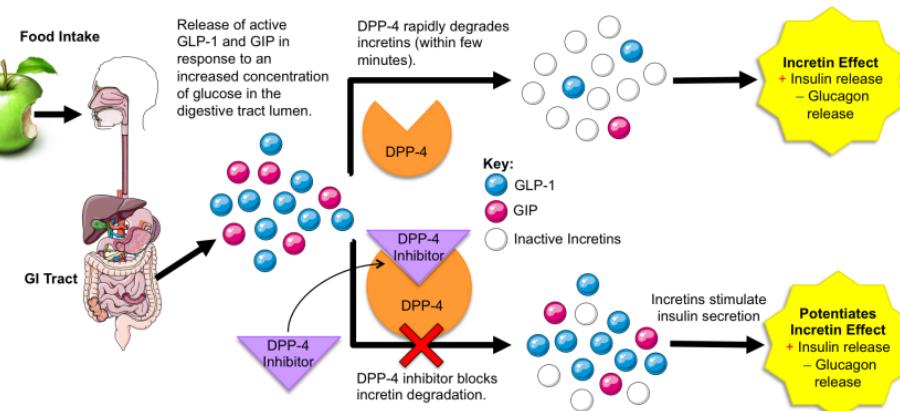
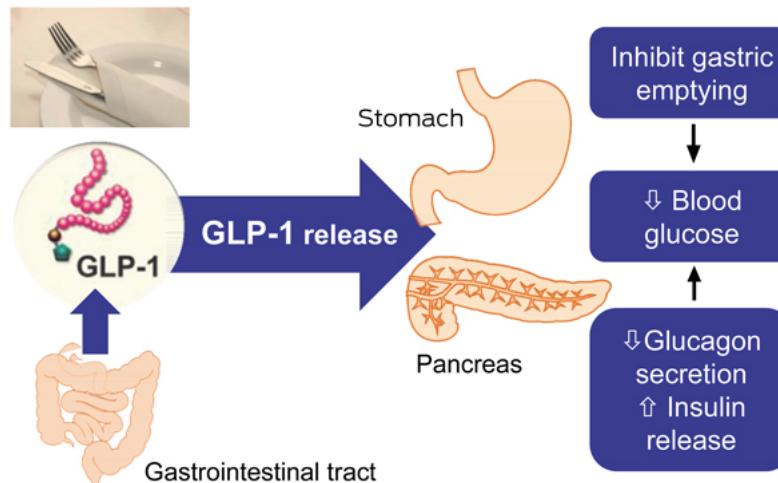
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Oral glucose results in a higher secretion of insulin than occurs when an equal load of glucose is given intravenously. This effect is referred to as the incretin effect. It demonstrates the important role of the gastrointestinal Hormones notably GLP-1 (Glucagon like peptide-1) and gastric inhibitory polypeptide (GIP) in the digestion and absorption of nutrients, including glucose.

Exenatide is an incretin mimetic with a polypeptide sequence about 50-percent homologous to GLP-1. Exenatide not only improves glucose-dependent insulin secretion but also slows gastric emptying time, decreases food intake, decreases postprandial glucagon secretion, and promotes β -cell proliferation. Consequently, weight gain and postprandial hyperglycemia are reduced, and HbA1c levels decline. Being a polypeptide, exenatide must be administered subcutaneously.

Sitagliptin inhibits the enzyme DPP-IV, which is responsible for the inactivation of incretin hormones (GLP-1).

Mechanism of Action



Synthetic Amylin Analogue

Pramlintide

This synthetic amylin (a polypeptide produced by pancreatic β cells which reduces glucagon secretion from α cells and delays gastric emptying) analogue attenuates postprandial hyperglycaemia when injected s.c. just before a meal, and exerts a centrally mediated anorectic action.

Adverse effects are mainly gastrointestinal and consist of nausea, anorexia, and vomiting.

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SGLT 2 Inhibitor

- These are the membrane transporters that reabsorb glucose back into the blood stream.
- 2 Types: SGLT1 and SGLT2
- SGLT1 is a high affinity, low capacity transporter requiring 1 glucose and 2 sodium molecules; responsible for 10% of glucose reabsorption.
- SGLT2 is a low-affinity, high capacity glucose transporter requiring 1 glucose and 1 sodium molecules; responsible for 90% of glucose reabsorption in our bodies.
- SGLT2 inhibitor act by blocking the reabsorption of glucose by the kidney, thus increasing glucose excretion through the urine, and ultimately lowering blood glucose levels.

