Insulin and Oral Hypoglycemic Drugs

Introduction

Pancreas produces:

1. Insulin by β cells
2. Glucagon by α cells
3. Somatostatin by δ cells

- Lack of insulin causes sever hyperglycemia >>> if not treated >>>> causes retinopathy, nephropathy, neuropathy and cardiovascular compilations.

Introduction

- 180 million people worldwide are affected with diabetes.

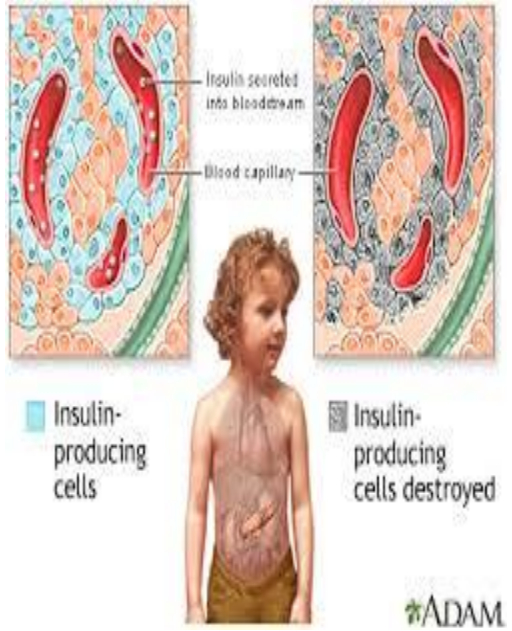
- Diabetes is NOT a single disease, it is a group of heterogenous syndromes that cause elevation in glucose blood level and insufficient insulin secretion.

- **4 clinical classifications of diabetes:**

1) Type 1: insulin dependant
2) Type 2: NON-insulin dependant
3) Gestational diabetes (during pregnancy>> affects fetus)
4) Diabetes due to other factor (genetics or medication induced).

Type 1 diabetes

- Most common affects individuals in puberty or early adulthood.
- Absolute deficiency of insulin caused by massive β-cell necrosis.
- Autoimmune mediated process directed against β-cell and it may be due to virus invasion or chemical toxins.
- **Symptoms:** Polydipsia, polyuria and weight loss
- Life threatening Ketoacidosis.
- Requires exogenous insulin (important) to control hyperglycemia and ketoacidosis and to maintain the accepted level of glyosylated hemoglobin (HbA1c) to avoid the long term complications.
- Can neither maintain normal insulin secretion level nor respond to variations in the circulating glucose and amino acid.



Type 2 diabetes

- Most diabetes are type 2
- Is influenced by genetic factors, aging, obesity and peripheral insulin resistance.
- Milder metabolic alterations than type 1.
- **No** ketoacidosis.
- The pancreas retains some β-cell function, but variable insulin secretion is insufficient to maintain glucose homeostasis.
- The β-cell mass may become gradually reduced in Type 2 diabetes.
- Lack of sensitivity of target organs to insulin >>> The major cause of type 2 diabetes.
- **Treatment:** to prevent the long time compilation.
- As the disease progress, β-cell function declines and insulin therapy is often required to achieve the satisfactory serum glucose levels.

Type 2 diabetes

TYPE 2 DIABETES

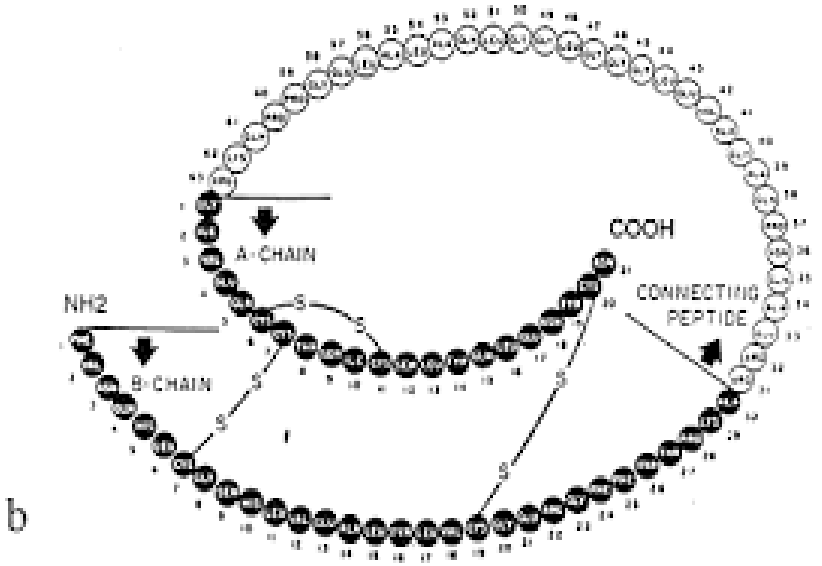
- Sedentary Lifestyle
- Familial Tendency
- Average Age 50 Years
- Hx of ↑ BP
- Fatigue ↓ Energy
- Obese
- Recurrent Infections
- Polyuria
- Polydipsia
- FBS > 126 mg/dl

Insulin and Its Analogs

Insulin

- Is a polypeptide hormone >>> it is degraded in the GIT if taken orally >>>> administered by subcutaneous injection.
- It is synthesized as a precursor (pro-insulin) that undergoes proteolytic cleavage to form insulin and C peptide, both of which are secreted by the β cells of the pancreas.
- Measurement of circulating C peptide provides a better index of insulin levels!!!! (WHY?!)
- **Insulin secretion is regulated by:**

1) Blood glucose (The most important)
2) Certain amino acids
3) Gastro intestinal hormones
4) Autonomic mediators



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Insulin and Its Analogs

- Glucose is taken into the pancreas >>> Glucose is posphoralated by glucokinase >> ATP production >>>> inhibits K+ influx >> depolarization >> Increased intracellular Ca++ secretion >>> Insulin secretion.

EFFECTS OF INSULIN

CARBOHYDRATES

↑ GLUCOSE UPTAKE

↑ GLYCOGEN SYNTHESIS(↑ STORAGE)

↓ GLUCONEOGENEIS(LIVER)

↑ GLYCOLYSIS (MUSCLE)

↑ CONVERSION OF CARBOHYDRATE TO FAT (LIPOGENESIS)

FAT

↓ LIPOLYSIS

PROTEIN

↑ AMINO ACID UPTAKE (PROTEIN SYTHESIS)

Insulin and Its Analogs

- Insulin preparations vary primarily in their times of onset and durations of activity. (WHY?!) due to differences in the amino acid sequences of the polypeptides and the type of formulation.

- For example, three such insulins (lispro, aspart, and glulisine) have a faster onset and shorter duration of action than regular insulin (Ultra short Ultra rapid), because they do not aggregate or form complexes. On the other hand, glargine and detemir are long-acting insulins and show prolonged, flat levels of the hormone following injection.

Insulin and Its Analogs

Adverse reactions to insulin

- Hypoglycemia is the most serious and common adverse reaction to an overdose of insulin.
- Weight gain
- Lipodystrophy (less common with human insulin)
- Allergic reactions, and local injection site reactions.

Types of Insulins

1) Rapid-acting and short-acting insulin preparations

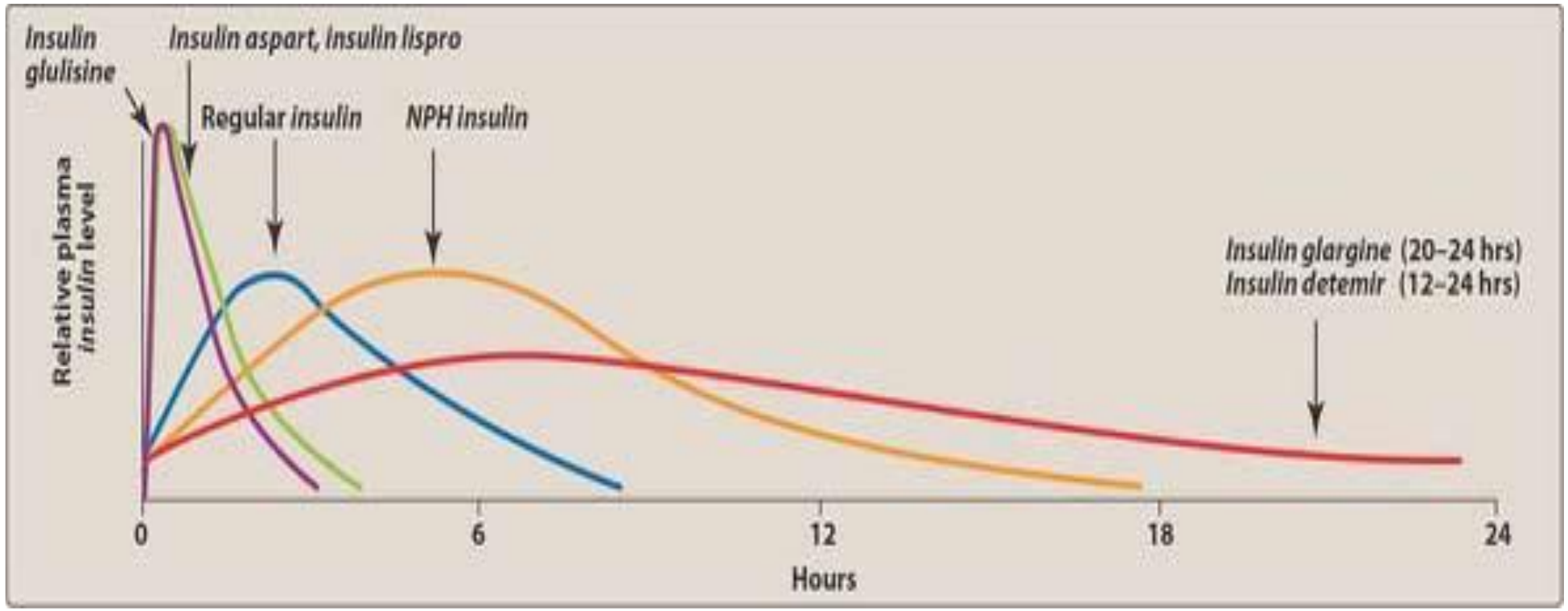
- Four insulin preparations fall into this category:

1. Regular insulin (soluble >> can be given intravenously in emergencies)
2. Insulin lispro
3. Insulin aspart
4. Insulin glulisine

more rapid absorption after SC injection than is seen with regular insulin; as a consequence, insulin lispro acts more rapidly.

- Rapidly lowers blood glucose.
- Pregnancy category B.
- They are administered to mimic the prandial (mealtime) release of insulin, and they are usually not used alone but, rather, along with a longer-acting insulin to assure proper glucose control.
- Usually administrated immediately before or following the meal.

Types of Insulins



Types of Insulins

2) Intermediate-acting insulin

- Neutral protamine Hagedorn (NPH) insulin = insulin isophane.
- Is a suspension >>>> should only be given subcutaneously (never intravenously)
- Neutral pH with a positively charged polypeptide, protamine >>> forming a less-soluble complex >>>> delayed absorption of the insulin >>>> Its duration of action is intermediate.

Types of Insulins

2) Intermediate-acting insulin

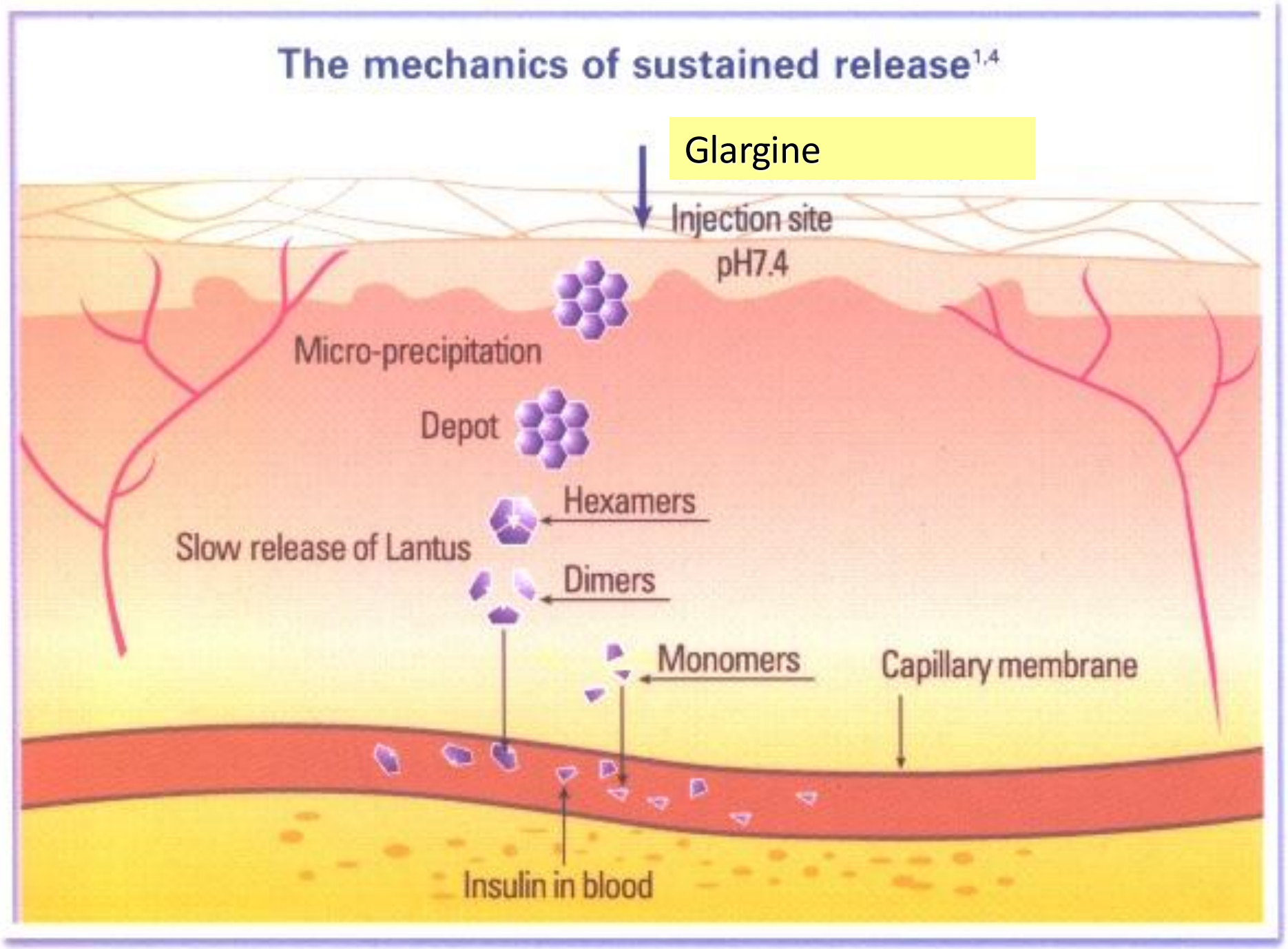
- Is useful in treating all forms of diabetes except diabetic ketoacidosis or emergency hyperglycemia (WHY?!)
- Is usually given along with rapid- or short-acting insulin for mealtime control.
- A similar compound called neutral protamine lispro (NPL) insulin, has been prepared that is used only in combination with insulin lispro.
- Various premixed combinations of human insulins, such as 70-percent NPH insulin plus 30-percent regular insulin, 50 percent of each of these, or 75 percent NPL insulin plus 25 percent insulin lispro.

Types of Insulins

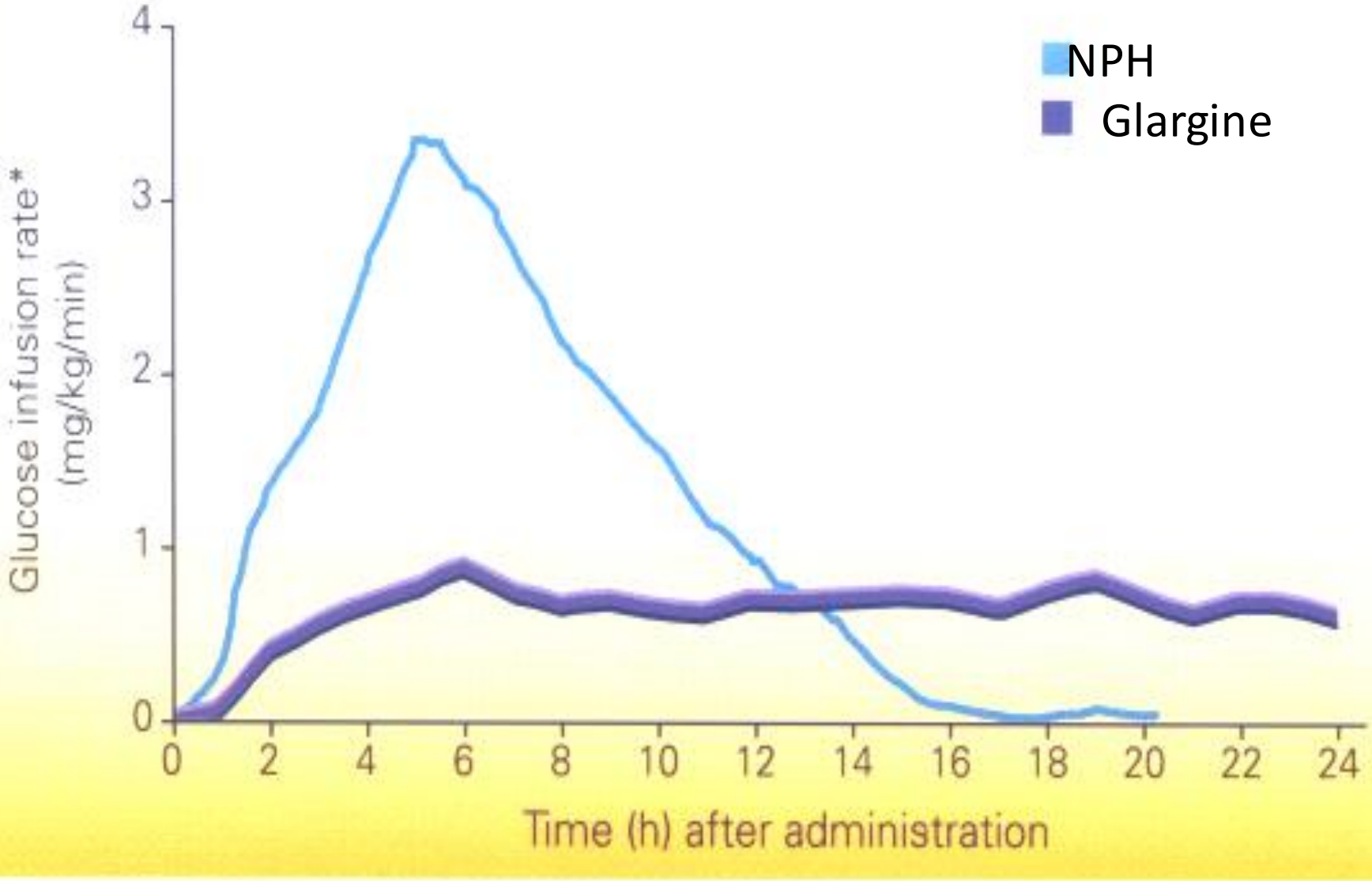
3) Long-acting insulin preparations

Insulin glargine

- The isoelectric point of insulin glargine is lower than that of human insulin, leading to precipitation at the injection site, thereby extending its action.
- It is slower in onset than NPH insulin
- Prolonged hypoglycemic
- It has no peak. (flat)
- It must be given subcutaneously.


The mechanics of sustained release[1,4]
Glargine
Injection site
pH7.4
Micro-precipitation
Depot
Hexamers
Slow release of Lantus
Dimers
Monomers
Capillary membrane
Insulin in blood

Profile of Insulin Glargine vs NPH



Types of Insulins

3) Long-acting insulin preparations

Insulin detemir

- Insulin detemir has a fatty-acid side chain >>>> enhances association to albumin.
- Slow dissociation from albumin results in long-acting properties similar to those of insulin glargine.

Synthetic Amylin Analog

Pramlintide

- Is a synthetic amylin analog **(WHAT is Amylin??!)**

- Indicated as an adjunct to **mealtime** insulin therapy in Type 1 or 2 diabetes.

1. Delays gastric emptying
2. Decreases postprandial glucagon secretion

- Is administered by subcutaneous injection
- Should be injected immediately prior to meals. **(WHY?!)**

Synthetic Amylin Analog

Pramlintide

- When pramlintide is initiated, the dose of rapid- or short-acting insulin should be decreased by 50% prior to meals **(WHY?!)** to avoid a risk of severe hypoglycemia.

- Adverse effects are **mainly gastrointestinal** and consist of nausea, anorexia, and vomiting.
- **Should not be given to patients with:**

1. Diabetic gastroparesis (delayed stomach emptying)
2. History of hypoglycemic unawareness.

Oral Agents: Insulin Secretagogues

Sulfonylureas

- Promote insulin release from the β cells of the pancreas.

- Mechanisms of action:

1) stimulation of insulin release from the β cells by blocking the ATP-sensitive K+ channels, resulting in depolarization and Ca2+ influx >>> may cause hypoglycemia
2) Reduction in hepatic glucose production
3) Increase in peripheral insulin sensitivity.

Oral Agents: Insulin Secretagogues

Sulfonylureas

- **First generation:** tolbutamide (shortest action)

2nd generation derivatives are: (longer duration of action)

1. Glyburide (is reasonably safe alternative to insulin therapy for diabetes in pregnancy)
2. Glipizide
3. Glimepiride.

Oral Agents: Insulin Secretagogues

Sulfonylureas

Adverse effects:

1. Weight gain
2. Hypoglycemia
3. Renal impairment is a particular problem in agents metabolized to active compounds, such as glyburide.

Oral Agents: Insulin Secretagogues

Meglitinide analogs

- Their action is dependent on functioning pancreatic β cells.

- **MOA:** They bind to a distinct site on the sulfonylurea receptor of ATP-sensitive K+ channels, initiating a series of reactions culminating in the release of insulin.(Same as sulfunylurea)

- The meglitinides have a rapid onset and a short duration of action than sulfonylurea >>>>> effective in the early release of insulin that occurs after a meal >>>> postprandial glucose regulators.

Oral Agents: Insulin Secretagogues

Meglitinide analogs

- Hypoglycemia appears to be lower than sulfonylurea.
- Meglitinides should not be used in combination with sulfonylureas (WHY?!) >>> sever hypoglycemia
- **This class of agents includes:**

1. Repaglinide
2. Nateglinide

Oral Agents: Insulin Secretagogues

Meglitinide analogs

- Drugs inhibit CYP3A4 (ketoconazole, erythromycin, and clarithromycin) may enhance the effect of repaglinide >>>> They must be used with caution in hepatic impairment

- CYP3A4 inducers: barbiturates, carbamazepine, and rifampin, decreases the effect of repaglinide.

- Weight gain is of less problem than sulfonylureas.

Insulin Sensitizers

Biguanides

- The only drug member is Metformin
- Increases glucose uptake by target tissues, thereby decreasing insulin resistance.
- Metformin requires insulin for its action.
- It does **not** promote insulin secretion. (IMPORTANT)

The main mechanism of actions:

1. Inhibiting hepatic gluconeogenesis.
2. Slows intestinal absorption of sugars
3. Improves peripheral glucose uptake and utilization.
4. Reduces LDL, VLDL and increases HDL. These effects need 4 to 6 weeks of use.

- The patient often loses weight (WHY?!) because of loss of appetite.

Insulin Sensitizers

Biguanides

- Metformin is recommended as the drug of choice for Type 2 diabetics.
- **Not** metabolized in the liver but excreted unchanged renally.
- Metformin is effective in the treatment of polycystic ovary disease (HOW?) Its ability to lower insulin resistance in these women can result in ovulation and, possibly, pregnancy.

Insulin Sensitizers

Biguanides

- Adverse effects >>> GI disterbane.
- Metformin is contraindicated in

1. Renal and hepatic disease (WHY?!)
2. Acute MI and **CHF**
3. Severe infection
4. Diabetic ketoacidosis.

- Lactic acidosis has occurred.
- **Long-term use may interfere with vitamin B12 absorption.**
- Hypoglycemia is less than with sulfonylurea. (WHY?!)

Insulin Sensitizers

Thiazolidinediones or glitazones

- Insulin is required for their action, but do not promote its secretion.

- Two members of the class are

1. pioglitazone
2. Rosiglitazone

MOA: They are target the peroxisome proliferator activated receptor (PPARγ): a nuclear hormone receptor >>>> regulate fat and glucose metabolism >>>> increased insulin sensitivity in adipose tissue, liver, and skeletal muscle.

Insulin Sensitizers

Thiazolidinediones or glitazones

- LDL is not affected by pioglitazone, whereas LDL has increased with rosiglitazone (cardiovascular toxicity and also due to water retension). HDL increases with both drugs.

- The TZDs lead to redistribution of fat from visceral to subcutaneous tissues >>>> **weight gain**.

Insulin Sensitizers

Thiazolidinediones or glitazones

- The glitazones are recommended as a second-line alternative for patients who fail or have contraindications to metformin therapy.

- Both drugs are absorbed well from GIT
- It is recommended that these agents **NOT** be used in nursing mothers.
- The relief of insulin resistance causes ovulation to resume in premenopausal women with polycystic ovary syndrome.

- Women taking oral contraceptives and TZDs may become pregnant (WHY?!) because TZDs have been shown to reduce plasma concentrations of the estrogen-containing contraceptives.

Insulin Sensitizers

Thiazolidinediones or glitazones

- Adverse effects:
- Very few cases of liver toxicity
- Weight increase.
- Osteopenia and increased fracture risk.
- Increased risk of myocardial infarction and death.

α-Glucosidase Inhibitors

Drug Members:

1. Acarbose
2. Miglitol

- Used for the treatment of patients with Type 2 diabetes.
- Are taken at the beginning of meals. (WHY?!) They act by delaying the digestion of carbohydrates, thereby resulting in lower postprandial glucose levels.
- **Mechanism of action:**

1. Reversible inhibiting α-glucosidase in the intestinal brush border. (This enzyme is responsible for the hydrolysis of oligosaccharides to glucose)
2. Inhibits pancreatic **α**-amylase. (WHAT is **α-amylase?)**

α-Glucosidase Inhibitors

- Acarbose is poorly absorbed.
- Miglitol is very well absorbed but has no systemic effects.

- **The major side effects are:**

1. Flatulence, diarrhea, and abdominal cramping. (WHY?!)
2. Patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction should not use these drugs.

Dipeptidyl Peptidase-IV Inhibitors (DPP-IV)

Sitagliptin

- Orally inhibits the enzyme DPP-IV!!!

What is **DPP-IV?**

- Is responsible for the inactivation of incretin hormones, such as glucagon-like peptide-1 (GLP-1)
- Sitagliptin prevents incretin hormone inactivation >>> results in:

1. Increased insulin release in response to meals
2. Reduction in inappropriate secretion of glucagon.

Dipeptidyl Peptidase-IV Inhibitors

Sitagliptin

- Is well absorbed after oral administration.

- The majority of sitagliptin is excreted **unchanged** in the urine>>>>>> Dosage adjustments are recommended for patients with renal dysfunction.

The most common adverse effects being:

1. Nasopharyngitis
2. Headache

- Rates of hypoglycemia is very low.

Incretin Mimetics

- 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) and is apparently reduced in Type 2 diabetes.

Exenatide

- Is an incretin mimetic.

1. Improves glucose-dependent insulin secretion
2. Slows gastric emptying time
3. Decreases food intake
4. Decreases postprandial glucagon secretion
5. Promotes β-cell proliferation.

Should ne administrated before meal

- Consequently, **weight gain** and **postprandial hyperglycemia** are reduced, and **HbA1c** levels decline.

Exenatide

- Is polypeptide >>> administered subcutaneously NOT orally

- Similar to pramlintide, the main adverse effects consist of:
- Nausea, vomiting, and diarrhea.(GIT side effects)

SGLT2 inhibitors

- Sodium–glucose cotransporter 2 inhibitors

Drugs members:

1. Canagliflozin
2. Dapagliflozin

- Drugs for type **2 diabetes**.

MOA:

The sodium–glucose cotransporter 2 (SGLT2) is responsible for reabsorbing filtered glucose in the tubular lumen of the kidney. By inhibiting SGLT2, these agents decrease reabsorption of glucose, increase urinary glucose excretion, and lower blood glucose.

SGLT2 inhibitors

- Inhibition of SGLT2 also decreases reabsorption of sodium and causes osmotic diuresis >>>> reduce systolic blood pressure.
- However, they are not indicated for the treatment of hypertension!!!!!

Adverse effects:

- The most common adverse effects with SGLT2 inhibitors are :
- Female genital mycotic infections (vulvovaginal candidiasis)
- Urinary tract infections.