Medical University Pleven

Studying Course of Endocrinology

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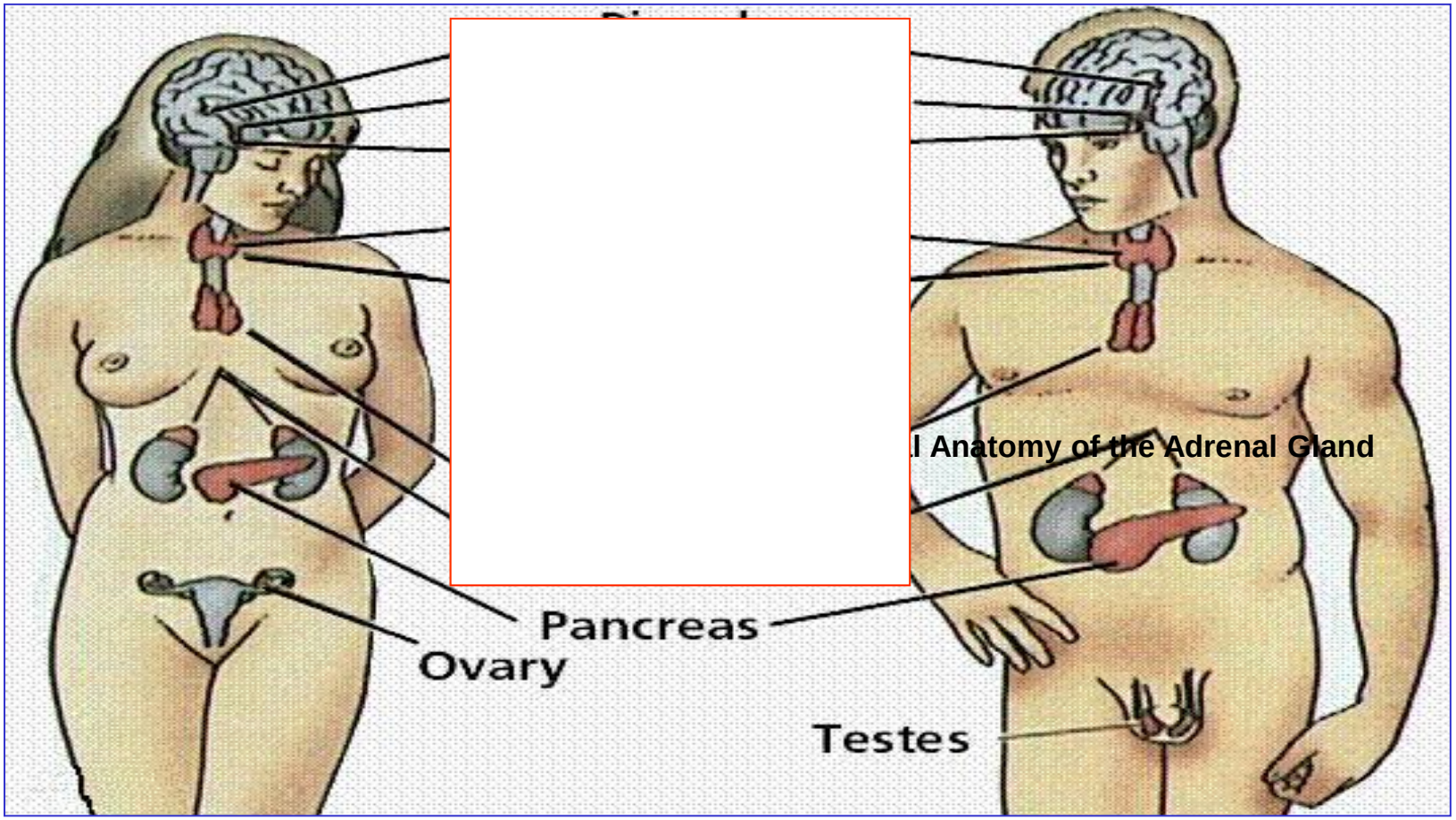
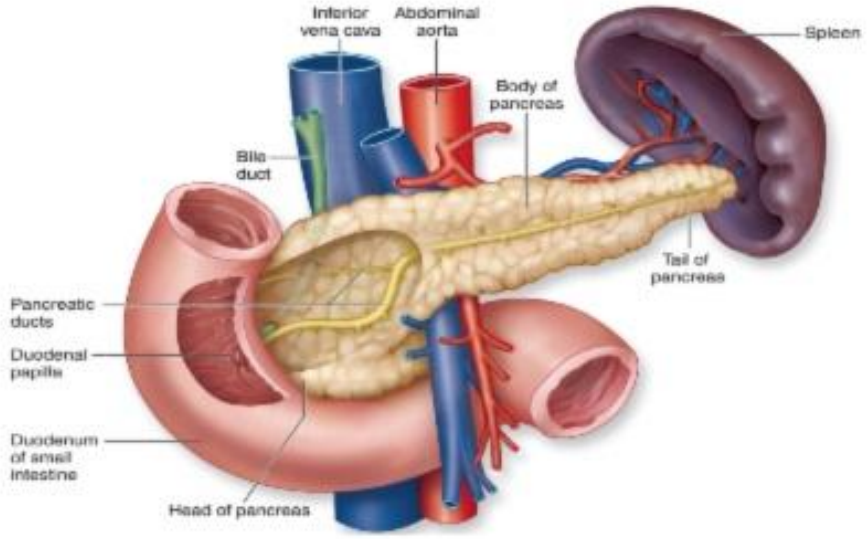
Pancreas



All Image source:
http://www.endocrinesurgeon.co.uk/index.php/what-does-the-thyroid-gland-doall

Functional Anatomy of the Endocrine Pancreas

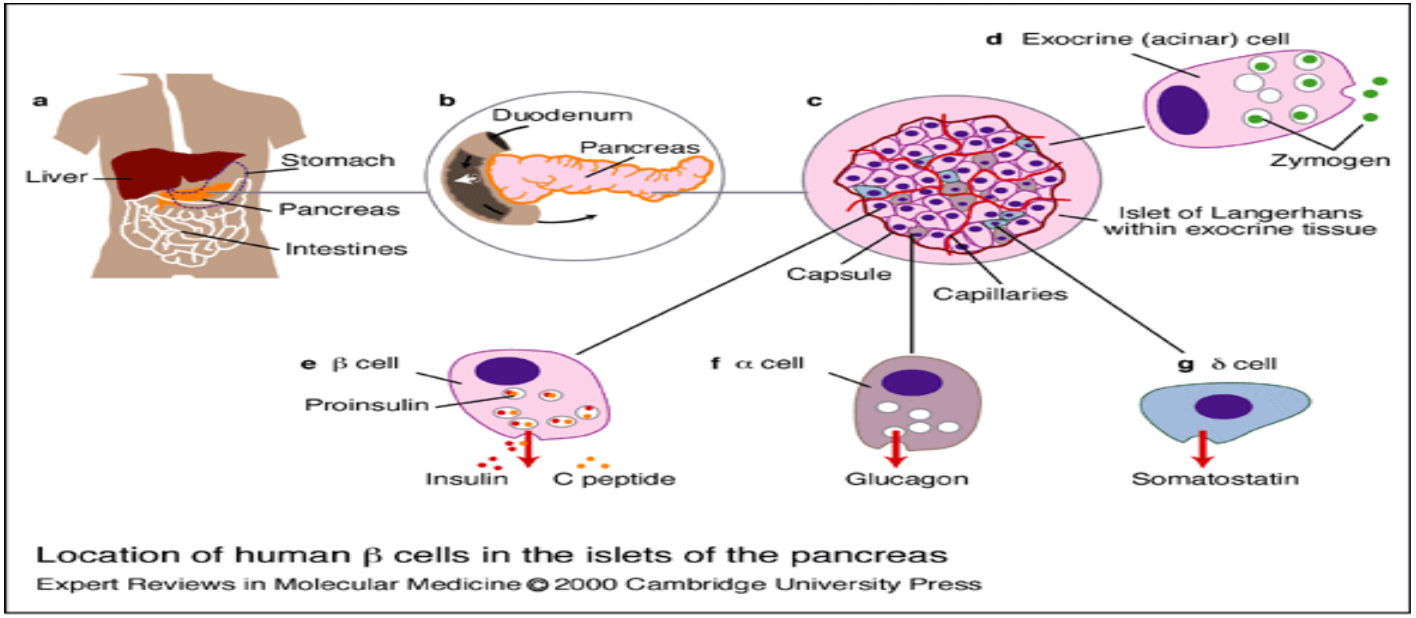
The pancreas is located in the upper abdomen, close to the liver and behind the stomach. The pancreas secretes digestive enzymes via its duct into the duodenum. An islet is a collection of endocrine cells supplied by capillaries. A thin fibrous capsule separates them from the surrounding exocrine cells, which produce and secrete zymogen.



Histological consideration

The two different types of parenchyma tissue are exist.

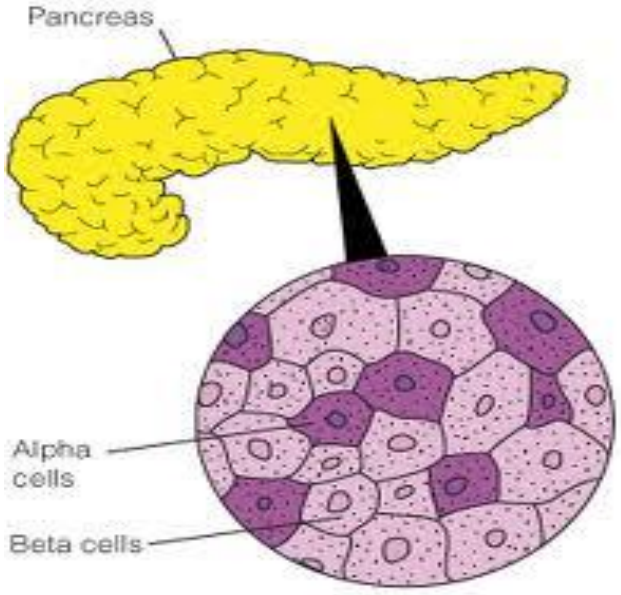
In humans, the secretory activity of the pancreas is regulated directly via the **effect of hormones in the blood** on the islets of Langerhans and indirectly through the effect of the **autonomic nervous system** on the blood flow.

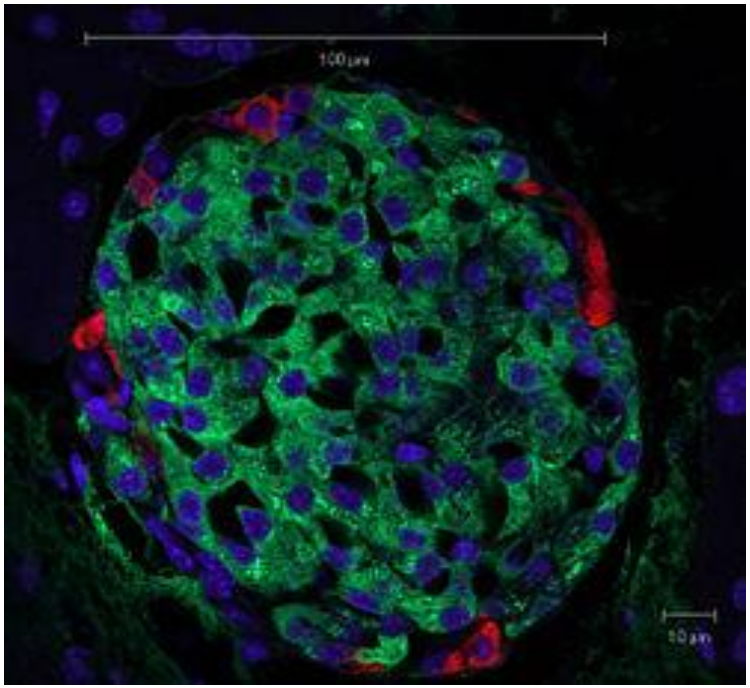


Location of human β cells in the islets of the pancreas

Functional Anatomy of the Endocrine Pancreas

The endocrine cells include: (in pink) **b cells**, which synthesise proinsulin, which is cleaved **into insulin** (stored in granules) and C peptide; (dark pink) **a cells**, which secrete **glucagon**; and (red) **d cells**, which secrete **somatostatin**, (regulates/stops α and β cells), and **PP cells or gamma** cells, secrete **pancreatic polipeptide**.





I.Steps in insulin synthesis

Insulin is synthesized in significant quantities only in **beta cells in the pancreas**.

Since it is a protein, a polypeptide structure it is synthesized like most other proteins via **transcription and translation of DNA into mRNA** and amino acid chains or polypeptide chains.

Thereafter the protein undergoes structural changes to achieve its final form.

I.Steps in insulin synthesis

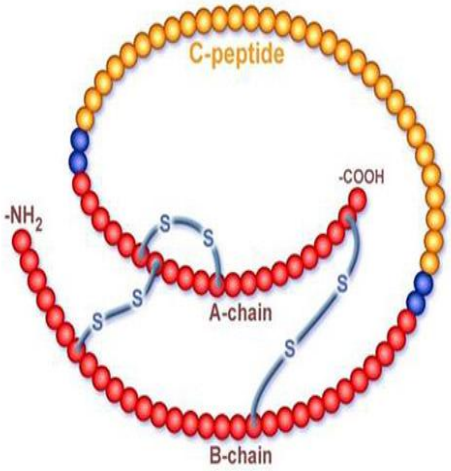
The first product of the insulin gene is a peptide known as
1.Preproinsulin

2.Proinsulin consists of three domains:

an amino-terminal B chain

a carboxy-terminal A chain

a connecting peptide in the middle known as the C



Insulin and free C peptide are packed in the Golgi bodies into secretory granules which accumulate in the cytoplasm.

II.Secretion of insulin

1. Insulin is secreted in primarily in response to elevated blood concentrations of glucose.

2.There are some other stimuli like

sight and taste of food,

increased blood levels of amino acids and fatty acids may also promote the release of insulin .

III.The steps in regulation of insulin release

1. Glucose from blood transported into the beta cell by facilitated diffusion through a glucose transporter GLUT2.

2. This leads to elevated concentrations of glucose within the beta cell.

3. The glucose undergoes glycolysis and releases multiple high-energy ATP molecules

3. The high levels of ATP lead to closing of the potassium channels (K+). This leads to **membrane depolarization** that causes a burst of incoming Calcium within the beta cell.

The calcium comes in via the voltage controlled calcium channels (Ca2+).

4**. Increased calcium within the cell leads to exocytosis** of insulin-containing secretory granules.

The steps in regulation of insulin release

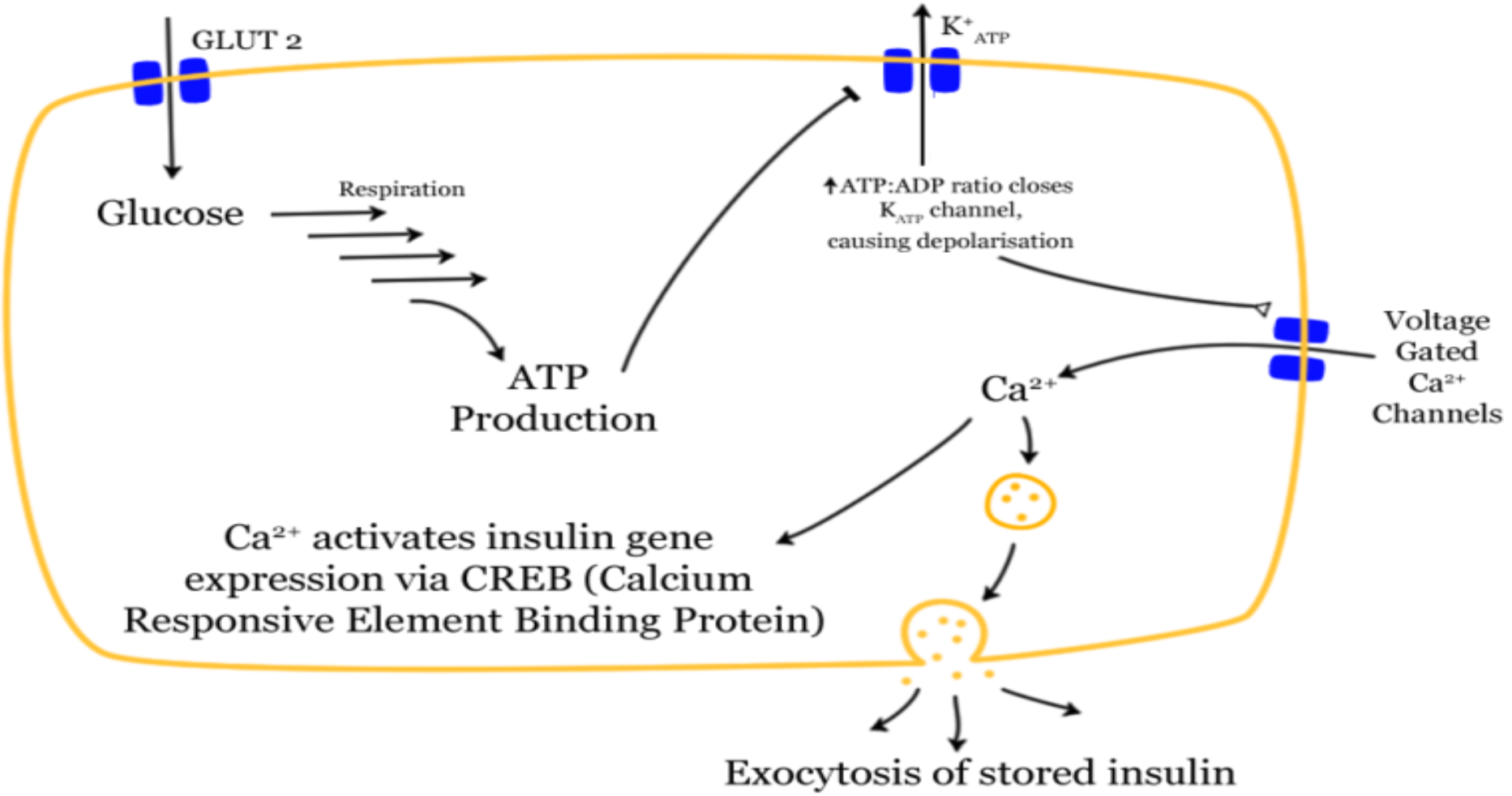
5. There are other pathways that regulate insulin release as well.

   -amino acids from ingested proteins,

   - acetylcholine, released from vagus nerve endings (parasympathetic NS),

   - glucose-dependent insulinotropic peptide (GIP), released by enteroendocrine cells of intestinal mucosa.

Regulation of insulin release



Fluctuations in insulin release

1. During digestion (around one or two hours following a meal), insulin release is not continuous, but occurs in bursts.
2. The oscillations occur within a period of 3–6 minutes and result in changes of blood insulin levels from more than ~800 pmol/l to less than 100 pmol/l.

Degradation and termination of action

After the insulin acts on its receptor site it may be released back into the extracellular environment, or it may be degraded by the cell.

The degradation mainly takes place in the liver with enzyme insulinaze.

An insulin molecule produced by the beta cells of the pancreas is degraded within approximately one hour after its initial release into circulation.

Physiology

Insulin is produced by beta cells.

Insulin binds to receptors on the cells causing receptors specific to glucose to open allowing glucose in to the cell. It lowers the blood glucose level in the blood.

Three main destinations; muscle, fat and liver. Insulin helps the tissues store glucose as an energy source.

Physiology

Insulin stimulates uptake of glucose especially in liver and muscle cells.

Glucose uptake to muscle and fat cells is dependent upon activation of GLUT4 by insulin.

1. Insulin causes glucose channels in the plasma membranes to open allowing more glucose to enter.
2. insulin stimulates increase in respiration rate.
3. activates enzyme which glucose is converted to glycogen.

Pathophysiology

This system fails when

1. Insulin secretion is not sufficient.
2. Loss of sensitivity to insulin action.

The liver's **gluconeogenesis** starts and progresses.

The blood levels is rising.

Pathophysiology

2**. Lipolysis and hepatic gluconeogenesis** are activated by glucagon, growth hormone and catecholamines to meet this “low energy crisis”.

3. Massive amounts of fatty acids are released to the circulation and the liver converts these to **ketone bodies.**

4. The high blood glucose levels lead to diuresis with loss of water, Na^+, K^+ and glucose, while the “ketones” (which are actually carboxy acids) lead to a pronounced fall in blood pH.

5. Diabetic coma and death follow if effective treatment is not initiated.

Classification of diabetes

Type 1 diabetes

Type 2 diabetes

Gestational diabetes mellitus.

Other specific types: include a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use.

Classification of diabetes(1

Type 1 diabetes (T1DM) – is a result of pancreatic beta cell destruction and is prone to ketoacidosis.

This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown.

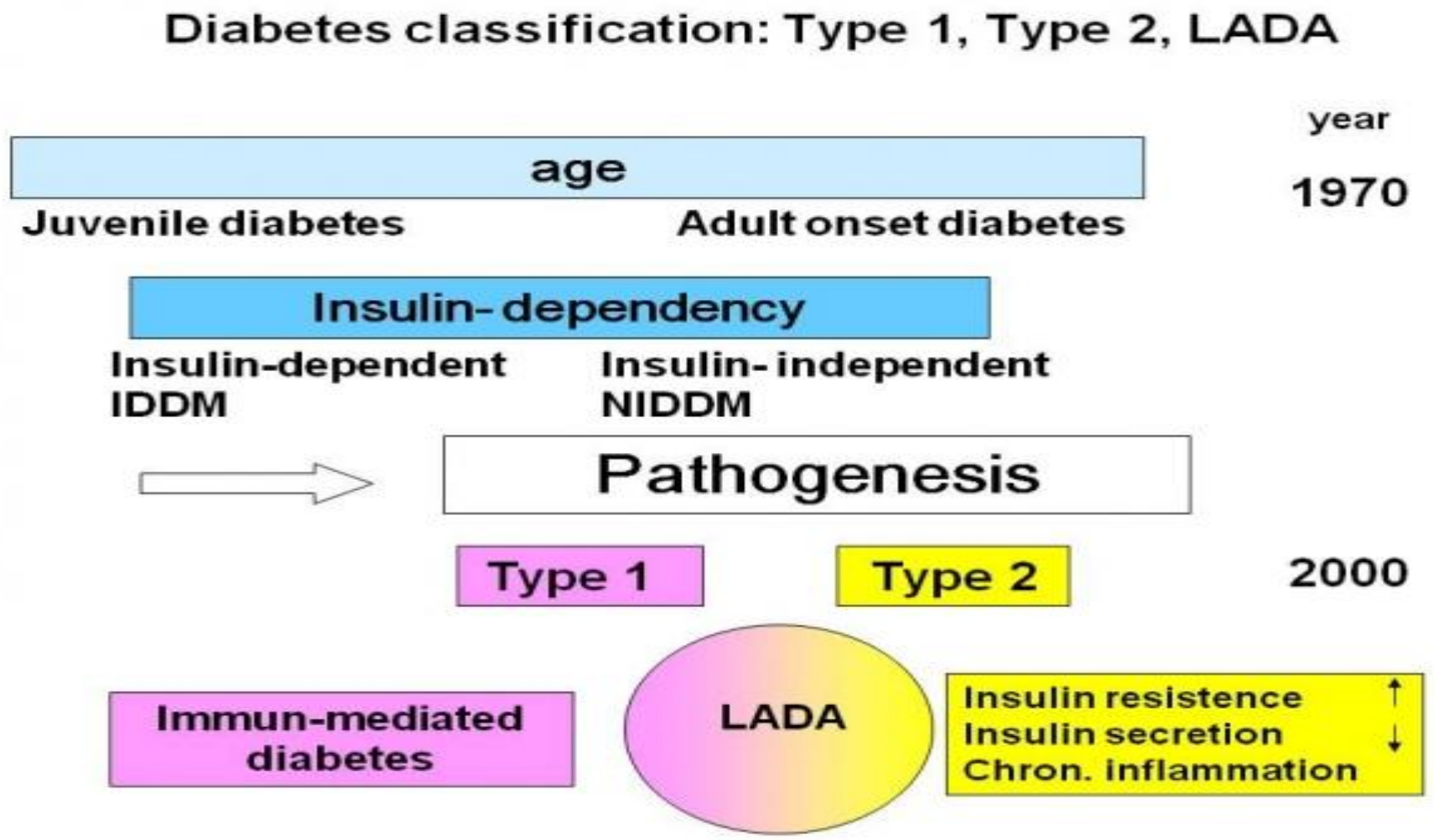
Classification of diabetes

Type 2 diabetes (T1DM) may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance.

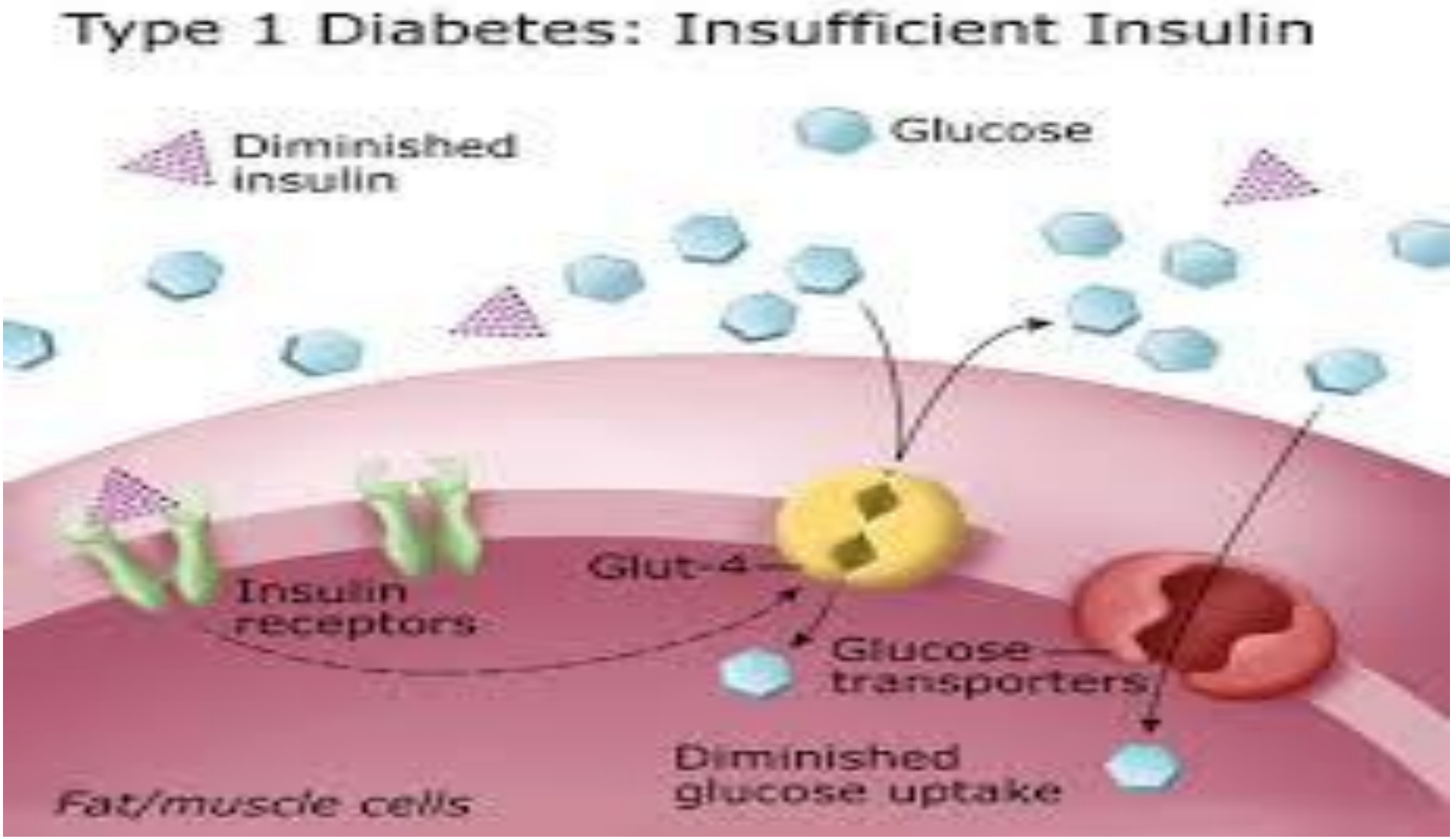
Includes **latent autoimmune diabetes in adults** (LADA); the term used to describe the small number of people with apparent type 2 diabetes who appear to have immune-mediated loss of pancreatic beta cells.

Classification of diabetes

The type of diabetes a patient has is determined only by the cause—fundamentally by whether the patient is insulin resistant (type 2) or insulin deficient without insulin resistance (type 1)



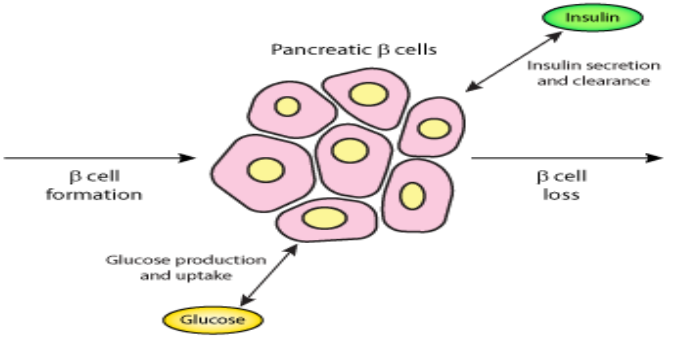
Diabetes mellitus type 1



Cause

Diabetes type 1 is induced by one or more of the following: genetic susceptibility, a diabetogenic trigger and/or exposure to a driving antigen.

In type 1, pancreatic B cells in the islets of Langerhans are destroyed, decreasing endogenous insulin production. This distinguishes type 1's origin from type 2.



Cause

1. Genetic predisposition

Type 1 diabetes is a polygenic disease, meaning many different genes contribute to its onset. Depending on locus or combination of loci, it can be dominant, recessive, or somewhere in between.

The strongest gene, ***IDDM1***, is located in the MHC Class II region on chromosome 6, at staining region 6p21.

Certain variants of this gene increase the risk for decreased histocompartibility characteristic of type 1.

Cause

2. Viral infection

One theory, proposes that T1DM is a virus-triggered autoimmune response in which the immune system attacks virus-infected cells along with the beta cells in the pancreas. The Coxsackie virus family or rubella is implicated, although the evidence is inconclusive.

Cause

3. Diet

Some researchers believe the autoimmune response is influenced by antibodies against cow ‘s milk proteins.

Vitamin D in doses of 2000 IU per day given during the first year of a child's life has been connected in one study in northern Finland (where intrinsic production of Vitamin D is low due to low natural light levels) with an 80% reduction in the risk of getting type 1 diabetes later in life

Pathophysiology

The pathophysiology in diabetes type 1 is a destruction of beta cells in the pancreas.

A process that appears to be common to most risk factors is an **autoimmune response towards B-cells**.

1. **Autoimmune attack by autoantibodies against own B-cells or insulin.**

2. **Absolute insulin deficiency**

Diabetes mellitus type 1

Absolute insulin deficiency

T1DM can be distinguished from T2DM by autoantibody testing - **glutamic acid decarboxylase autoantibodies** (GADA), **islet cell autoantibodies** (ICA), **insulinoma-associated (IA-2) autoantibodies**, and **zinc transporter autoantibodie**s (ZnT8) are present in individuals with type 1 diabetes, but not type 2 diabetes.

The risk of T1DM in offspring

The risk of a child developing type 1 diabetes is about 10% if the father has it,

about 10% if a sibling has it,

about 4% if the mother has type 1 diabetes and was aged 25 or younger when the child was born, and

about 1% if the mother was over 25 years old when the child was born.

Signs and symptoms

The classical symptoms of T1DM include: **polyuria,**

polydipsia (increased thirst),

Xerostomia (dry mouth), poliphagya (increased hunger),

fatigue, and weight loss.

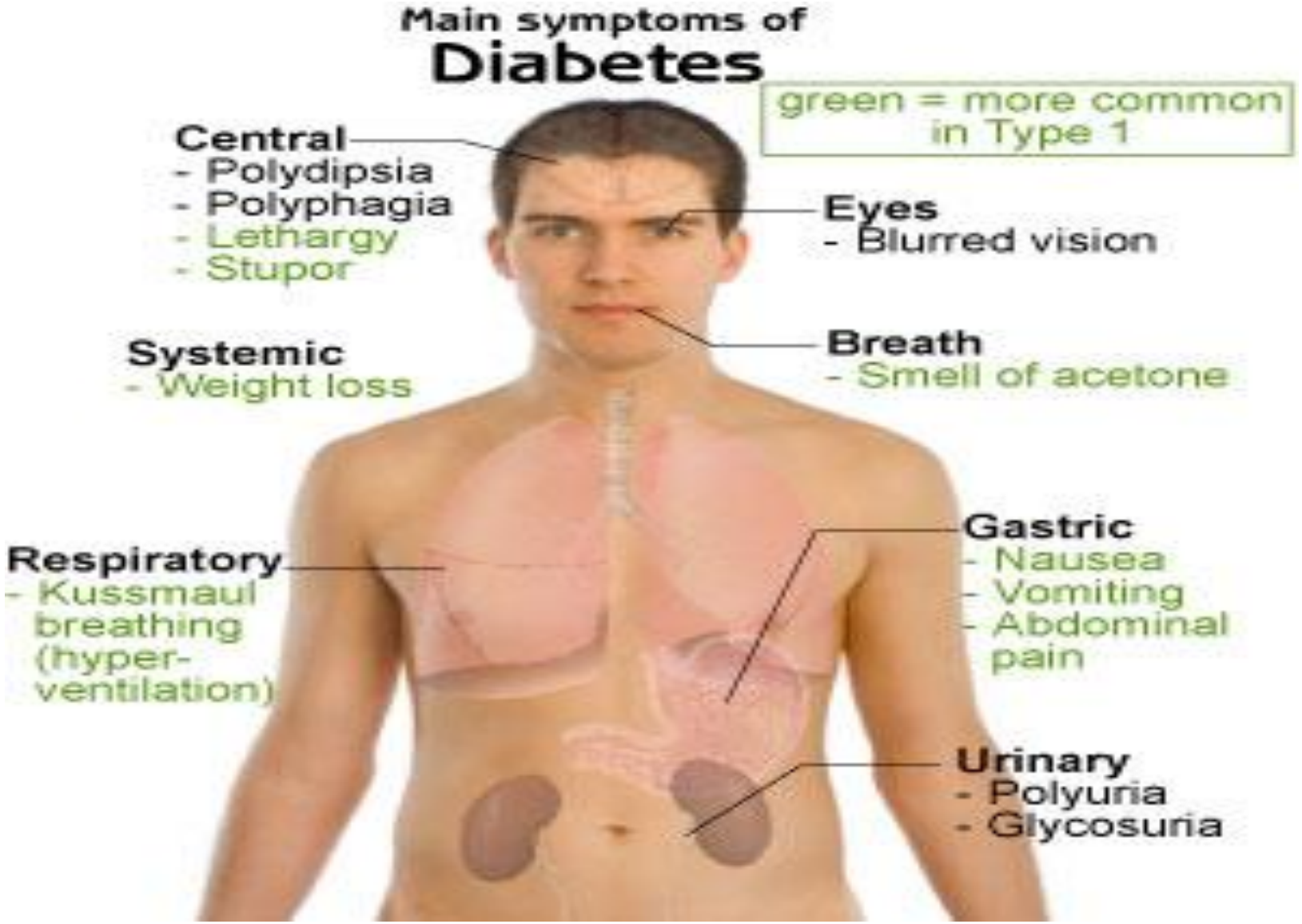
Type 1 diabetics are often first diagnosed with **diabetic ketoacidosis**.

These symptoms could be:

xeroderma (dry skin), rapid deep breathing,

drowsiness, abdominal pain, and vomiting.

Clinical symptoms



Diagnosis

Diabetes is diagnosed on the basis of history (polyuria, polydipsia and unexplained weight loss) PLUS

1. Fasting plasma glucose level at or above **7.0 mmol/L** (126 mg/dL) OR whole blood >= 6.1 mmol/l.
2. Plasma glucose at or above **11.1 mmol/L** (200 mg/dL) two hours after a 75 g oral glucose load as in a OGTT.
3. Symptoms of hyperglycemia and casual plasma glucose at or above **11.1 mmol/L** (200 mg/dL).
4. Glycated haemoglobin (hemoglobin A1C) at or above **6.5%**.

Diagnosis of prediabetes

Test Result Prediabetes category

FPG (mmol/L) 6.1–6.9 IFG (impaired fasting glucose)

2hPG in a 75 g OGTT (mmol/L) 7.8–11.0 IGT (impaired glucose tolerance)

Hb A1C (%) 6.0–6.4 Prediabetes

Treatment of diabetes

People with type 1 diabetes **always need to use insulin.** Insulin is the oldest medical therapy available for diabetes. It was discovered in 1921 and clinical testing in humans began in 1922.

The goal is lowering blood glucose (BG) to the near normal range, approximately **4.4–7.8 mmol/L.**

The ultimate goal of normalizing BG is to avoid **long-term complications that affect the kidney, the eyes, the nervous system, and the cardiovascular system**.

Insulin treatment

1. Basal–Bolus regimen

These is combining a long-acting agent that is used once or twice daily and provides basal insulin needs and a rapid-acting agent for prandial coverage used with meals.

When initiating therapy with insulin analogues as glargine or detemir as the basal insulin, traditionally **50%** of the total daily dose is given as **basal insulin** and the rest as prandial insulin **divided equally before meals**.

Insulin treatment

Meal dose of insulin can be fixed, but it is better to determine the dose based on carbohydrate content of the meal.

This requires learning carbohydrate counting and knowing the dose of insulin required to cover counted carbohydrates.

Patient are, also, provided with sliding scale (supplemental insulin) to use as a third component of therapy at the time when blood glucose is higher than desired.

Insulin treatment

The starting daily insulin dose is typically 0.3 U/kg total (divided between long acting and rapid acting) daily.

Key to good control is blood glucose self-monitoring by the patient and frequent adjustment of the regimen until control is achieved.

Insulin treatment

2. Insulin Pump Therapy

The insulin pump allows the use of varying basal insulin rates in different periods of the day. It also allows the administration of the meal bolus as a single discrete bolus or as an extended bolus over a set period of time.

This which allows a better match between insulin delivery and glucose absorption from the meal in patients with abnormalities of gastric emptying.

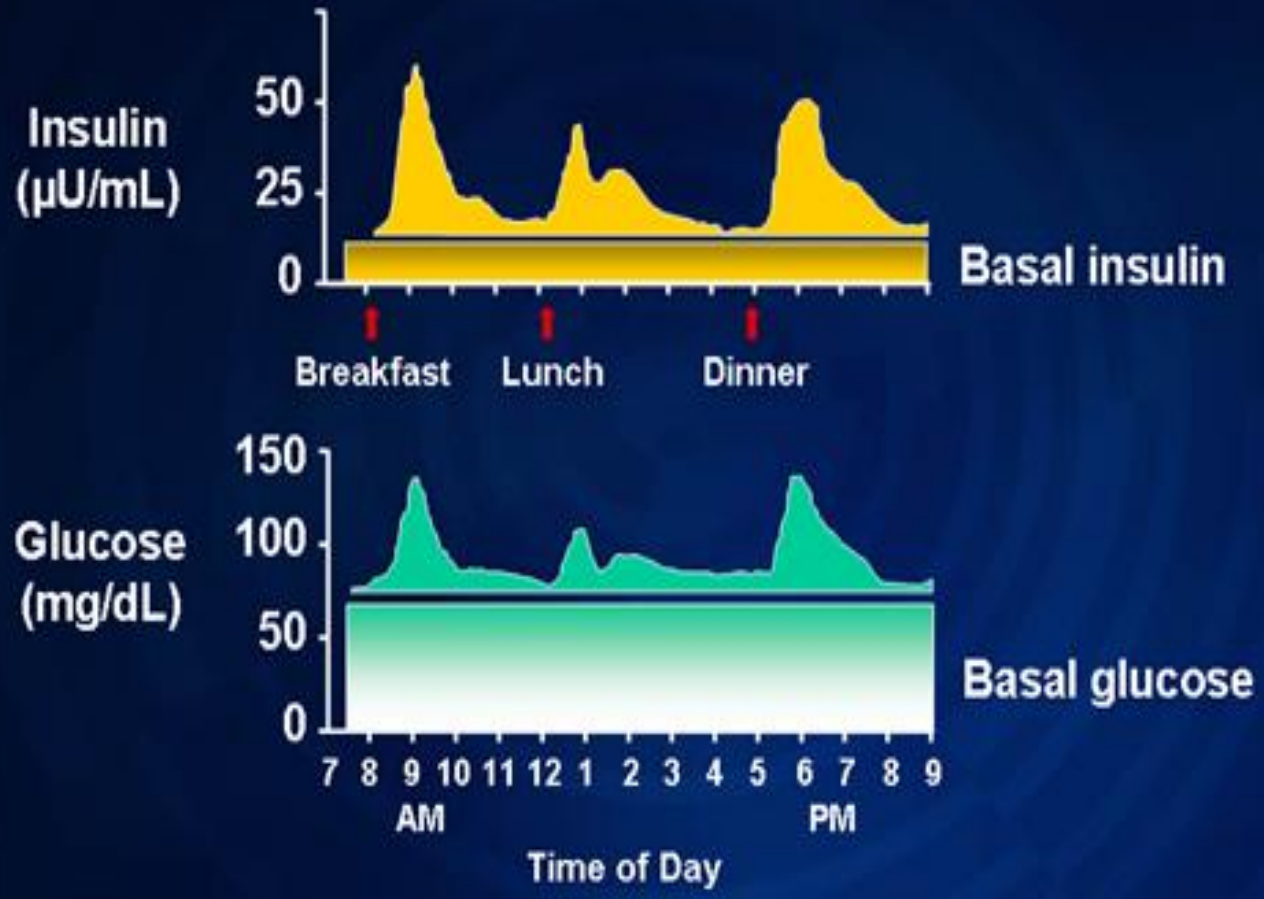
Insulin treatment

The use of insulin pump therapy should be considered in the following patients:

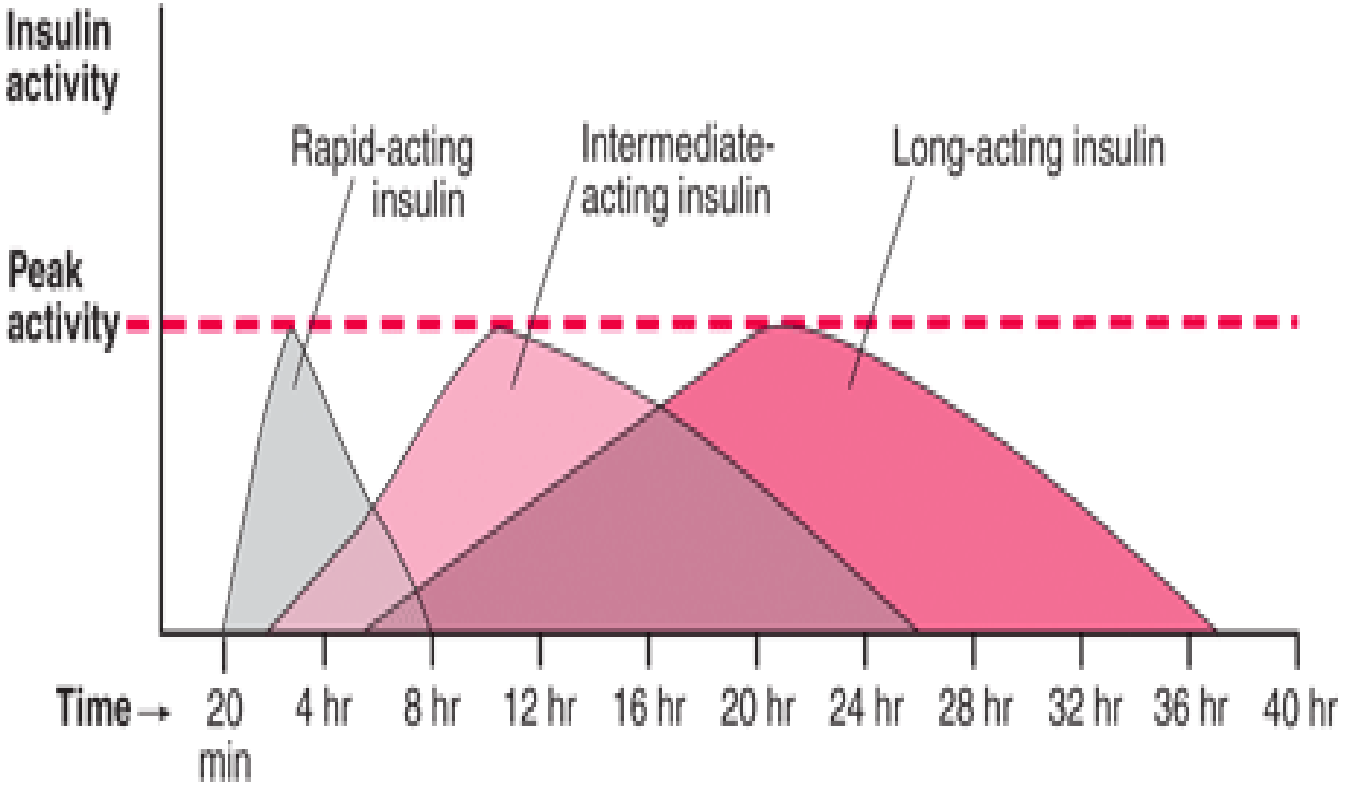
1. Those unable to achieve target goals with basal–bolus regimens
2. Patients with frequent hypoglycemia, dawn phenomenon, or brittle diabetes
3. Pregnant patients
4. Patients with insulin sensitivity or those requiring more intense monitoring due to complications
5. Patients who are able to monitor blood glucose several times daily and make insulin dosage adjustments

Insulin treatment

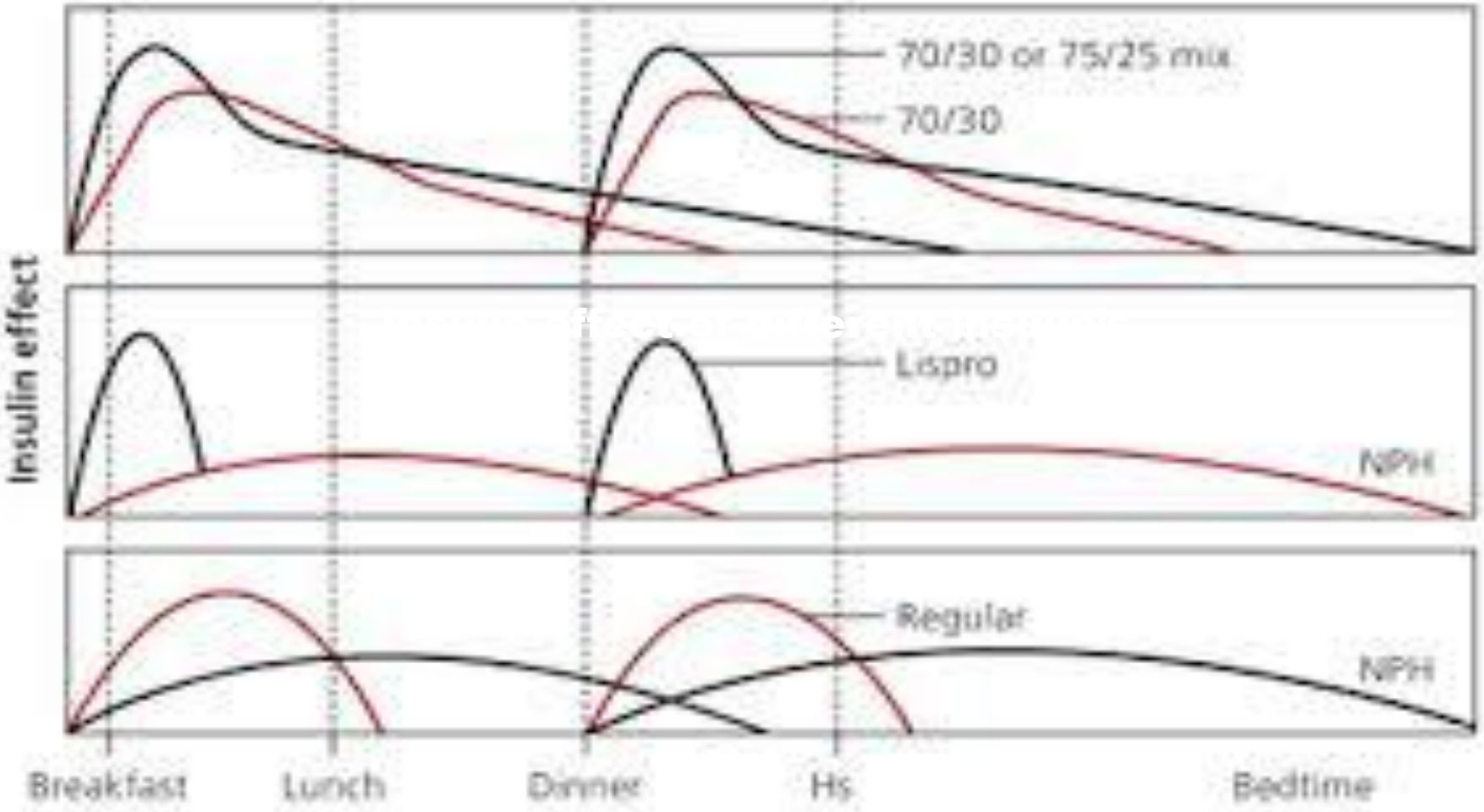
Physiologic Insulin Secretion: 24-Hour Profile



Metabolic profile of insulin's

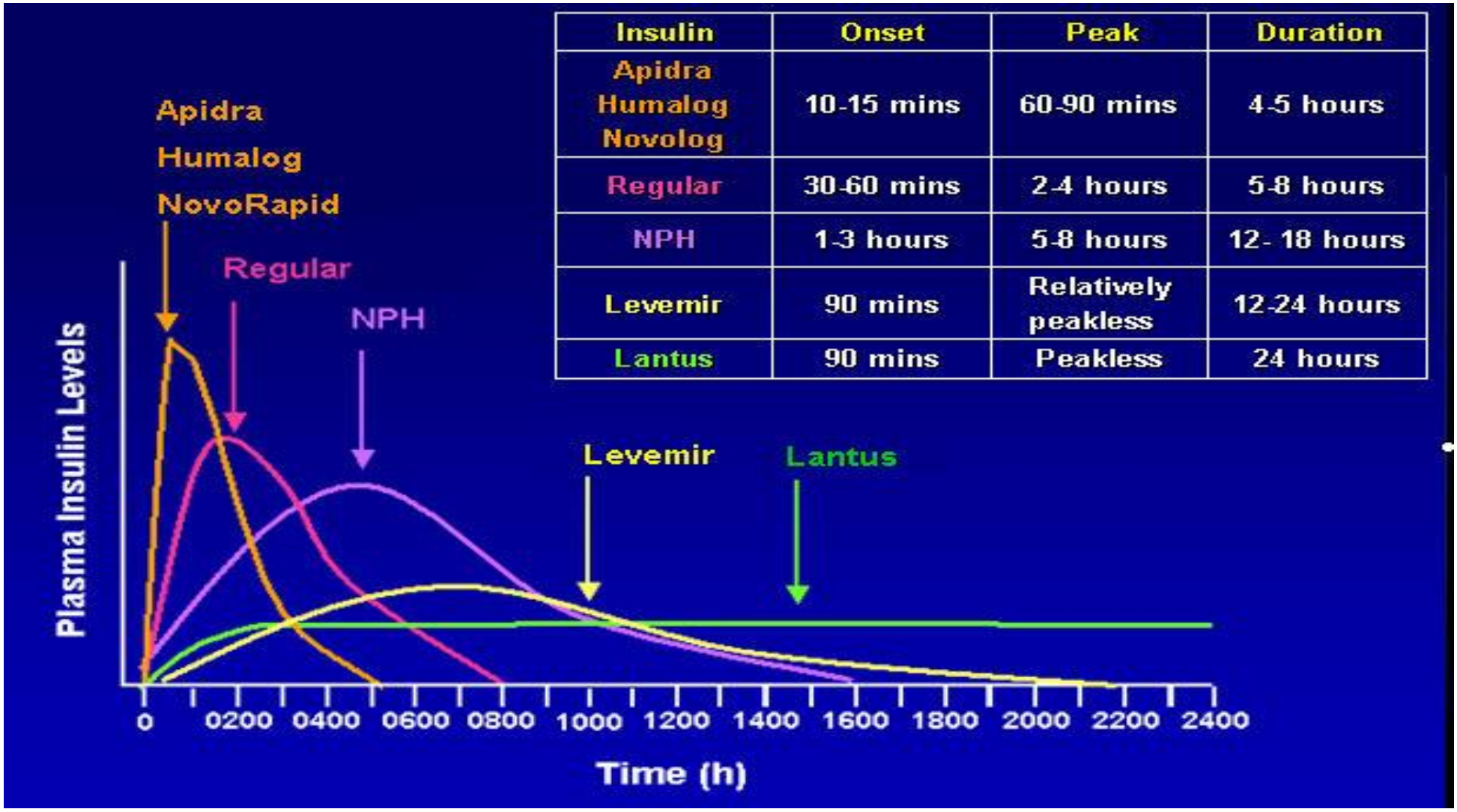


Insulin effect of different insulin's

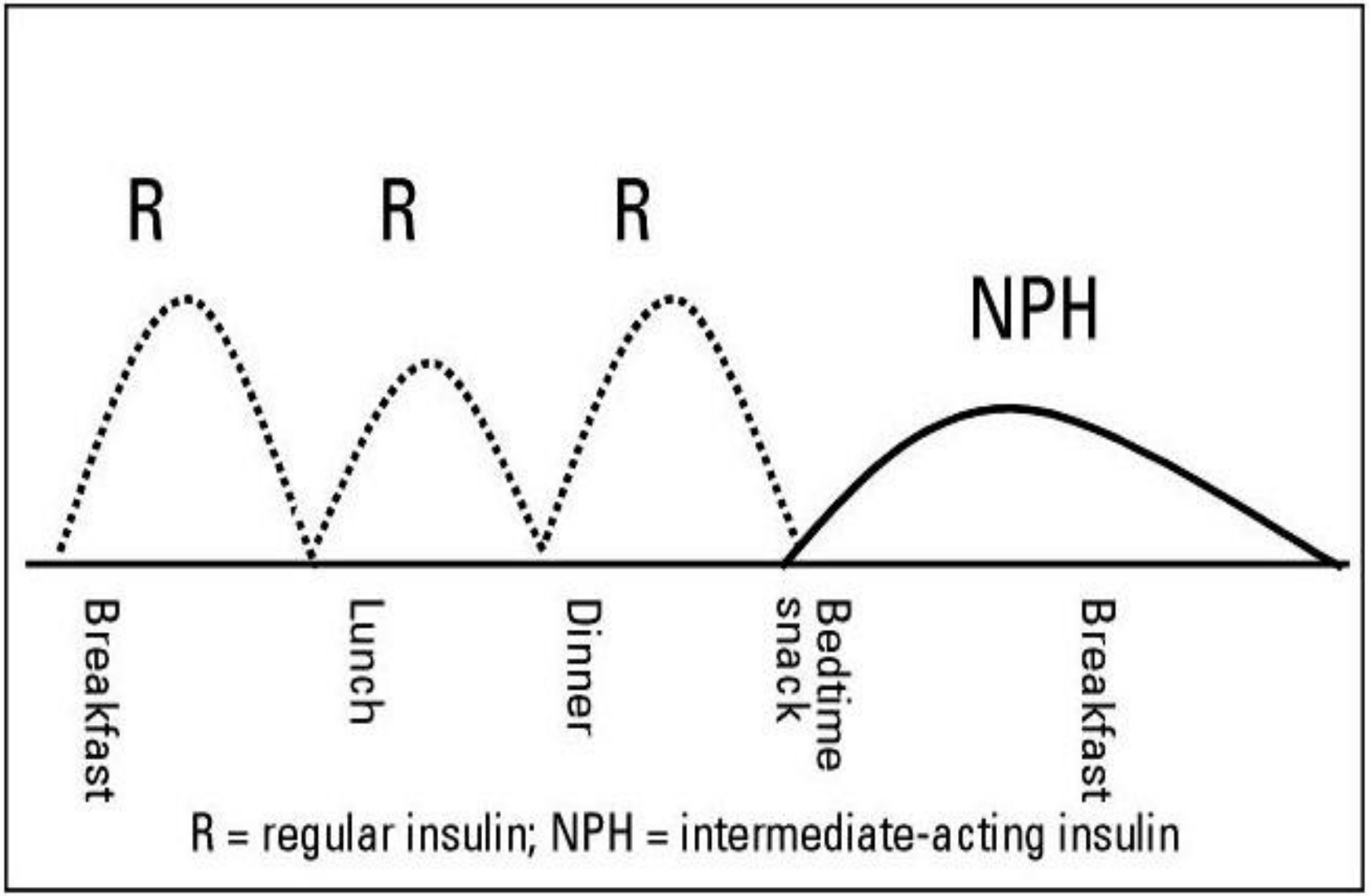


Metabolic profile of insulin's

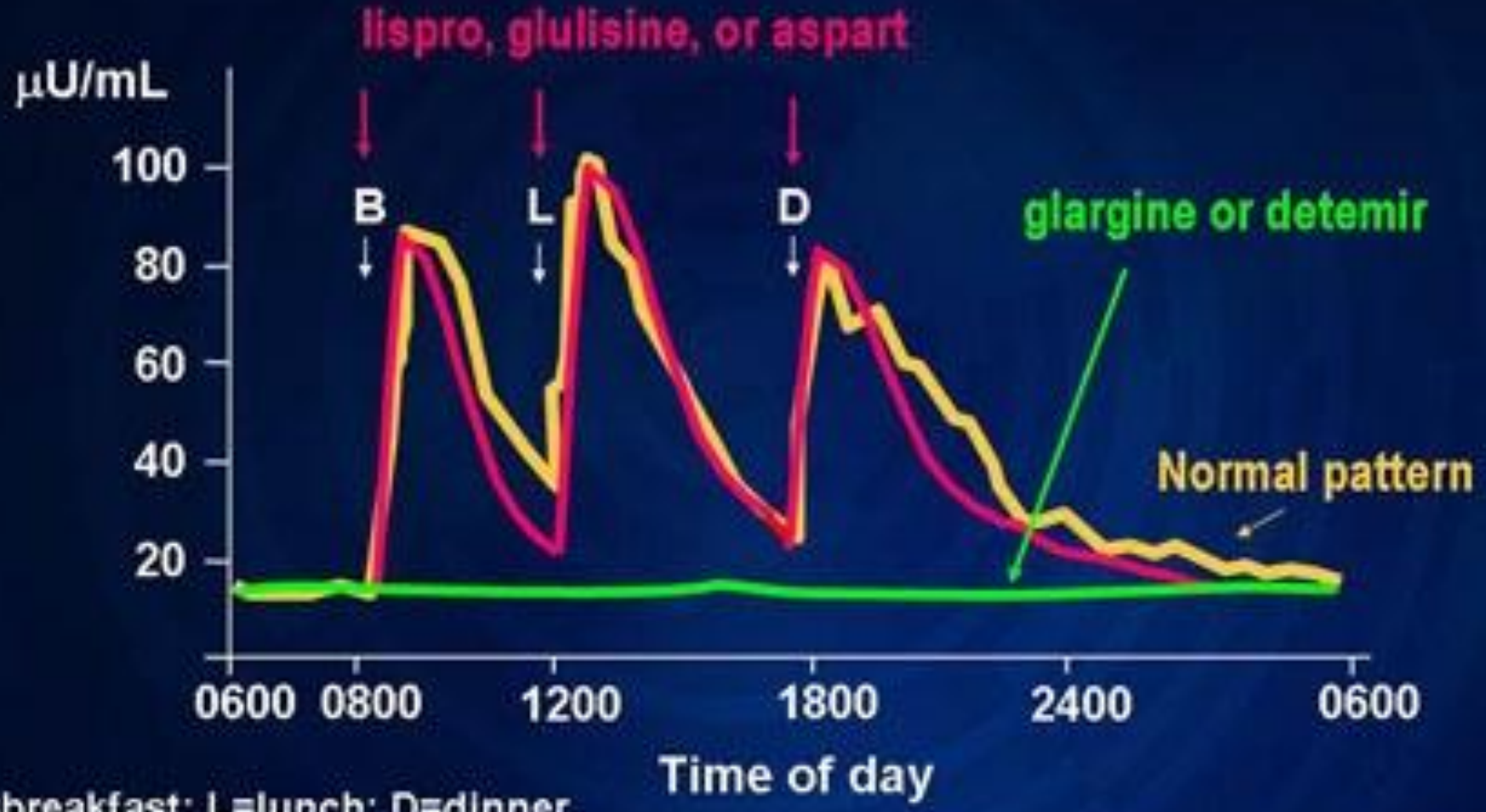
Insulin	Onset	Peak	Duration
Apidra Humalog Novolog	10-15 mins	60-90 mins	4-5 hours
Regular	30-60 mins	2-4 hours	5-8 hours
NPH	1-3 hours	5-8 hours	12- 18 hours
Levemir	90 mins	Relatively peakless	12-24 hours
Lantus	90 mins	Peakless	24 hours



Basal–Bolus regimen



Basal-Bolus Insulin Treatment With Insulin Analogs



B=breakfast; L=lunch; D=dinner

Joslin Diabetes Center

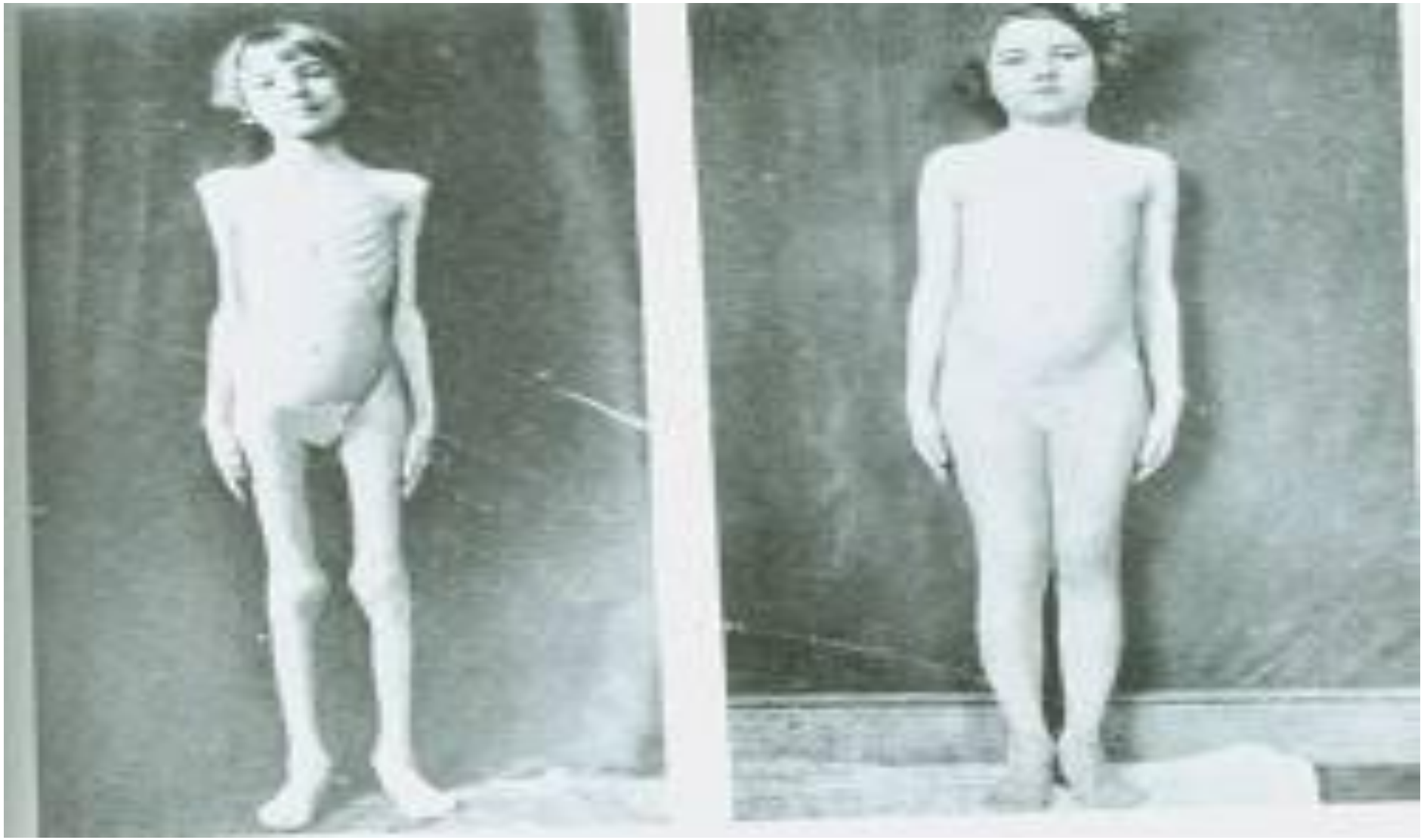
Supplemental insulin according to BG

Titration Algorithm for Implementing the Above Guidelines

Pre-prandial BG value		Dose change
<4.4 mmol/L	<80 mg/dL	−2U
4.4–6.1 mmol/L	80–110 mg/dL	0
6.2–7.8 mmol/L	111–140 mg/dL	+2U
7.9–10.0 mmol/L	141–180 mg/dL	+4U
>10.0 mmol/L	>180 mg/dL	+6U

Ref: Unnikrishnan et al. 2009 (25)

Before and 3 months after insulin's treatment



Insulin Pump Therapy

Complication of insulin's treatment

Insulin treatment can lead to low BG (hypoglycemia), i.e. BG less than 3.9 mmol/l.

Hypoglycemia is a very common occurrence in people with T1DM, usually the result of a mismatch in the balance among insulin, food and physical activity, although the nonphysiological method of delivery also plays a role.

Pancreas transplantation

In more extreme labile T1DM cases, a pancreas transplant can restore proper glucose regulation. The surgery and accompanying immunesupression required is considered to be more dangerous than continued insulin replacement therapy, so is generally only used with or some time after a kidney transplant.

Islet cell transplantation

Islet cell transplantation is less invasive than a pancreas transplant, which is currently the most commonly used approach in humans.

In one variant of this procedure, islet cells are injected into the patient's liver.

Patients also need to undergo treatment involving immunosupressants, which reduce immune system activity.

Specific Areas of Research

GAD65 vaccine

Injections with a vaccine containingGAD65, an autoantigen involved in T1DM, has in clinical trials delayed the destruction of beta cells when treated within six months of diagnosis.

Patients treated with the substance showed higher levels of regulatory cytokines, thought to protect the beta cells.

Specific Areas of Research

T helper cell shift

If a biochemical mechanism can be found to prevent the immune system from attacking beta cells, it may be administered to prevent commencement of diabetes type 1.

Several groups are trying to achieve this by causing the activation state of the immune system to change from type 1 T helper cell (Th1) state ("attack" by killer T Cells) to Th2 state (development of new antibodies). This Th1-Th2 shift occurs via a change in the type of cytokine signaling molecules being released by T-cells.

Instead of proinflammatory cytokines, the T-cells begin to release cytokines that inhibit inflammation.

This phenomenon is commonly known as acquired immune tolerance.

Complications of T1DM

1. **Acute complications**

Hypoglycemic coma,

Ketoacidosis

2. Chronic microvascular complications:

Diabetic nephropathy,

Rethinopathy,

Polyneuropathy

Ketoacidosis

Metabolic state associated with high concentrations of ketone bodies, formed by the breakdown of fatty acids and the de-amination of amino acids.

The two common ketones produced in humans are acetoacetic acid and b- hydroxybutirate.

Ketoacidosis is a pathological metabolic state marked by extreme and uncontrolled ketosis.

In ketoacidosis, the body fails to adequately regulate ketone production causing such a severe accumulation of keto acids that the pH of the blood is substantially decreased.

In extreme cases ketoacidosis can be fatal.

Ketoacidosis

Ketoacidosis occurs when the body is producing large quantities of ketones via the metabolism of fatty acids and the body is producing insufficient insulin to slow this production.

The excess ketones can significantly acidify the blood. The presence of a hyperglicaemia caused by the lack of insulin can lead to further acidity.

In healthy individuals this normally does not occur because the pancreas produces insulin in response to rising ketone/blood glucose concentration.

Ketoacidosis

Acidity results from the dissociation of the H^+ ion at physiological pH of metabolic ketone bodies such as acetoacetate and b- hydroxybutirate.

Acetone has no easily liberated proton, and is thus non-acidic in human biochemical environments.

Ketoacidosis

In diabetic patients, ketoacidosis is usually accompanied by insulin deficiency, hyperglicaemia, and dehydratation.

Hyperglycemia results in glucose overloading the kidneys and glucosuria (transport maximum for glucose is exceeded).

Dehydration results following the osmotic movement of water into urine (Osmotic diuresis), exacerbating the acidosis.

Ketoacidosis

In diabetic ketoacidosis, the body shifts from its normal fed metabolism (using **carbohydrates** for fuel) to a fasting state (using **fat for fuel**). The resulting increase in blood sugar occurs, because insulin is unavailable to transport sugar into cells for future use.

As blood sugar levels rise, the kidneys cannot retain the extra sugar, which is dumped into the urine, thereby increasing urination and causing dehydration.

Ketoacidosis

Commonly, about 10% of total body fluids are lost as the patient slips into diabetic ketoacidosis. Significant loss of potassium and other salts in the excessive urination is also common.

Ketoacidosis

The most common early symptoms of DKA are the insidious increase in polydipsia and polyuria. The following are other signs and symptoms of DKA:

Malaise, generalized weakness, and fatigability

Nausea and vomiting; may be associated with diffuse abdominal pain, decreased appetite, and anorexia

Rapid weight loss in patients newly diagnosed with type 1 diabetes

Diagnosis

On examination, general findings of DKA may include the following:

Ill appearance

Dry skin

Labored respiration

Dry mucous membranes

Decreased skin turgor

Decreased reflexes

Characteristic acetone (ketotic) breath odor

Tachycardia

Hypotension

Tachypnea

Hypothermia

Diagnosis

In addition, evaluate patients for signs of possible intercurrent illnesses such as

Myocardial Infarct,

Urine Tract Infection,

Pneumonia, and perinephric abscess.

Search for signs of infection is mandatory in all cases.

Initial and repeat laboratory studies for patients with DKA include the following:

Serum glucose levels

Serum electrolyte levels (eg, potassium, sodium, chloride, magnesium, calcium, phosphorus)

Amylase levels

Urine dipstick

Ketone levels

Serum or capillary beta-hydroxybutyrate levels

Arterial pH, Bicarbonate levels

Diagnosis Testing

CBC count

BUN and creatinine levels

Urine and blood cultures if intercurrent infection is suspected

ECG (or telemetry in patients with comorbidities)

Diagnosis Testing

Note that

High serum glucose levels may lead to dilutional hyponatremia;

High triglyceride levels may lead to factitious low glucose levels;

and High levels of ketone bodies may lead to factitious elevation of creatinine levels.

Diagnosis
Imaging tests

Radiologic studies that may be helpful in patients with DKA include the following:

Chest radiography: To rule out pulmonary infection such as pneumonia

Head CT scanning: To detect early cerebral edema; use low threshold in children with DKA and altered mental status

Head MRI: To detect early cerebral edema (order only if altered consciousness is present[2])

Do not delay administration of hypertonic saline or mannitol in those pediatric cases where cerebral edema is suspected, as many changes may be seen late on head imaging.

Management

Treatment of ketoacidosis should aim for the following:

Fluid resuscitation

Reversal of the acidosis and ketosis

Reduction in the plasma glucose concentration to normal

Replenishment of electrolyte and volume losses

Identification the underlying cause

Pharmacotherapy

Regular and analog human insulins are used for correction of hyperglycemia.

1. **Rapid-acting insulins (eg, insulin aspart, insulin glulisine, insulin lispro)**
2. **Electrolyte supplements (eg, potassium chloride)**
3. **Alkalinizing agents (eg, sodium bicarbonate)**

Management Conclusion

Correction of fluid loss with intravenous fluids

Correction of hyperglycemia with insulin

Correction of electrolyte disturbances, particularly potassium loss

Correction of acid-base balance

Treatment of concurrent infection, if present

Management

Managing DKA in an intensive care unit during the first 24-48 hours always is advisable.

Patients usually are not discharged from the hospital unless they have been able to switch back to their daily insulin regimen without a recurrence of ketosis.

When the condition is stable, pH exceeds 7.3, and bicarbonate is greater than 18 mEq/L, the patient is allowed to eat a meal preceded by a subcutaneous (SC) dose of regular insulin.

Management

Insulin infusion can be discontinued 30 minutes later.

If blood glucose fall below 14 mmol/L (250 mg/dL), 10% glucose should be added to allow for the continuation of fixed-rate insulin infusion

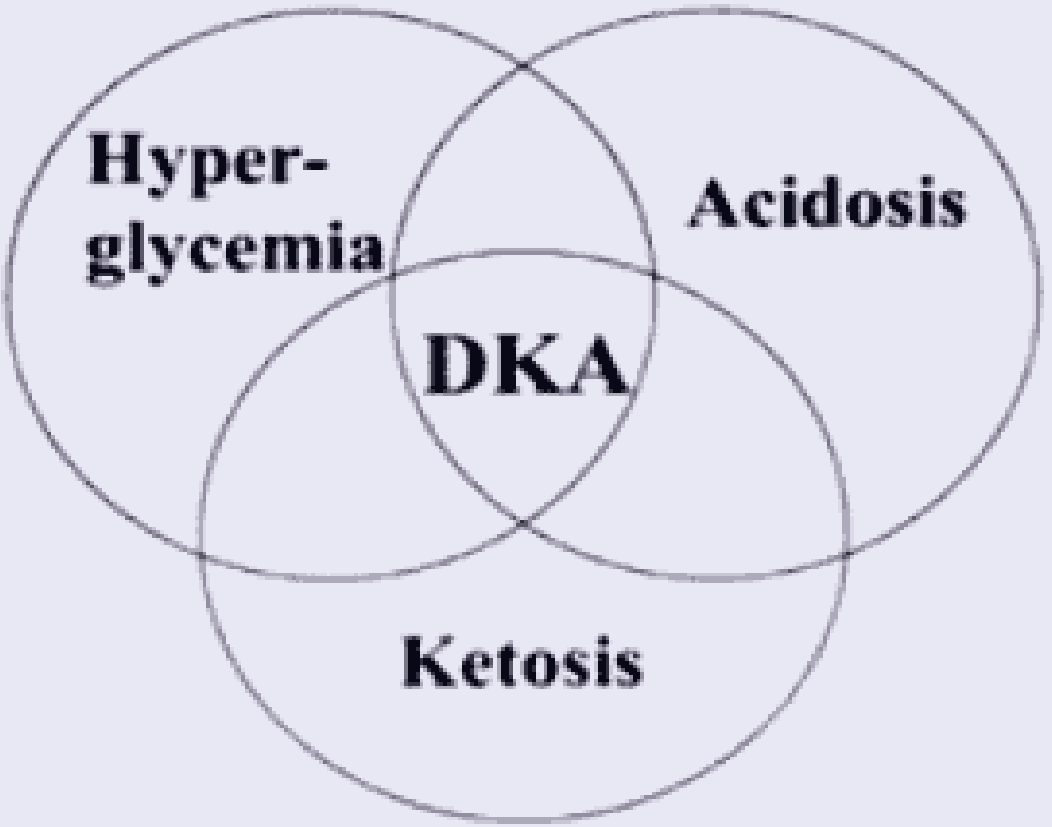
If the patient is still nauseated and cannot eat, dextrose infusion should be continued and regular or ultra–short-acting insulin should be administered SC every 4 hours, according to blood glucose level, while trying to maintain blood glucose values at **6.0-8.0 mmol/L** (100-180 mg/dL.)

Reason for acidosis

Other Hyperglycemic States
Diabetes Mellitus
Non-Ketotic Hyperosmolar Coma
Impaired Glucose Tolerance
Stress Hyperglycemia

Other Ketotic States
Ketotic Hypoglycemia
Alcoholic Ketosis
Starvation Ketosis

Other Metabolic Acidotic States
Lactic Acidosis
Hyperchloremic Acidosis
Salicylism
Uremic Acidosis
Drug-Induced Acidosis



Hypoglycemia

Hypoglycemia is characterized by a reduction in plasma glucose concentration (ussualy bellow 3.9 mml/l) to a level that may induce symptoms or signs such as altered mental status and/or sympathetic nervous system stimulation.

This condition typically arises from abnormalities in the mechanisms involved in glucose homeostasis.

The most common cause of hypoglycemia in patients with diabetes is injecting a shot of insulin and skipping a meal or overdosing insulin.

Symptoms of hypoglycemia

Neurogenic or neuroglycopenic symptoms of hypoglycemia may be categorized as follows:

Neurogenic (adrenergic) (sympathoadrenal activation) symptoms: Sweating, shakiness, tachycardia, anxiety, and a sensation of hunger

Neuroglycopenic symptoms: Weakness, tiredness, or dizziness; inappropriate behavior (sometimes mistaken for inebriation), difficulty with concentration; confusion; blurred vision; and, in extreme cases, coma and death

Diagnosis

Rapid diagnosis and treatment is essential in any patient with suspected hypoglycemia, regardless of the cause.

The Whipple triad is characteristically present:

1. **documentation of low blood sugar,**
2. **presence of symptoms, and**
3. **reversal of these symptoms when the blood glucose level is restored to normal.**

Physical findings, however, are nonspecific in hypoglycemia and are generally **related to the central and autonomic nervous systems**.

Laboratory studies

1. Glucose and electrolyte levels (including calcium, magnesium)
2. Complete blood count

Management
Pharmacotherapy

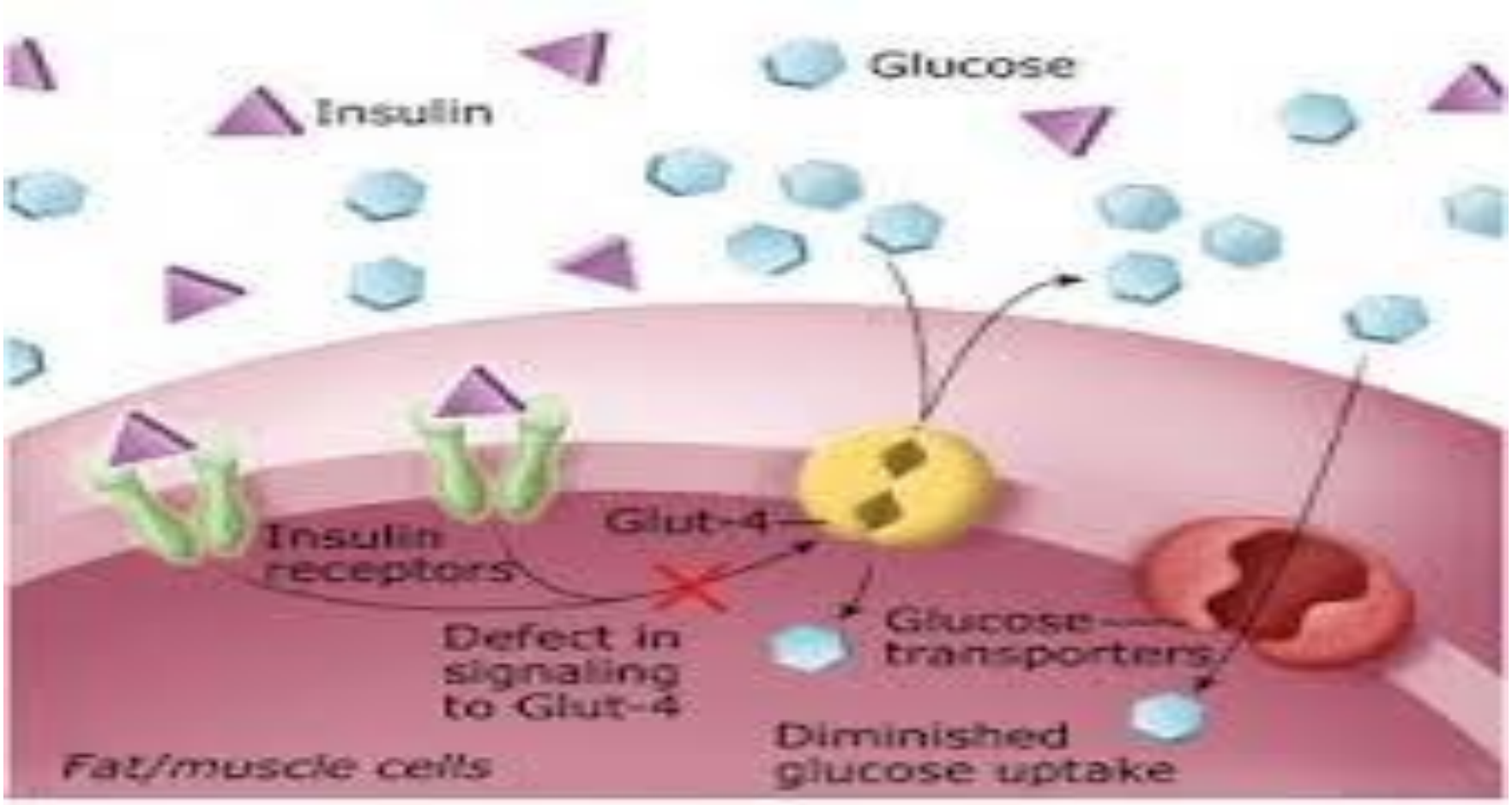
1. **Glucose solution 40% , administered intravenously until patient's recovering in severe hypoglycemia,**
2. **or glucose as oral supplements (eg, dextrose solution) in mild hypoglycemia.**

2.Glucose-elevating agents (eg, 1 mg dose of glucagon , administered by subcutaneous or intramuscular injection).

The most important of therapy for hypoglycemia is glucose.

Other medications may be administered based on the underlying cause or the accompanying symptoms.

Type 2 DM



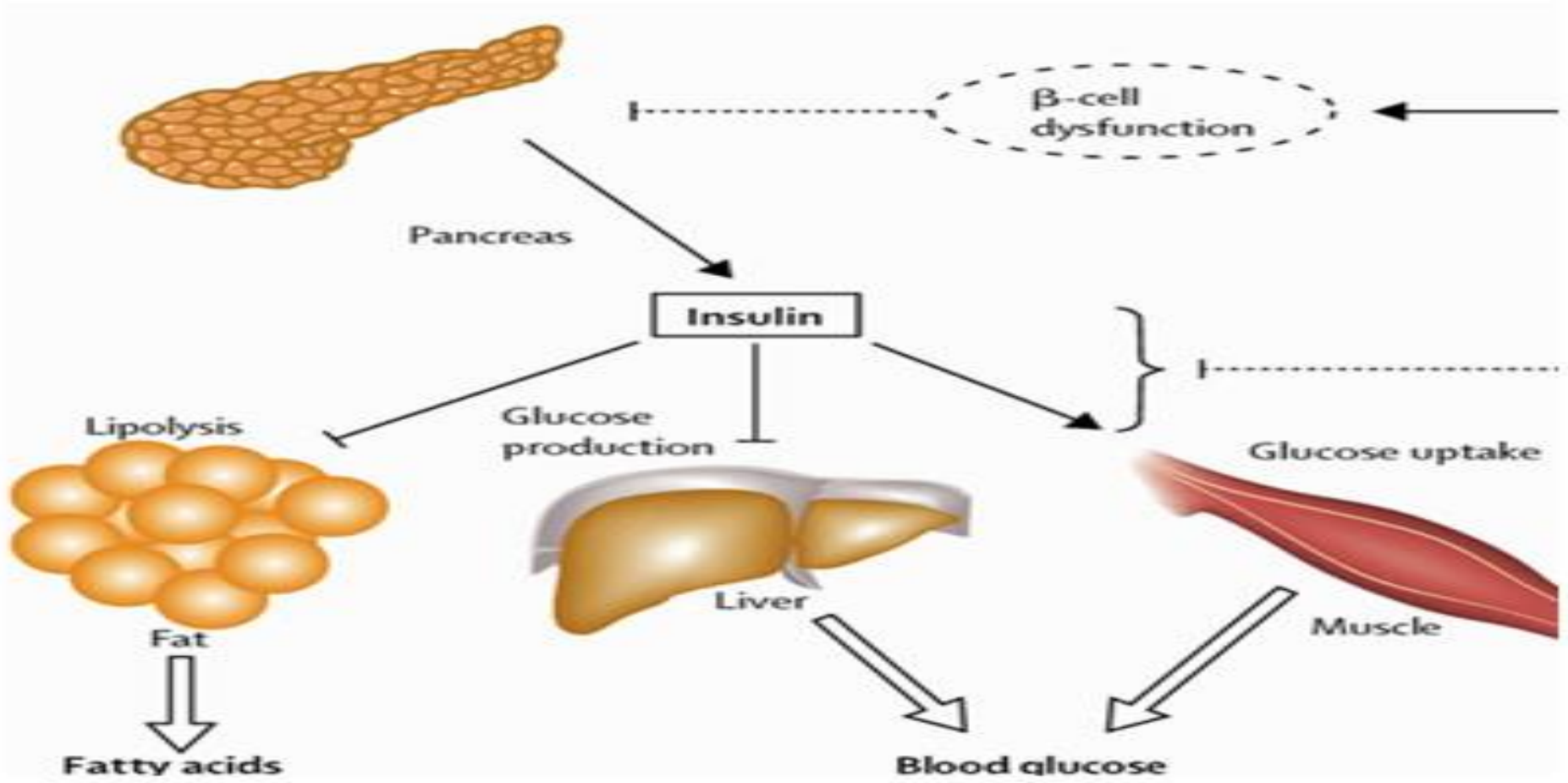
Type 2 Diabetes: Insulin Resistance

Secretion of insulin

Pathogenesis

1. Insulin's resistance

2. B-cells dysfunction



Treatment of T2DM
1. Insulin Sensitizers

1.1.Biguanides (Metformin)

Available since the late 1950s, metformin can trace its roots back to medieval Europe, where biguanides in the form of French lilac were used in diabetes treatment.

Its primary mechanism of action is suppression of hepatic glucose output, but it also enhances insulin sensitivity of muscle and fat.

Biguanides (Metformin)

It affects primarily fasting glycemia; however, some decreases in postprandial glucose concentrations, especially after the midday meal, are also seen.

Metformin is well tolerated. The most common side effects are gastrointestinal complaints.

Metformin causes a small increase in basal and postprandial lactate concentrations in the blood. It is best to avoid use in patients with hepatic impairment.

Biguanides (Metformin)

The use of metformin is contraindicated in patients with a serum creatinine ≥1.5 mg/dL in male patients or ≥1.4 mg/dL in female patients.

The major benefits of metformin are that it usually does not lead to hypoglycemia when used as monotherapy.

It can lead to weight loss (3% to 5% of body weight), and it has been shown to decrease plasma triglycerides concentration by 10% to 20%.

Biguanides (Metformin)

Dosing is typically twice daily; however, it can be dosed 3 times daily.

The typical starting dose is 500 mg per day. The maximum dose is 2550 mg per day but most practitioners use 2000 mg per day as a maximum. Typically, the metformin dosage is gradually increased, starting with a dose of 500 mg with breakfast and increasing by 500 mg in weekly intervals until a dose of 1000 mg with breakfast and dinner is reached.

This approach can help to prevent GI side effects.

1. Insulin Sensitizers
1.2Thiazolidinediones

Thiazolidinediones (TZDs) are agonists of peroxisome proliferator-activated receptor gamma (PPARγ) and they primarily enhance sensitivity of muscle and fat, and mildly of the liver, to exogenous and endogenous insulin. TZDs lower fasting and postprandial blood glucose levels.

The only TZD medication FDA approved for use in the U.S. is pioglitazone.

Thiazolidinediones

Major side effects include weight gain, with an increase in subcutaneous adiposity, and fluid retention which typically manifests as peripheral edema, but heart failure has been shown to occur on occasion.

These agents should be avoided in patients with functional class III or IV heart failure. These effects are most commonly observed in patients who are taking higher doses.

Thiazolidinediones

TZDs have been shown to have an association with an increased risk of fractures, particularly in women. In June 2011 the FDA added a warning to the pioglitazone label about a potentially increased risk of bladder cancer when pioglitazone is used for longer than 1. The TZDs do not cause hypoglycemia when used as monotherapy.

Dosing is once daily. It takes 2 to 12 weeks for TZDs to become fully effective. For pioglitazone, the starting dose is 7.5 mg/day and the maximum dose is 45 mg/day.

2. Insulin Secretagogues

Insulin secretagogues stimulate secretion of insulin from the pancreas, thereby decreasing hepatic glucose production and enhancing glucose uptake by muscles and fat.

Insulin Secretagogues

2. 1. Sulfonylureas

Sulfonylureas reduce fasting and postprandial glucose levels. The main adverse effects include weight gain (about 2 kg upon initiation) and hypoglycemia.

The hypoglycemia episodes can be significant (leading to need for assistance, coma, or seizure) and are seen more often in the elderly. The benefits include a 25% reduction in microvascular complications with or without insulin.

Sulfonylureas

Dosing is typically once or twice daily.

Caution should be used in patients with liver or kidney dysfunction or those who often skip meals.

Newer, second-generation, sulfonylureas (glipizide and glimepiride) may carry less risk of hypoglycemia than older ones (glibenclamide) due to a somewhat glucose-dependent mechanism of action.

Insulin Secretagogues

2.2 Glinides

Glinides work in a manner similar to that of the sulfonylureas; however, they have a more-rapid onset of action and a shorter duration of action, so they are a good option for patients who have erratic timing of meals.

Glinides are associated with a lower risk of hypoglycemia than are sulfonylureas.

Glinides are also linked to a similar risk of weight gain with initiation of therapy. Caution must be used in patients with liver dysfunction.

Doses are taken immediately before meals.

3. Incretin based therapies

Exenatide

Exenatide is a synthetic form of exendin-4, a hormone found in the saliva of the Gila monster. Exenatide mimics glucagon-like peptide type-1 (GLP-1). GLP-1 is produced in the small intestine.

It stimulates insulin secretion, and inhibits glucagon secretion and hepatic glucose production in a glucose-dependent manner.

Exenatide

It also delays gastric emptying and suppresses appetite through central pathways.

It primarily decreases **postprandial blood** glucose levels; however, a moderate reduction in fasting blood glucose levels can also be seen.

Due to its delaying effects on gastric emptying, the major side effects are gastrointestinal complaints such as nausea, vomiting, and diarrhea.

Exenatide

Hypoglycemia does not occur when exenatide is used as monotherapy or with metformin, but it does occur when exenatide is combined with a sulfonylurea.

Benefits include weight loss up to 2 to 3 kg in the first 6 months and up to 5.5 kg in the first 2 years.

As with all incretin-based therapy there is a slightly increased risk of acute pancreatitis in patients taking exenatide.

The medication should be stopped if the patient develops abdominal pain.

Exenatide

Dosing is twice daily by subcutaneous injection—with meals. The starting dose is 5 mcg. If this dose is tolerated, it can be increased to 10 mcg after 1 month.

The new, extended action, preparation of exenatide was released in the spring of 2012. This formulation is administered as a weekly subcutaneous injection.

Side effects and indications are same as for short acting exenatide.

Liraglutide

Liraglutide is another GLP-1 analog that is derived from the native human GLP-1 and maintains 97% homology with it.

In a head-to-head study with exenatide liraglutide showed slightly better glycemic control with the same rate of hypoglycemia and slightly more weight loss.

Liraglutide

Liraglutide is taken once a day, at any time of the day; there is no need to take it with meals. Side effects include nausea, vomiting, and diarrhea but only a small percentage of patients stopped therapy due to side effects.

The initial dose is 0.6 mg/day which is increased to 1.2 mg/day after 1 week.

This dose is considered therapeutic but can be increased to 1.8 mg/day after another week if glycemic goals are not achieved.

4. Dipeptidyl Peptidase 4 Inhibitors

Dipeptidyl peptidase 4 (DPP 4) is a cell membrane protein that rapidly degrades GLP-1 and glucose-dependent insulinotropic polypeptide (GIP).

Suppression of DPP 4 leads to higher levels of insulin secretion and suppression of glucagon secretion in a glucose-dependent manner.

Dipeptidyl Peptidase 4 Inhibitors

DPP 4 inhibitors act primarily on **postprandial blood glucose levels**, but reductions in fasting glycemia are also seen.

It is generally well tolerated, and the most common side effect is headache.

An increase in nasopharyngitis has also been seen.

Benefits include that it is weight neutral and does not cause hypoglycemia when used as monotherapy or in combination with metformin or TZDs.

Dipeptidyl Peptidase 4 Inhibitors

Dosing is 100 mg orally once daily with or without meals.

Dose reduction in required in patients with renal impairment.

In those with a creatinine clearance 30 mL/min to 50 mL/min, dosing is 50 mg once daily.

In those patients with a creatinine clearance <30 mL/minute, dosing is 25 mg once daily.

5. Pramlintide

Pramlintide is a synthetic form of amylin, a hormone secreted by beta-cells that acts to suppress glucagon secretion, slow gastric emptying, and suppress appetite through central pathways.

It acts primarily on **postprandial blood glucose** levels.

Pramlintide

As with exenatide, the major side effects are gastrointestinal complaints, especially nausea, and hypoglycemia.

Benefits of therapy include weight loss of 1 to 1.5 kg over 6 months and up to 4.5 kg with prolonged therapy.

Currently in the U.S. pramlintide is approved only as an adjunctive therapy with insulin, but it can be used both in patients with T1DM and T2DM.

Pramlintide

Patients can see up to a 50% reduction in insulin requirements with the addition of pramlintide.

Starting dose for T2DM is generally 60 mcg subcutaneously before meals and for T1DM is 15 mcg before each meal.

It can be used in patients taking insulin, metformin, or sulfonyureas.[1]

6. Bromocriptine

The exact mechanism of action by which bromocriptine improves glycemic control is not known.

Bromocriptine is a central dopamine agonist and when given in rapid-release form in the morning within 2 hours of awakening it improves glycemic control for patients with DMT2.

The initial dose is 0.8 mg. This is increased in weekly increments by 0.8 mg until the therapeutic dose of 1.6 to 4.8 mg is achieved. Bromocriptine is taken with food in order to diminish nausea.

Insulin

Patients with T2DM often require insulin, which can be combined with oral hypoglycemic agents.

Regimens include:

only basal

twice-daily premixed insulin,

basal – bolus insulin therapy.

ADA recommendation -2012

Monotherapy

Initiate monotherapy when HbA_{1c} levels are 6% to 7%

Options include:

Metformin

Thiazolidinediones

Secretagogues

Dipeptidyl-peptidase 4 inhibitors

Alpha-glucosidase inhibitors

Monitor and titrate medication for 2 to 3 months

Consider combination therapy if glycemic goals are not met at the end of 2 to 3 months

ADA recommendation -2012
Combination Therapy

Initiate combination therapy when levels are 7% to 8%

Secretagogue + metformin

Secretagogue + thiazolidinedione

Secretagogue + alpha-glucosidase inhibitor

Thiazolidinedione + metformin

Dipeptidyl-peptidase 4 inhibitor + metformin

Dipeptidyl-peptidase 4 inhibitor + thiazolidinedione

Secretagogue + metformin + thiazolidinedione

Fixed-dose (single pill) therapy

Thiazolidinedione (pioglitazone) + metformin

Thiazolidinedione (rosiglitazone) + metformin

Thiazolidinedione (rosiglitazone) + secretagogue (glimepiride)

Thiazolidinedione (pioglitazone) + secretagogue (glimepiride)

Secretagogue (glyburide) + metformin

ADA recommendation -2012 Combination Therapy

Initiate or intensify combination insulin therapy using options listed above when HbA_{1c} levels are 8% to 10%.

Initiate or intensify insulin therapy when HbA_{1c} levels are >10%

Rapid-acting insulin analogue or inhaled insulin with long-acting insulin analogue or NPH

Premixed insulin analogues

Chronic Complications of Diabetes Mellitus

Chronic complications can be divided into **vascular and nonvascular** complications.

The vascular complications of DM are further subdivided into **micro vascular** (retinopathy, neuropathy, and nephropathy) and **macro vascular** complications (coronary artery disease, peripheral arterial disease, cerebrovascular disease).

Chronic Complications of Diabetes Mellitus

Nonvascular complications include problems such as **gastroparesis, infections, and skin changes**. Long-standing diabetes may be associated with **hearing loss**.

The risk of chronic complications increases as a function **of the duration of hyperglycemia**; they usually become apparent in the second decade of hyperglycemia.

Complications of Diabetes

Microvascular

- Retinopathy
- Neuropathy
- Nephropathy

Macrovascular

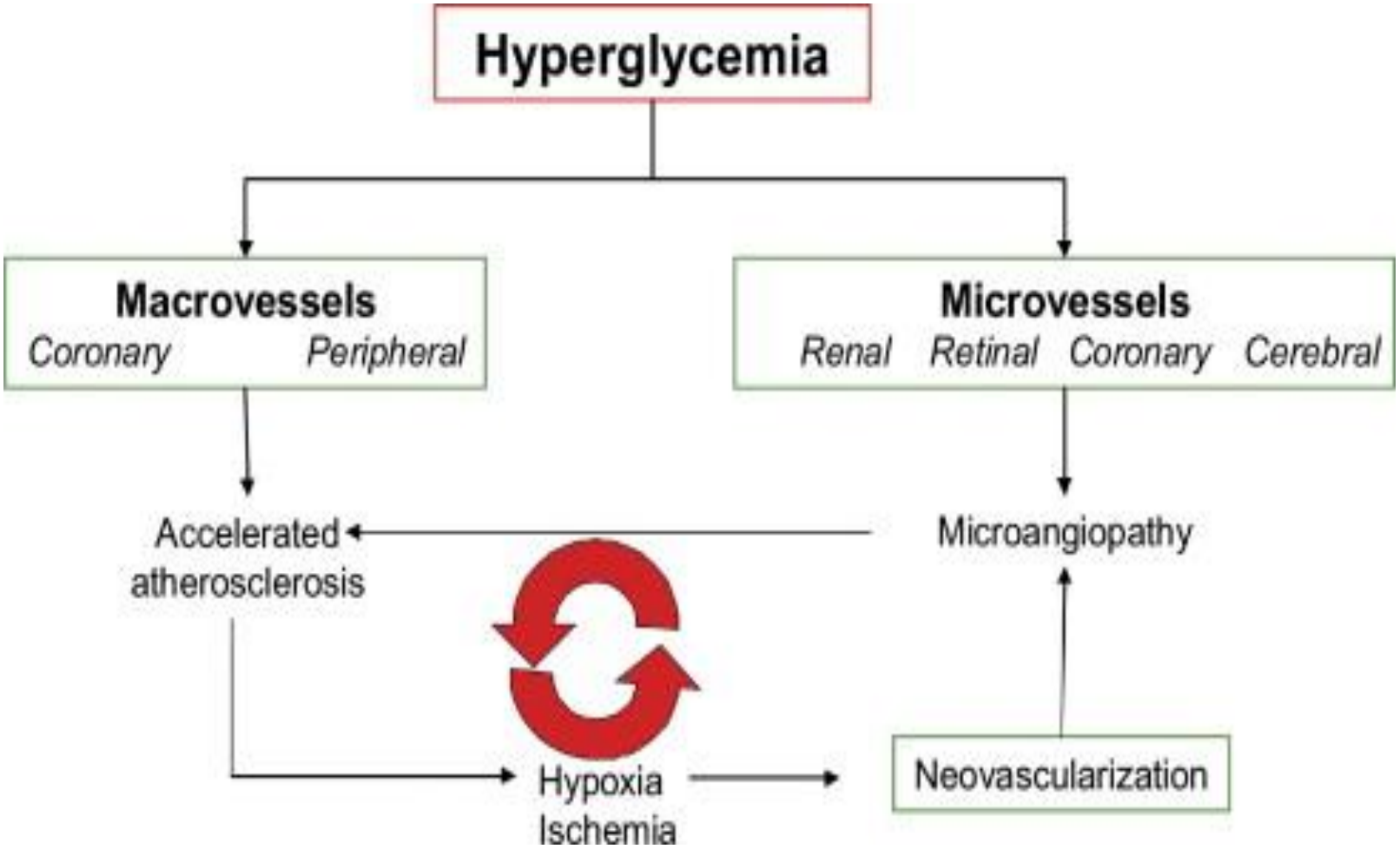
- Cerebrovascular disease
- Peripheral vascular disease
- Coronary heart disease

Chronic Complications of Diabetes Mellitus

The **microvascular** complications (retinopathy, neuropathy, and nephropathy) are typical for T1DM

The **macrovascular** complications coronary artery disease, peripheral arterial disease, cerebrovascular disease are more typical for T2DM .

Mechanisms of Complications



Mechanisms of Complications

Microvessels—the smallest functional unit of the CV system—consist of arterioles, capillaries, and venules. These vessels differ significantly from macrovessels with respect to architecture and cellular components.

In contrast to **larger vessels** providing blood to organs, microvessels have specific roles regulating blood pressure and offering nutrient delivery.

The **microcirculation** also has regulatory systems such as vasomotion, permeability, and myogenic responses that can adapt flow to local metabolic needs.

Disturbances in microvascular function may arise before overt hyperglycemia and vascular pathologic changes .

Mechanisms of Complications

The most consistent structural diabetic microvascular modification is a **thickening of the capillary basement membrane, including arterioles in the glomeruli, retina, myocardium, skin, and muscle, resulting in the classic diabetic microangiopathy**.

This thickening alters vessel function, directly promoting hypertension, reduced wound healing, and tissue hypoxia.

Mechanisms of Complications

One prominent theory have been proposed to explain how hyperglycemia might lead to the chronic complications of DM.

Advanced Glycosylation End Products

Increased intracellular glucose leads to the formation of advanced glycosylation end products (AGEs) via the nonenzymatic glycosylation of intra- and extra cellular proteins. Nonenzymatic glycosylation results from the interaction of glucose with amino groups on proteins.

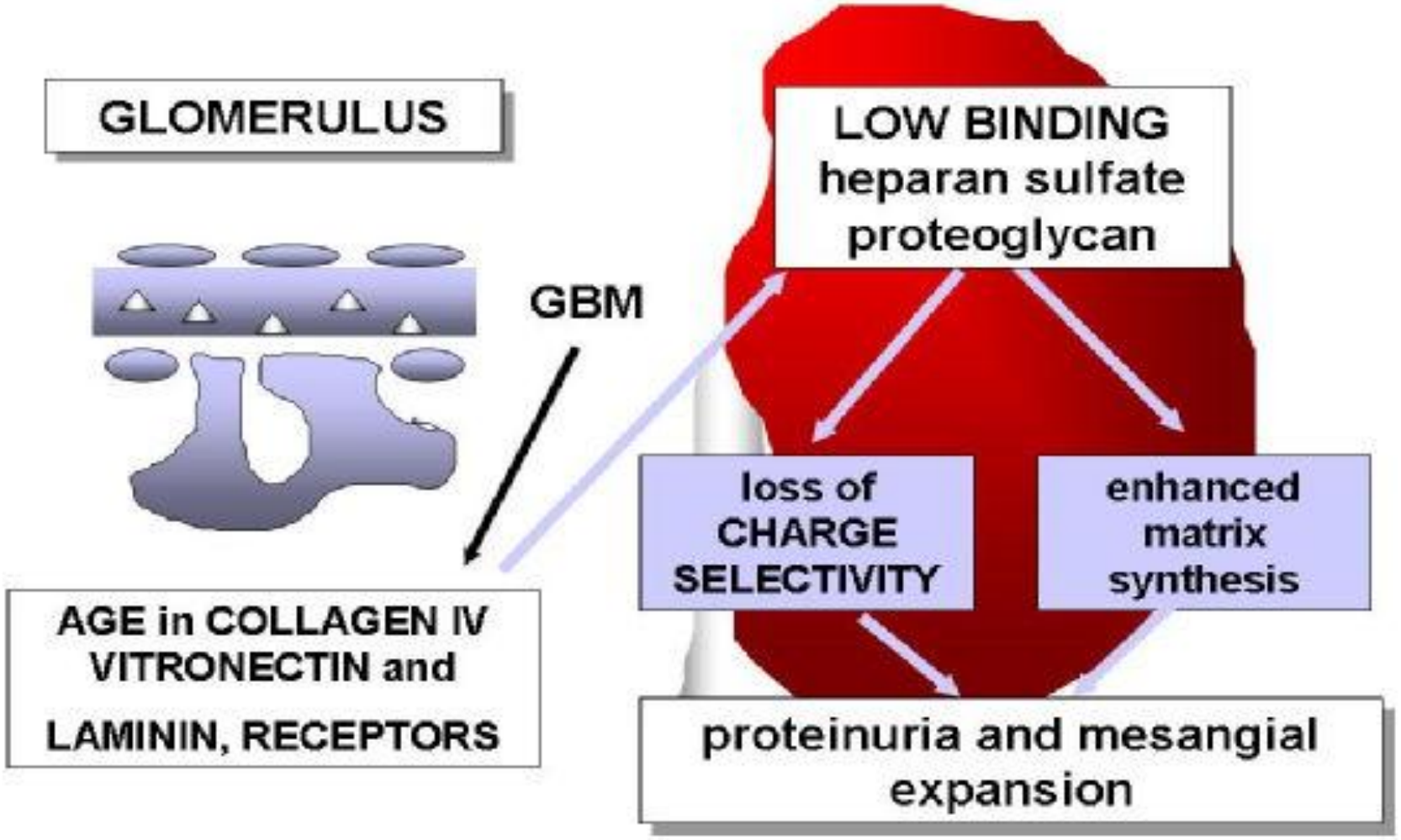
Mechanisms of Complications

AGEs have been shown to cross-link proteins (e.g., collagen, extracellular matrix proteins), **accelerate atherosclerosis, promote glomerular dysfunction, reduce nitric oxide synthesis, induce endothelial dysfunction, and alter extracellular matrix composition and structure**.

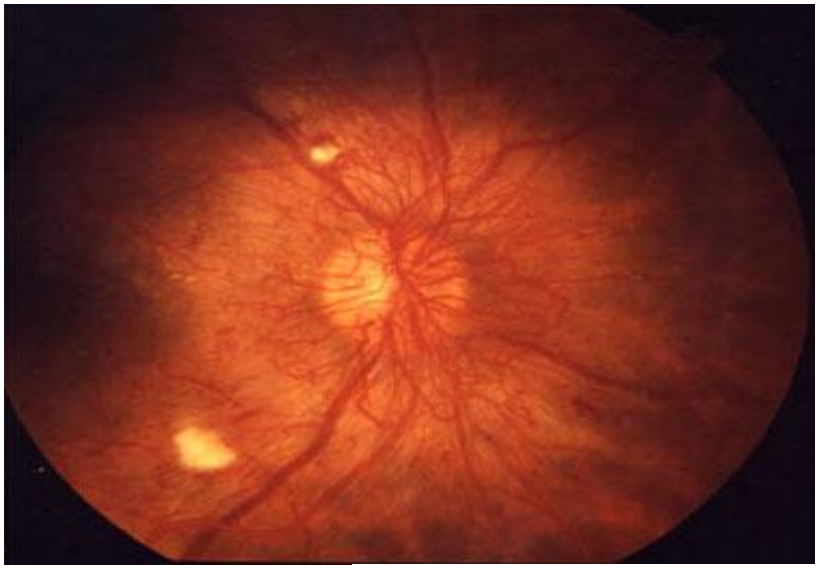
The serum level of AGEs correlates with the level of glycemia, and these products accumulate as glomerular filtration rate declines.

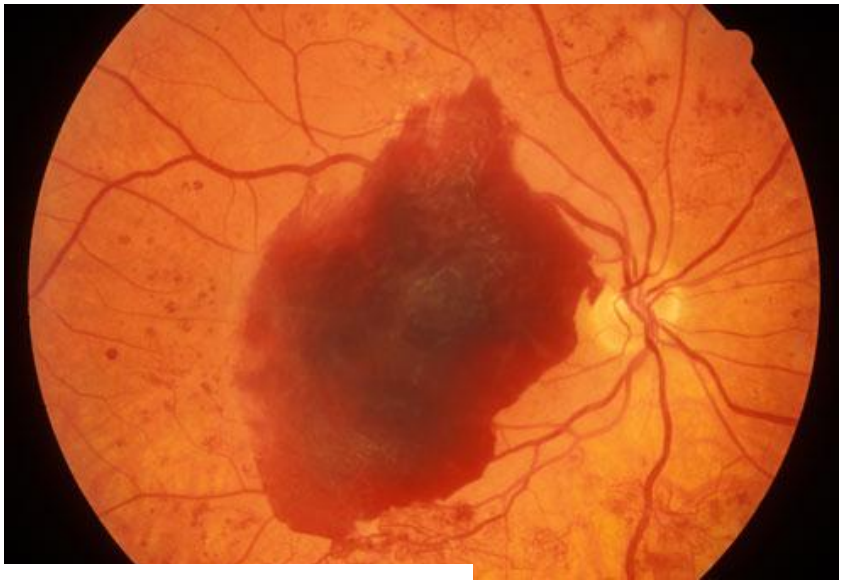
Mechanisms of Complications

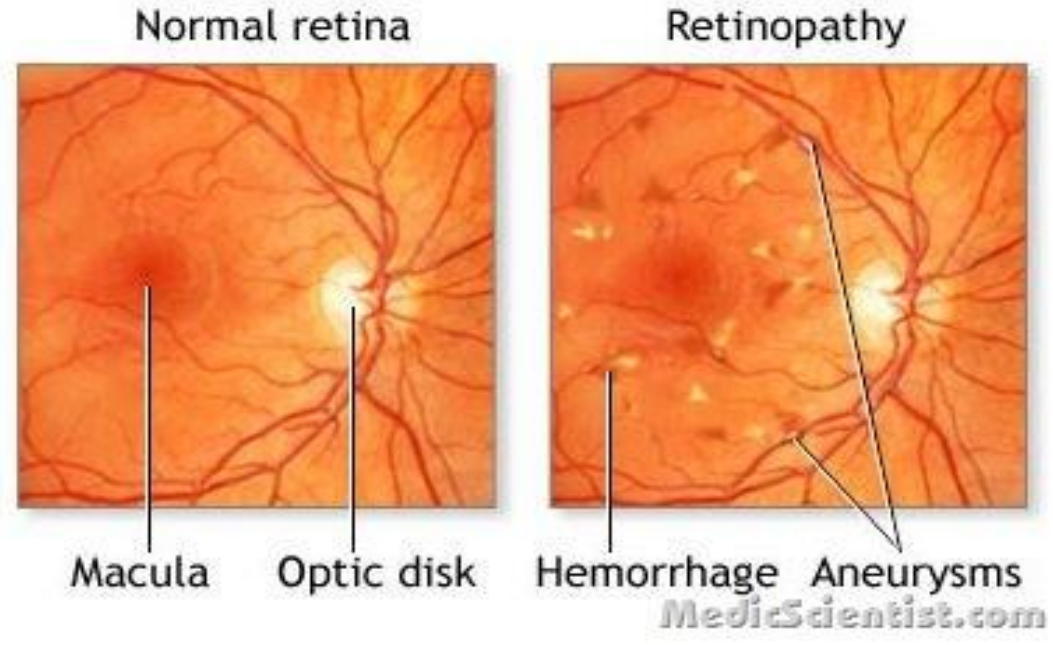
Fig 4



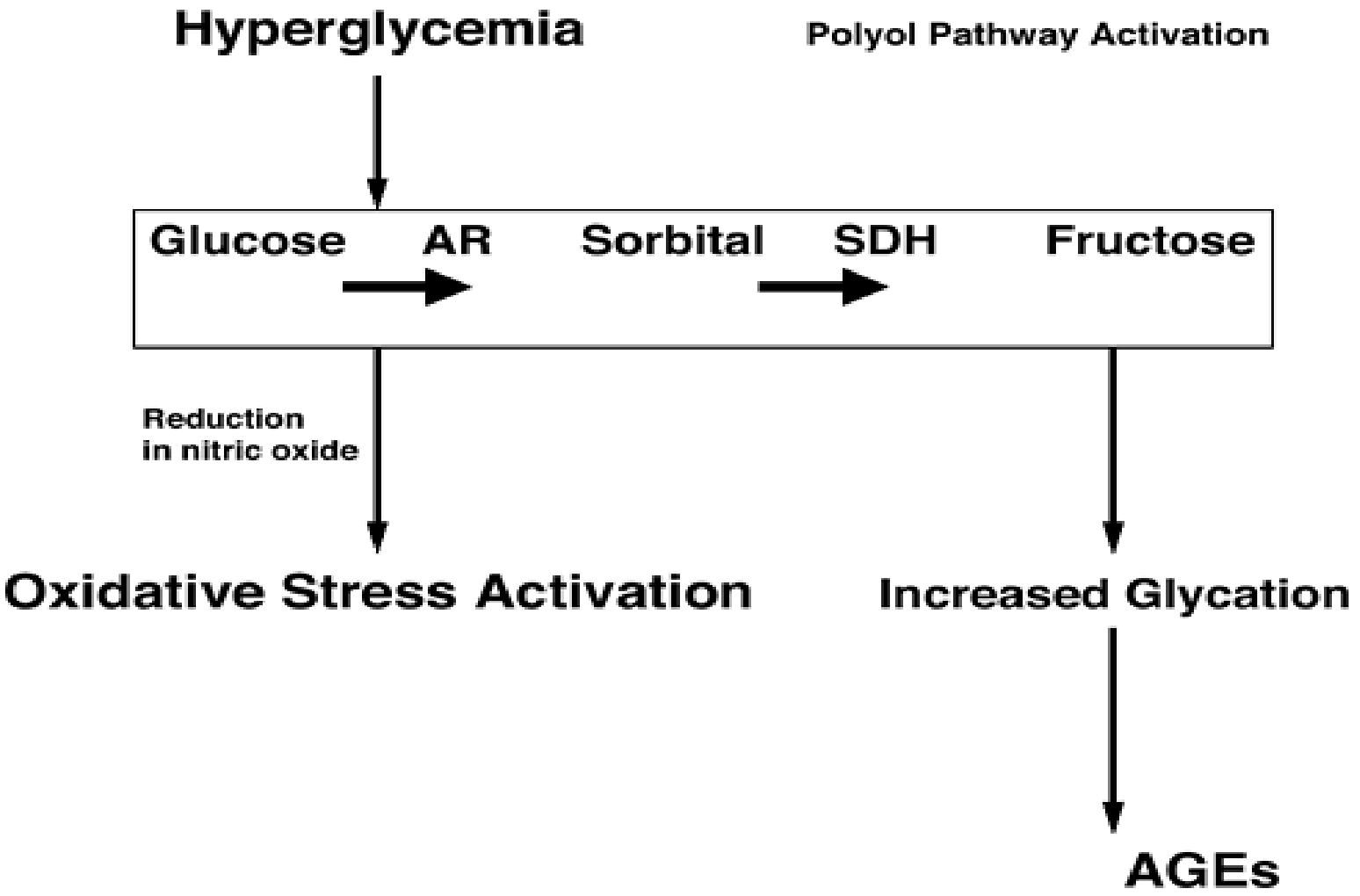
Diabetic Retinopathy







Mechanisms of Complications – T2DM



Mechanisms of Complications – T2DM

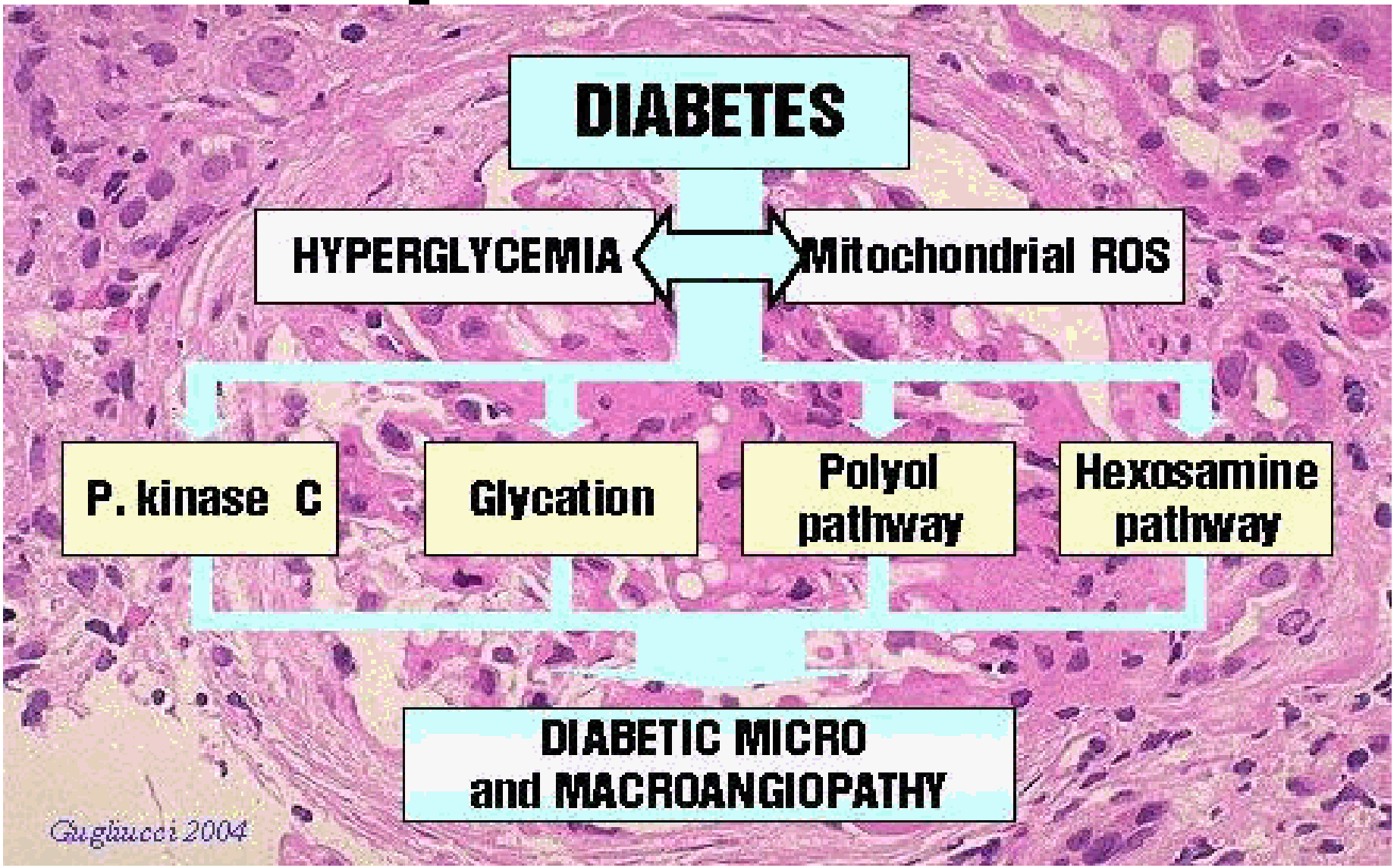
Oxidative stress has been implicated in both microvascular and macrovascular disease. Hyperglycemia promotes formation of reactive oxygen species, which can interact with both DNA)and proteins, causing damage. Mitochondrial DNA may be an especially relevant target.

Interestingly, reactive oxygen species-mediated cellular damage may be a form of pathologic “memory” in the microvasculature that persists even after glucose normalization, as suggested in human retinal vessels.

Mechanisms of Complications – T2DM

Oxidative stress may also link hyperglycemia with other pathways (polyol pathways) implicated in diabetic vascular complications, including AGE formation, protein kinase C activation, increased polyol flux, and hexosamine formation.

Mechanisms of Complications – T2DM



History

Diabetes was one of the first diseases described, with an Egyptian manuscript from 1500 BC mentioning "too great emptying of the urine".

Indian physicians around the same time identified the disease and classified it as "honey urine", noting the urine would attract ants.

The term "diabetes" or "to pass through" was first used in 230 BCE by the Greek Apollonius of Memphis.

History

Type 1 and type 2 diabetes were identified as separate conditions for the first time by the **Indian physicians Sushruta and Charaka** in 400-500 CE with type 1 associated with youth and type 2 with being overweight.

The term "mellitus" or "from honey" was added by the Briton John Rolle in the late 1700s to separate the condition from diabetes insipidus.

History

Effective treatment was not developed until the early part of the 20th century, when Canadians **Frederic Banting and Charles Best** isolated and purified insulin in 1921 and 1922.

This was followed by the development of the long-acting insulin NPH in the 1940s.