Introduction to Diabetes Mellitus

TUCOM

Dep. of Medicine

3rd year

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Learning objectives:

1. Define diabetes mellitus
2. Review the functional anatomy and physiology of endocrine portion of pancreas
3. List the main action of endogenous insulin
4. Classify diabetes mellitus
5. Explain the aetiology and pathogenesis of diabetes mellitus
6. Make a comparison of the two types of diabetes mellitus
7. List the symptoms of diabetes mellitus
8. Review the investigations and WHO diagnostic criteria of diabetes mellitus
9. Discuss the various treatment modalities of diabetes mellitus
10. List the complications of diabetes mellitus

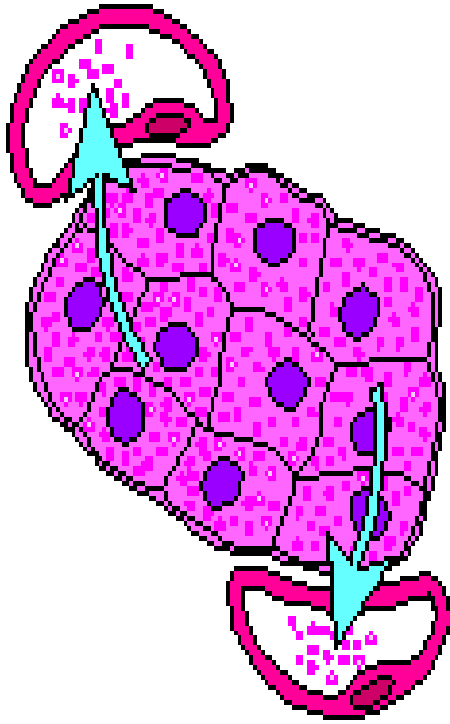
Diabetes mellitus

Is a heterogeneous group of metabolic diseases that are characterized by chronic hyperglycemia and disturbances in carbohydrate, lipid, and protein metabolism resulting from defects in insulin secretion and/or insulin action, which can leads to serious complications.

Insulin is an anabolic hormone with profound effects on the metabolism of carbohydrate, fat and protein.

Insulin is secreted from pancreatic β cells into the portal circulation, with a brisk increase in response to a rise in blood glucose.

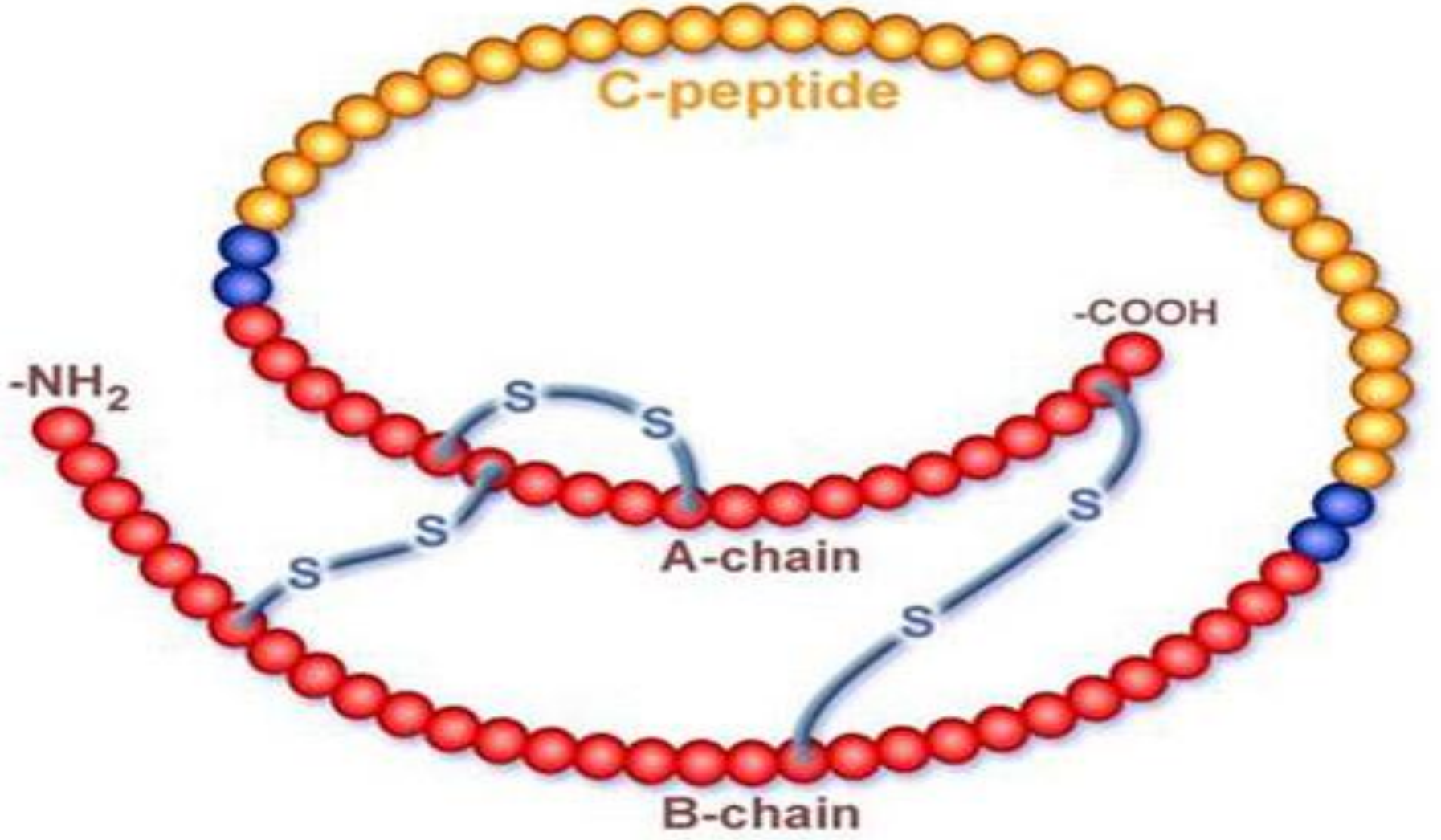
Endocrine function of pancreas



A(α) cells produce glucagon: Glucagon is a catabolic hormone. It mobilizes glucose, fatty acids and amino acids from stores into the blood.

B(β) cells produce insulin: Insulin is an anabolic hormone, that increases the storage of glucose, fatty acids and amino acids in cells and tissues. Composed of 2 polypeptide chains linked by disulphide bridges. Secreted as proinsulin and transformed to active form, insulin, by cleaveage of C peptide by protease enzymes.

D(δ) cells produce somatostatin: Somatostatin may regulate, locally, the secretion of the other pancreatic hormones.



Insulin is synthesised as a pro-hormone (pro-insulin) that consists of an α and a β chain, which are linked by C-peptide. The C-peptide is cleaved by β-cell peptidases to create insulin (which now consists of the α and β chains) and free C-peptide.

Some characteristics of normal insulin secretion are shown in the table (next slide). Insulin lowers blood glucose by suppressing hepatic glucose production and stimulating glucose uptake in skeletal muscle and fat, mediated by the glucose transporter, GLUT 4.

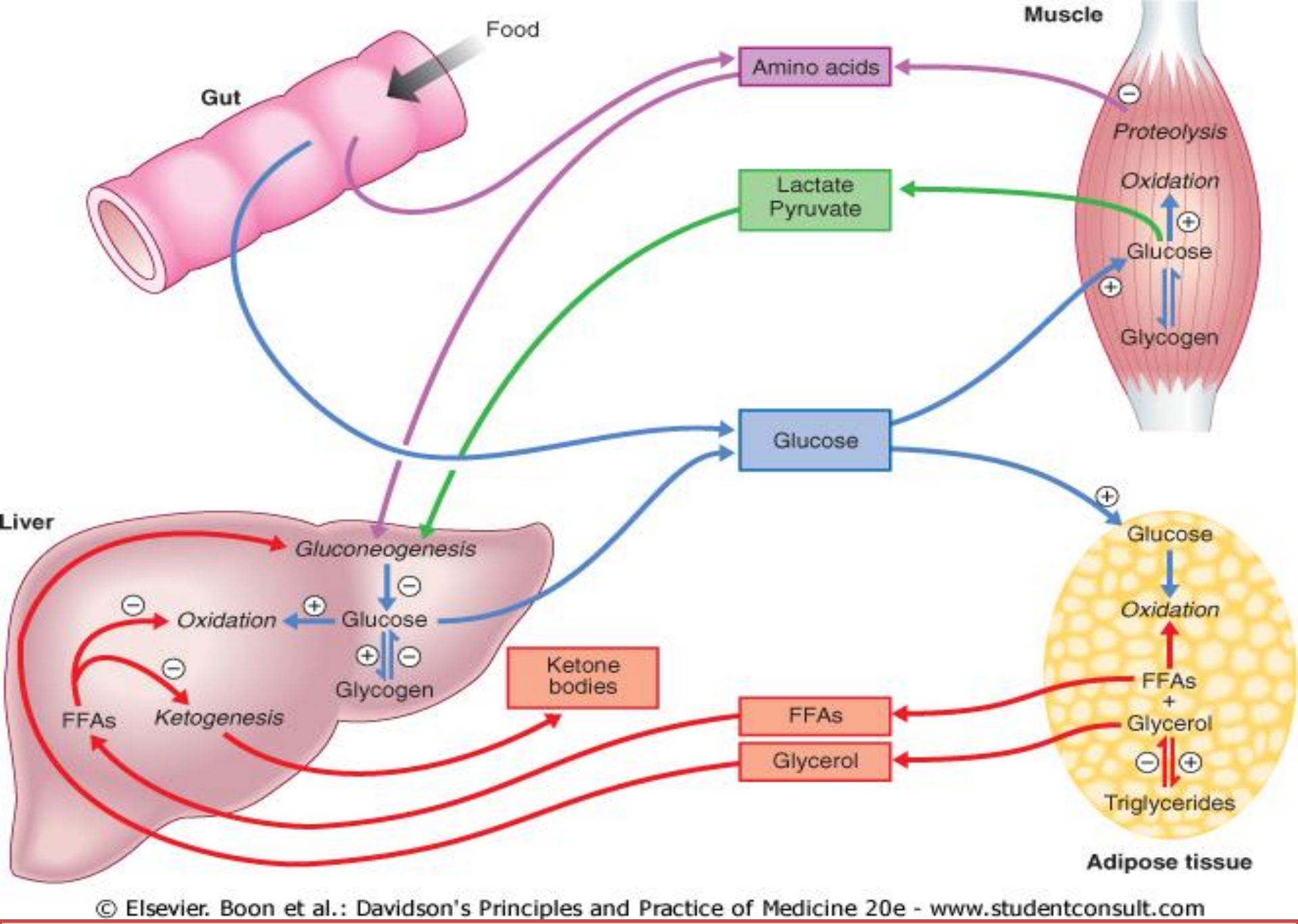
Insulin stimulates lipogenesis and inhibits lipolysis, so preventing fat catabolism.

In the fasting state, low insulin levels permit lipolysis and the release into the circulation of FFAs (and glycerol). Partial oxidation of FFAs in the liver provides energy to drive gluconeogenesis and also produces ketone bodies (**acetoacetate**, which can be reduced to **3-hydroxybutyrate** or decarboxylated to **acetone**) which are generated in hepatocyte mitochondria. Ketone bodies are formed in small amounts and utilised as metabolic fuel.

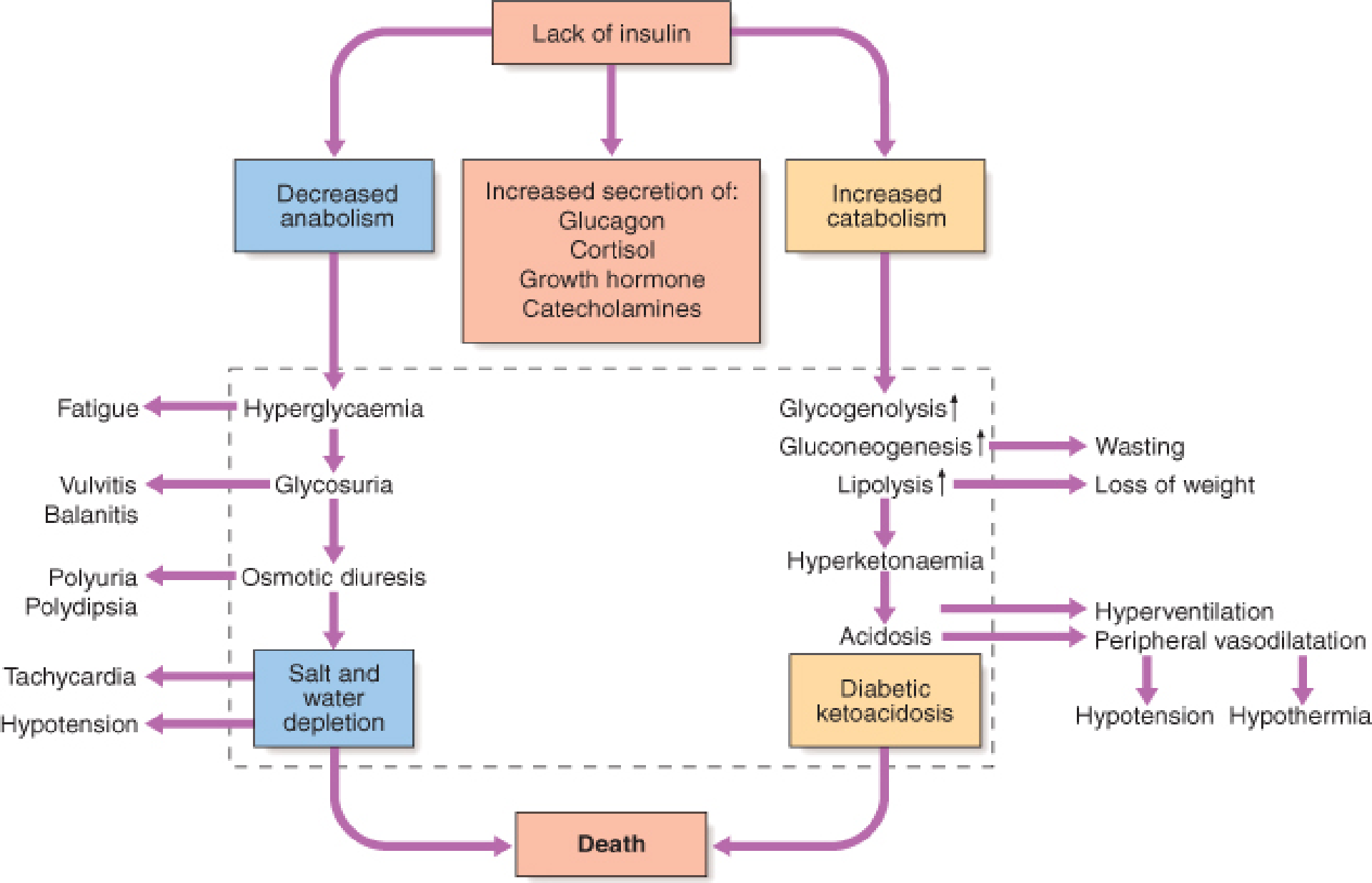
However, when the rate of production by the liver exceeds their removal, hyperketonaemia results. This occurs physiologically during starvation, when low insulin levels and high catecholamine levels increase lipolysis and delivery of FFAs to the liver.

21.1 Metabolic actions of insulin

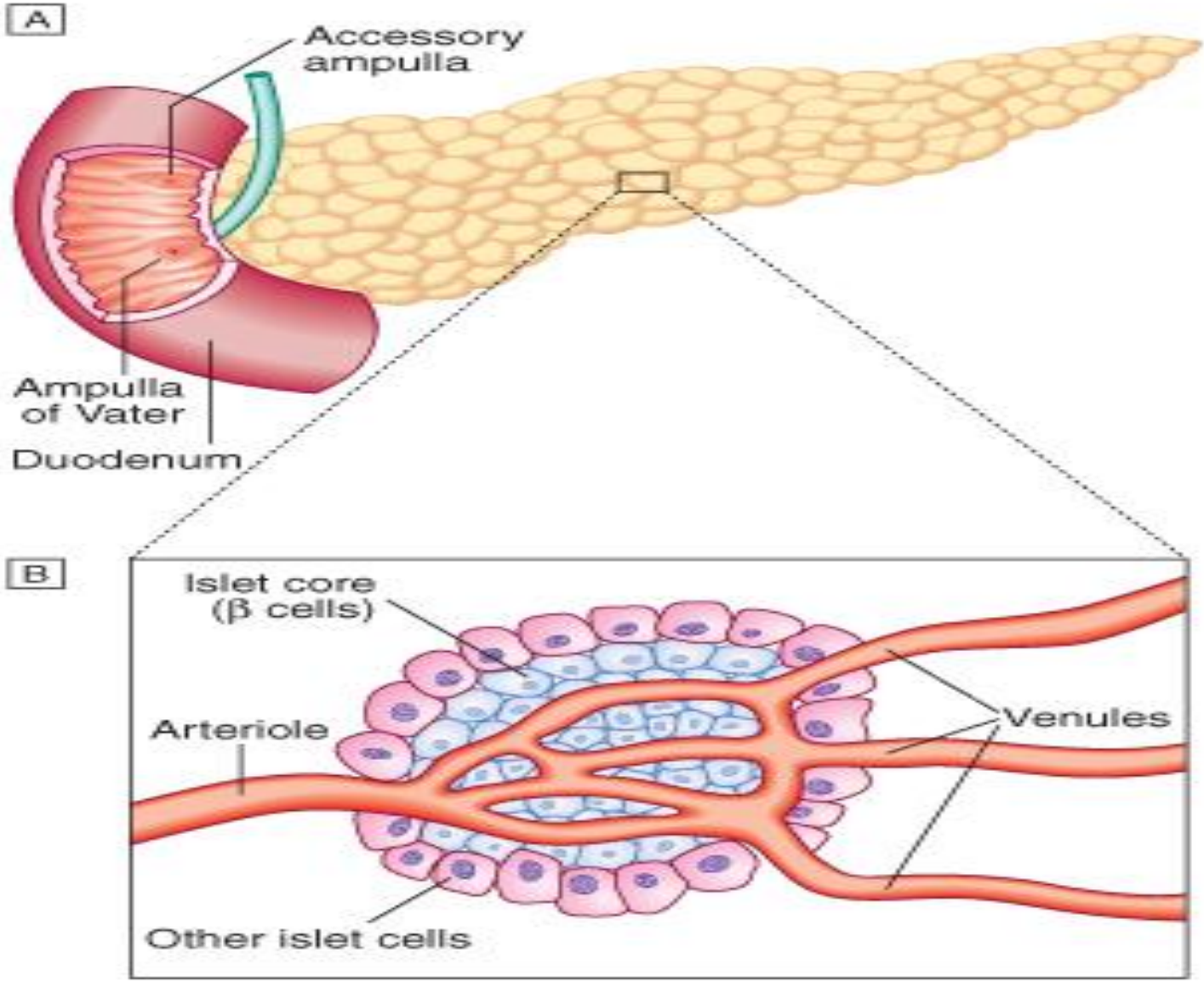
Increase	Decrease
Carbohydrate metabolism	
Glucose transport (muscle, adipose tissue)	Gluconeogenesis
Glucose phosphorylation	Glycogenolysis
Glycogen synthesis	
Glycolysis	
Pyruvate dehydrogenase activity	
Pentose phosphate shunt	
Lipid metabolism	
Triglyceride synthesis	Lipolysis
Fatty acid synthesis (liver)	Lipoprotein lipase (muscle)
Lipoprotein lipase activity (adipose tissue)	Ketogenesis
	Fatty acid oxidation (liver)
Protein metabolism	
Amino acid transport	Protein degradation
Protein synthesis	



Major metabolic pathways of fuel metabolism and the actions of insulin



Insulin deficiency can lead to hyperglycemia and many metabolic derangements which occur mainly in type 1 DM that can leads to death if not treated correctly.

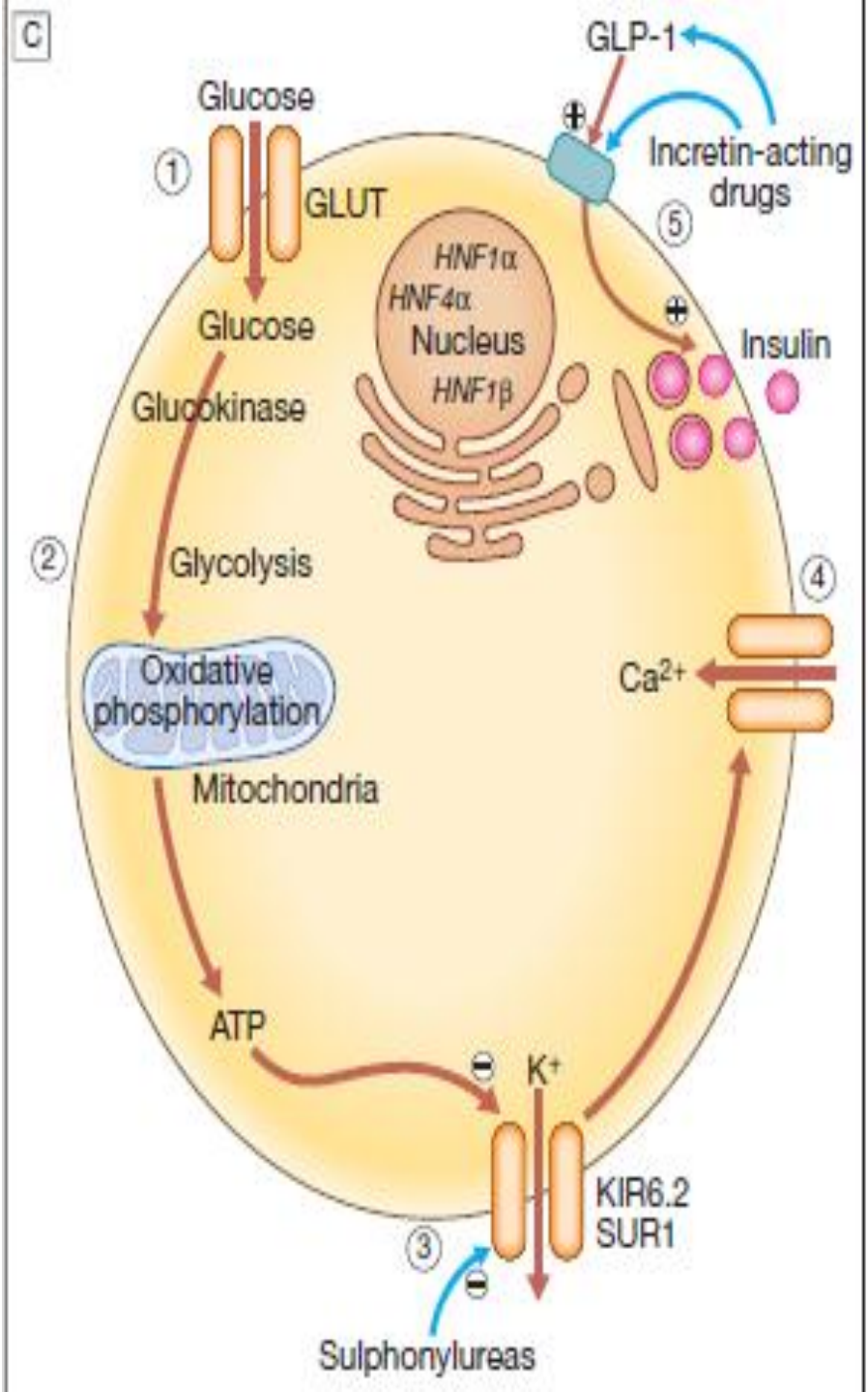


A- The normal adult pancreas contains about 1 million islets which are scattered throughout the exocrine parenchyma.

B- The core of each islet consists of β cells that produce insulin, and is surrounded by a cortex of endocrine cells that produce other hormones including glucagon (α cells), somatostatin (δ cells).

Schematic representation of the pancreatic β cell. ATP acts to close the KATP channel, results in calcium influx due to opening of a voltage-gated calcium channel. This rise in intracellular calcium causes insulin secretory vesicles to fuse with the cell membrane, leading to insulin secretion. Other stimuli, such as glucagon-like peptide-1 (GLP-1) or gastric inhibitory polypeptide (GIP), act on G-protein-coupled receptors to increase cyclic adenosine monophosphate (cAMP) and amplify the insulin secretion.

Two groups of drugs act on the β cell to promote insulin secretion. Sulphonylureas act to close the KATP channel, causing membrane depolarisation, calcium influx and insulin secretion. Incretin-acting drugs either increase the concentration of endogenous GLP-1 and GIP (the dipeptidyl peptidase 4, or DPP-4, inhibitors) or act as directly on the GLP-1 receptor (GLP-1 receptor agonists).



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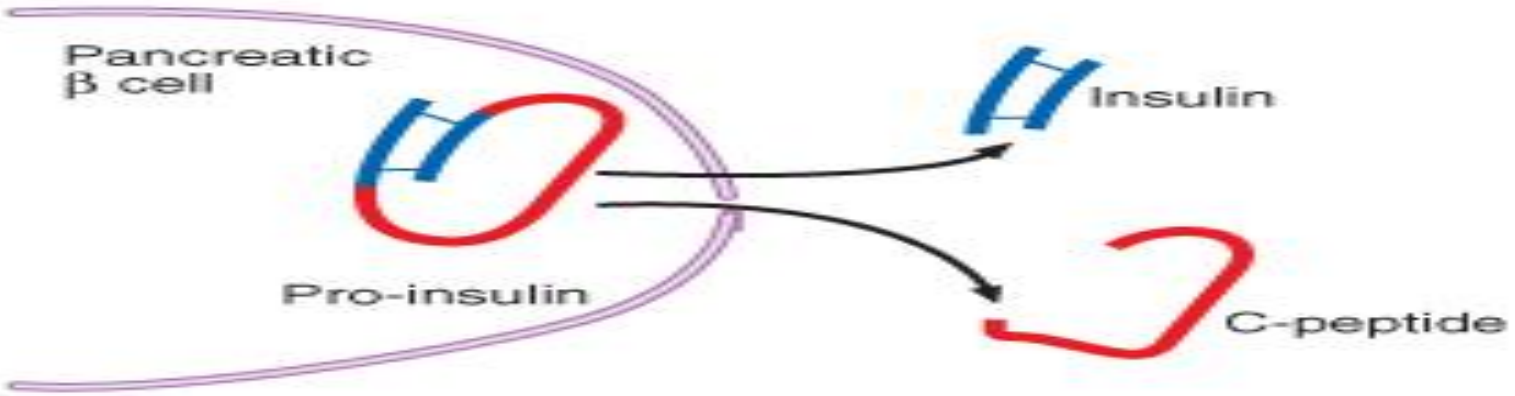

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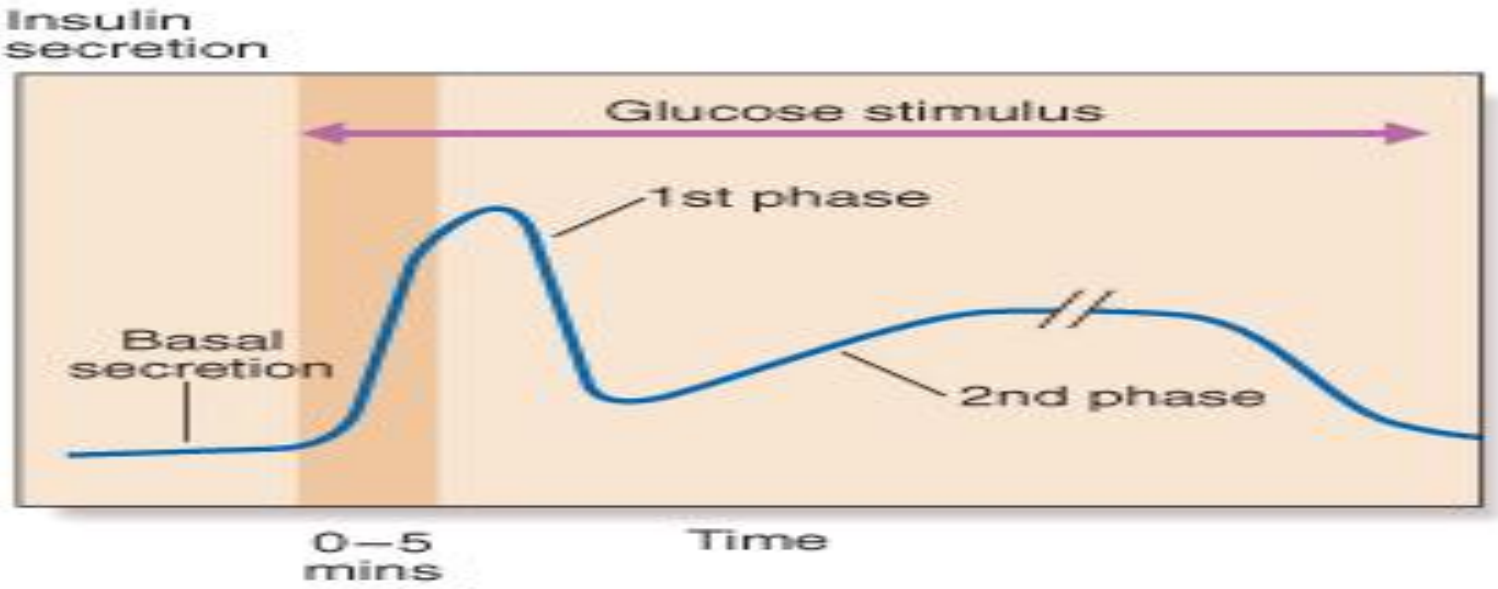


C- Pro-insulin in the pancreatic β cell is cleaved to release insulin and equimolar amounts of inert C-peptide (connecting peptide). Measurement of C-peptide can be used to assess endogenous insulin secretory capacity.

D- An acute first phase of insulin secretion occurs in response to an elevated blood glucose, followed by a sustained second phase.

AETIOLOGICAL CLASSIFICATION OF DIABETES MELLITUS

Type 1 diabetes Immune-mediated , Idiopathic

Type 2 diabetes

Other specific types

- Genetic defects of β-cell function (MODY)
- Pancreatic disease (e.g. pancreatitis, pancreatectomy, neoplastic disease, cystic fibrosis, haemochromatosis)
- Excess endogenous production of hormonal antagonists to insulin (e.g. growth hormone-acromegaly; glucocorticoids-Cushing's syndrome; glucagon-glucagonoma; catecholamines- phaeochromocytoma; thyroid hormones-thyrotoxicosis)
- Drug-induced (e.g. corticosteroids, thiazide diuretics, phenytoin)
- Viral infections (e.g. congenital rubella, mumps, Coxsackie virus B)
- Uncommon forms of immune-mediated diabetes (LADA)
- Associated with genetic syndromes (e.g. Down's syndrome; Klinefelter's syndrome; Turner's syndrome; DIDMOAD (Wolfram's syndrome)-diabetes insipidus, diabetes mellitus, optic atrophy, nerve deafness; Friedreich's ataxia; myotonic dystrophy)

Gestational diabetes

AETIOLOGY AND PATHOGENESIS OF DIABETES

In both of the common types of diabetes, environmental factors interact with genetic susceptibility.

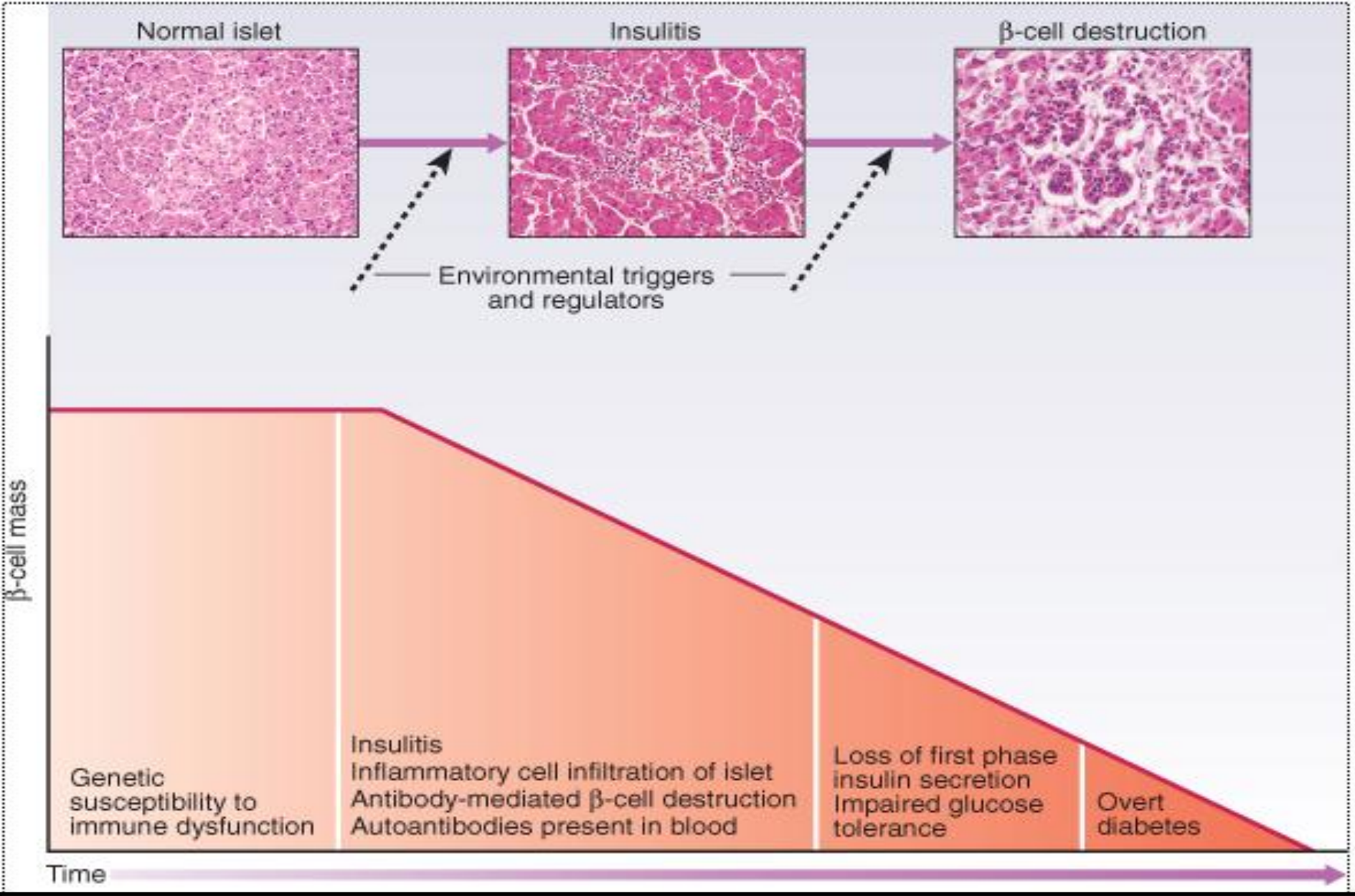
TYPE 1 DIABETES:

Pathology:

Is a slowly progressive T cell-mediated autoimmune disease, destruction of the insulin-secreting cells in the pancreatic islets takes place over many years.

Hyperglycemia accompanied by the classical symptoms of diabetes occurs only when 80-90% of β cells have been destroyed.

Pathologically characterized by 'insulitis': infiltration of the islets by activated macrophages and other inflammatory cells, that leads to specific destruction of β cells.



'insulitis' , infiltration of the islets with mononuclear cells containing activated macrophages. the initial patchiness of this lesion. the striking β-cell specificity of the destructive process, with the glucagon and other hormone-secreting cells in the islet invariably remaining intact.

Type 1 DM associated with other autoimmune disorders like: thyroid disease, coeliac disease, Addison's disease, pernicious anemia and vitiligo.

Genetic factors: account for about one-third of the susceptibility to type 1 diabetes, the inheritance is Polygenic, related to human leucocyte antigen (HLA). The HLA haplotypes DR3 and/or DR4 are associated with increased susceptibility to type 1 DM.

Environmental factors: induce autoimmune reaction

- Viral infection, including mumps, Coxsackie B4, retroviruses, rubella (in utero), cytomegalovirus and Epstein-Barr virus.
- Bovine serum albumin (BSA), from cow's milk.
- Various nitrosamines
- Stress

TYPE 2 DIABETES:

Pathology: More complex; is a combination of **resistance** to the actions of insulin in liver and muscle together with **impaired** pancreatic β-cell function leading to 'relative' insulin deficiency.

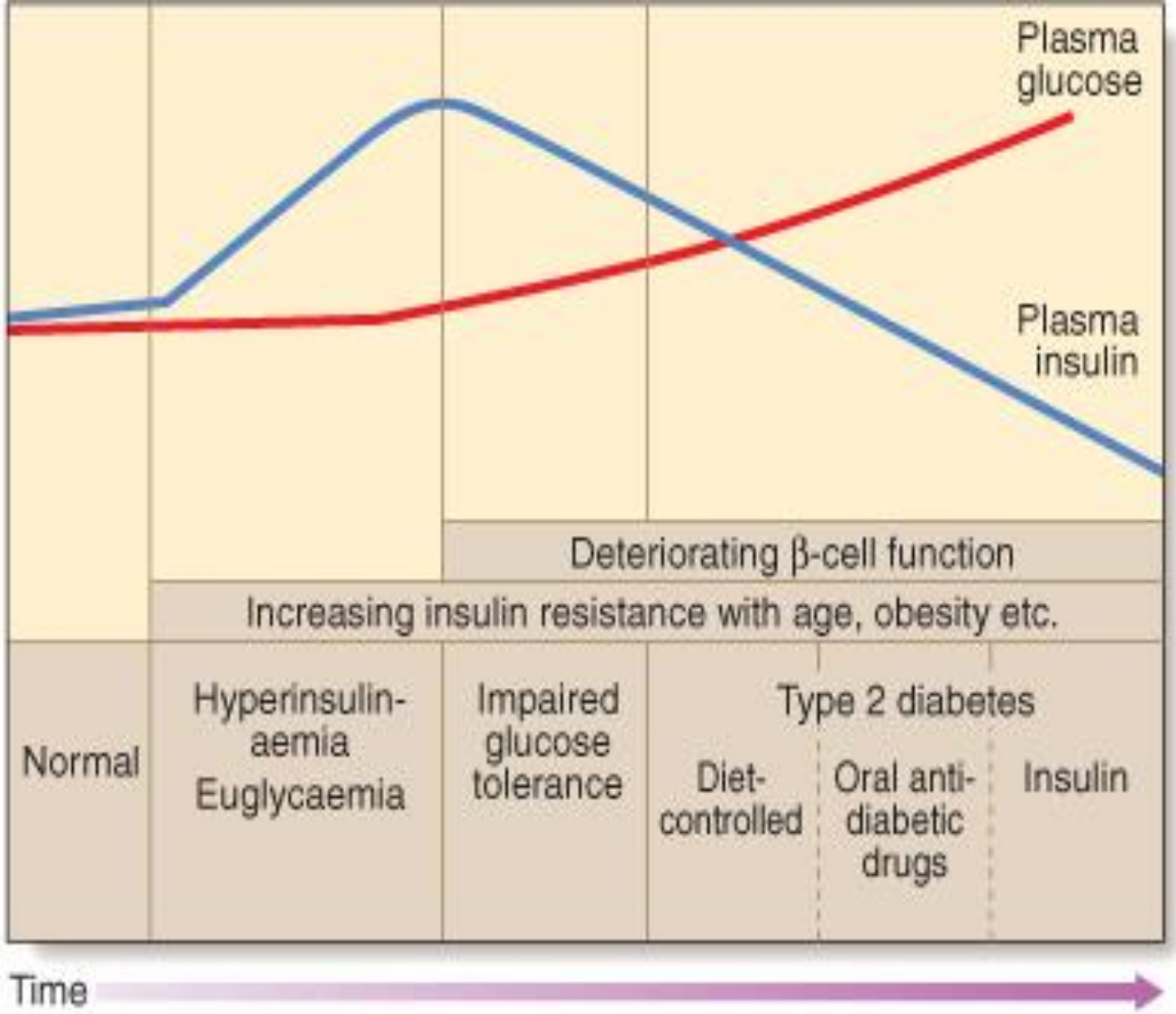
Coexisted with central obesity and 'metabolic syndrome', due to releases large quantities of FFAs, which may induce insulin resistance

Pathological change typical of type 2 DM is deposition of amyloid in the islets.

At the time of diagnosis, around 50% of β-cell function has been lost and this declines progressively.

Genetic factors: are important shown by marked differences in susceptibility in different ethnic groups and by studies in monozygotic twins where concordance rates for type 2 diabetes approach 100%.

Environmental and other risk factors: Diet, obesity, sedentary lifestyle and middle-aged and elderly persons



In the early stage of the disorder the response to progressive insulin resistance is an increase in insulin secretion by the pancreatic cells, causing hyperinsulinaemia. Eventually the β cells are unable to compensate adequately and blood glucose rises, producing hyperglycaemia. With further β-cell failure (type 2 diabetes) glycaemic control deteriorates and treatment requirements escalate.

LADA:

Latent autoimmune diabetes of adult, is form of type 1 DM occur in middle aged patients.

MODY:

Maturity onset diabetes of young, is a rare autosomal form of type 2 DM (less than 5% of cases of DM) affecting young people diabetes (before the age of 25 years) with positive family history.

Comparison of the Two Types of Diabetes Mellitus

	Type 1	Type2
Previous terminology	Insulin-dependent diabetes mellitus (IDDM), type I, juvenile-onset diabetes	Non-insulin-dependent diabetes mellitus, type II, adult-onset diabetes
Age of onset	Usually < 30yr	Usually > 40 yr
Genetic predisposition	Moderate; environmental factors required for expression; 35-50% concordance in monozygotic twins	Strong; 60-90% concordance in monozygotic twins
Family history	Uncommon	Common
Human leukocyte antigen associations	HLA haplotypes DR3 and/or DR4	None known

	Type 1	Type 2
Other associations	Autoimmune; Graves' disease, Hashimoto's thyroiditis, vitiligo, Addison's disease, pernicious anemia	Metabolic syndrome
Precipitating and risk factors	Largely unknown; microbial, chemical, dietary	Age, obesity (central), sedentary lifestyle, previous gestational diabetes.
Findings at diagnosis	85-90% of patients have one or more autoantibodies like: islet cell antibodies (ICA) and glutamic acide decarboxylase (GAD) antibodies.	Possibly complications =25% (microvascular and macrovascular) caused by significant hyperglycemia in the preceding asymptomatic period
Endogenous insulin levels	absent	Usually present (relative deficiency), early hyperinsulinemia
Insulin resistance	absent	present
Prolonged fast	Hyperglycemia, ketoacidosis	Euglycemia
Stress, withdrawal of insulin	Ketoacidosis	Nonketotic hyperglycemia

	Type 1	Type 2
Duration of symptoms	Weeks	Months to years
Body weight	Low	Obese
Ketonuria	Yes	No
Rapid death without treatment with insulin	Yes	No
Autoantibodies	Yes	No
Diabetic complications at diagnosis	No	25%
% of cases of DM	5- 15%	75- 85%
Other autoimmune disease	Common	Uncommon

SYMPTOMS OF HYPERGLYCAEMIA

- Thirst, dry mouth
- Polyuria
- Nocturia
- Tiredness, fatigue
- Recent weight loss
- Blurring of vision
- Pruritus vulvae, balanitis (genital candidiasis)
- Nausea, headache
- Hyperphagia and predilection for sweet foods
- Mood change, irritability, difficulty in concentrating, apathy

Investigations

1- Urine testing:

- **Glucose:** By using sensitive glucose-specific dipsticks 1-2 hours after a meal to maximize sensitivity. Glycosuria always warrants further assessment by blood testing.

Renal glycosuria: is a benign condition unrelated to diabetes due to low renal threshold, which is common during pregnancy and in young people.

- **Ketones:** By using dipsticks for ketones.

Ketonuria is not pathognomonic of diabetes but, if associated with glycosuria, the diagnosis of diabetes is highly likely. Other causes of ketonuria are fasting, sever prolonged exercise, repeated vomiting, or eating a diet high in fat and low in carbohydrate.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EXP:

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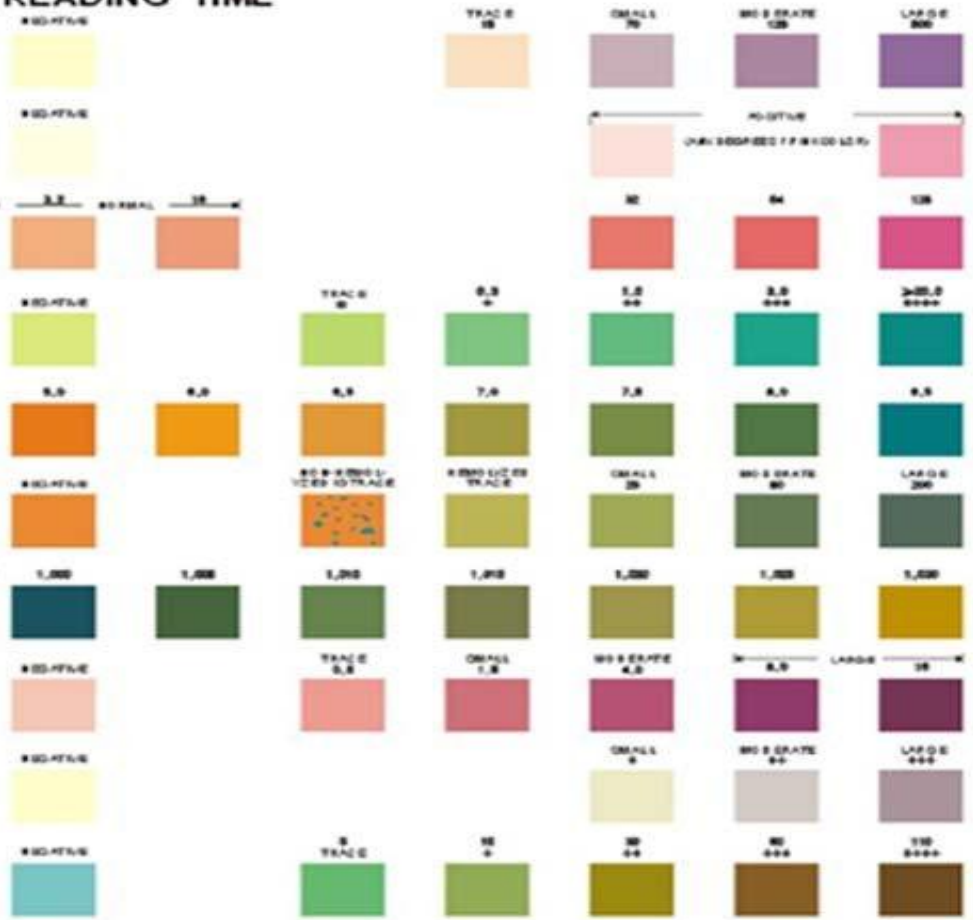
TESTS AND READING TIME



- **Protein:**

Standard dipstick testing for albumin detects urinary albumin at concentrations above 300 mg/L, but

Smaller amounts of urinary albumin from 30 to 300 mg/L (microalbuminuria) can only be measured using specific albumin dipsticks or by quantitative biochemical laboratory measurement.

Microalbuminuria or proteinuria, in the absence of urinary tract infection, is an important indicator of diabetic nephropathy and/or increased risk of macrovascular complications.

2- Blood testing:

- **Glucose:** Whole blood glucose concentrations are lower than plasma concentrations because red blood cells contain relatively little glucose. Venous plasma values are usually the most reliable for diagnostic purposes.
- **Ketones:** measured in in blood during diabetic ketoacidosis (DKA), useful in insulin adjustment to prevent or detect DKA and to monitored resolution of DKA in hospitalized patients
- **Glycated haemoglobin (HbA_{1c}):** a slow non-enzymatic covalent attachment of glucose to haemoglobin (glycation), with increase amount of HbA1 (HbA1c) fraction relative to nonglycated adult haemoglobin (HbA0).

provides an accurate and objective measure of glycaemic control over a period of weeks to months. The rate of formation of HbA1c is directly proportional to the blood glucose concentration; a rise of 1% in HbA1c corresponds to an approximate average increase of 2 mmol/L (36 mg/dL) in blood glucose. Although HbA1c concentration reflects the integrated blood glucose control over the lifespan of erythrocytes (120 days).

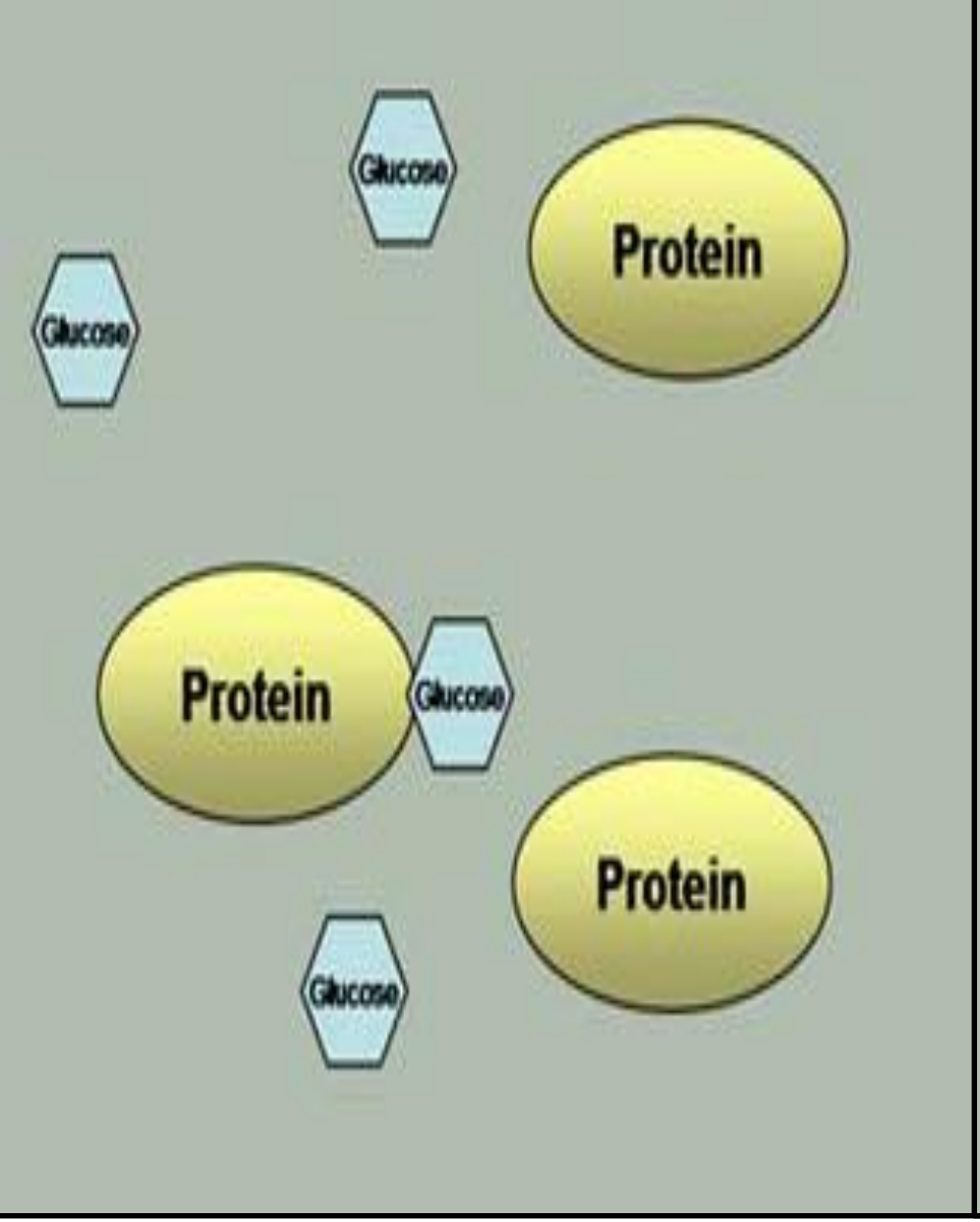
HbA1c estimates may be erroneously diminished in anaemia or during pregnancy, and may be difficult to interpret in uraemia or a haemoglobinopathy.

The World Health Organization (WHO) guidelines (2011) introduced the use of HbA1c for diagnosis of diabetes.

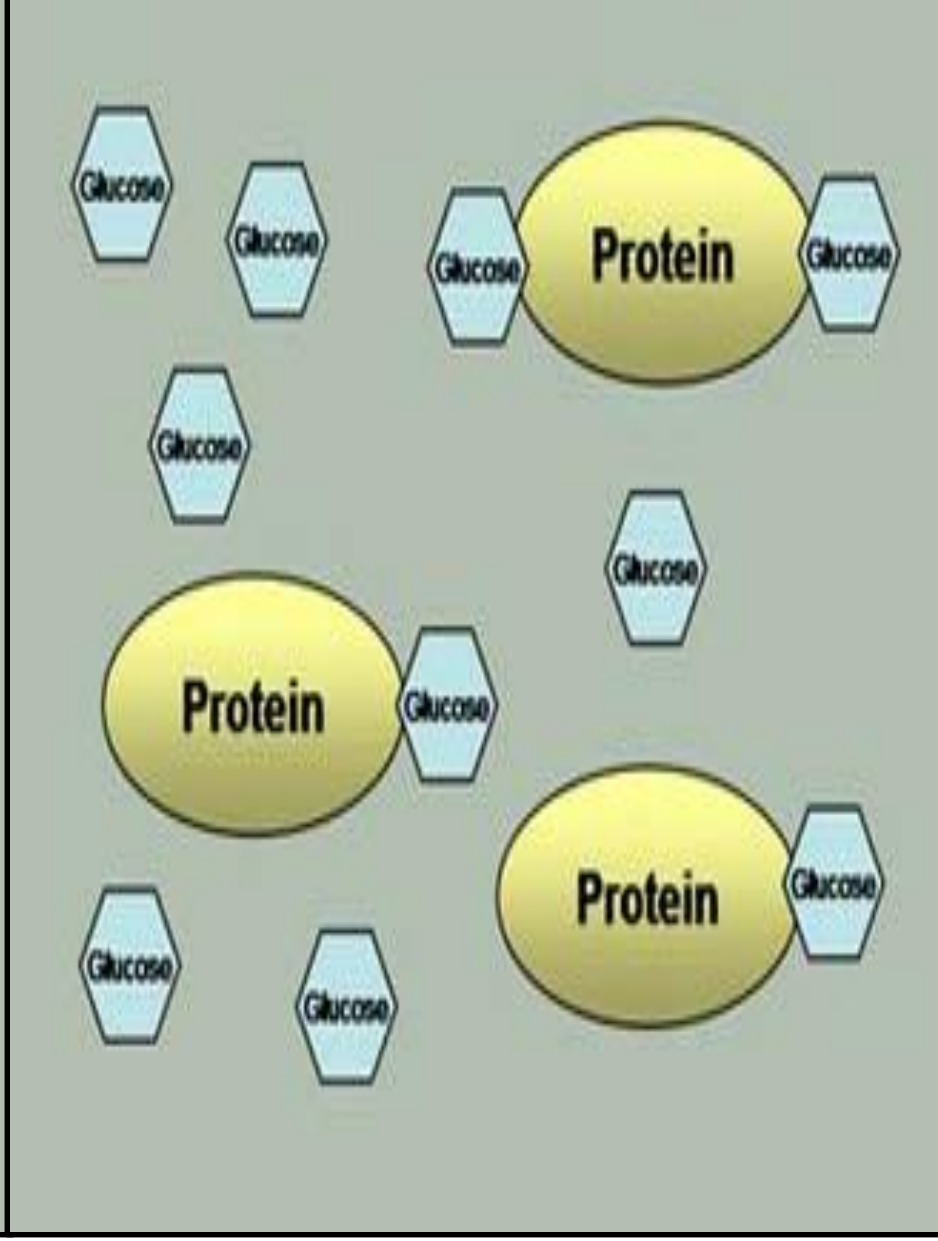
- **Oral glucose tolerance test (OGTT)**

Done when there is impaired fasting glucose (IFG): 6.1- 7.0 mmol/L (110- 126 mg/dL) or uncertainty about the diagnosis of diabetes. Plasma glucose measured before, and 2 hrs after, 75 g glucose load taken orally.

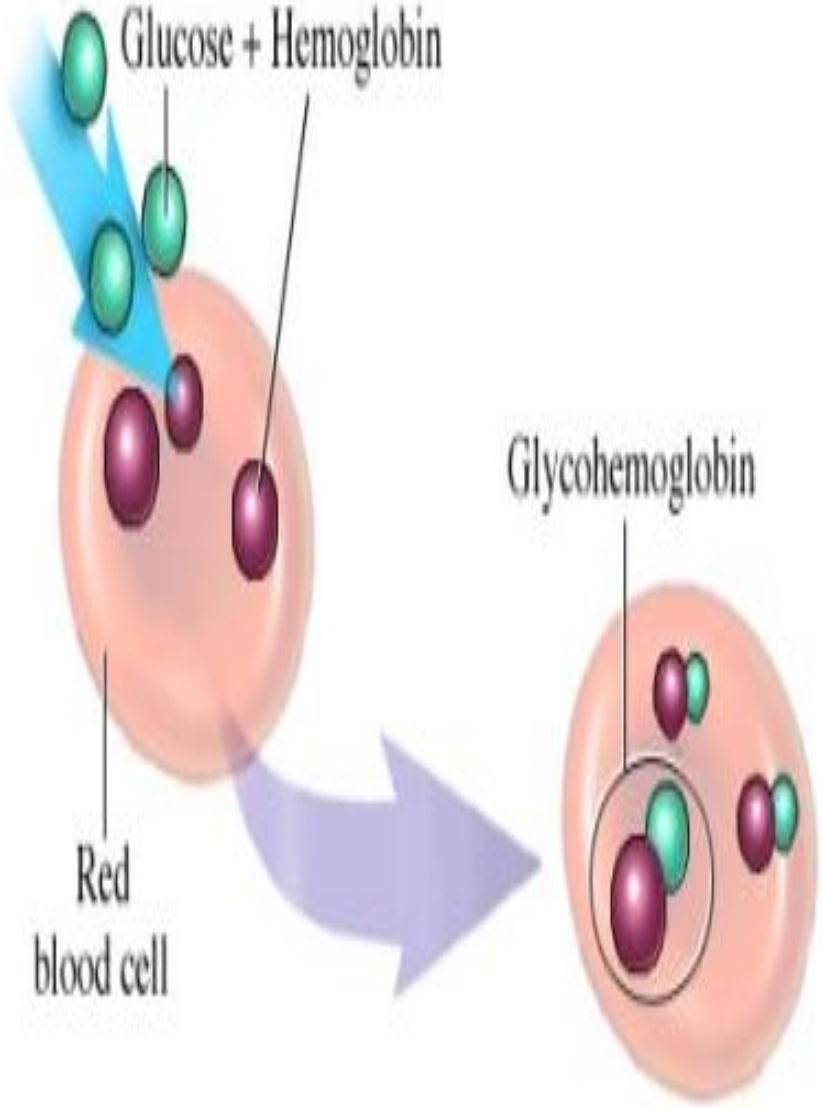
Interpretation (venous plasma glucose)		
	Fasting	2 hrs after glucose load
Impaired fasting glucose	6.1–6.9 mmol/L (110–125 mg/dL)	< 7.8 mmol/L (< 140 mg/dL)
Impaired glucose tolerance	< 7.0 mmol/L (< 126 mg/dL)	7.8–11.0 mmol/L (140–199 mg/dL)
Diabetes	≥ 7.0 mmol/L (> 126 mg/dL)	≥ 11.1 mmol/L (> 200 mg/dL)



With normoglycemia, a relatively small amount of serum protein is glycated.



With persistent hyperglycemia, increased protein glycation occurs.



Diabetes Control Card

HbA_{1c} test score	MEAN BLOOD GLUCOSE mg/dL	MEAN BLOOD GLUCOSE mmol/L	
14.0	380	21.1	action suggested
13.0	350	19.3	action suggested
12.0	315	17.4	action suggested
11.0	280	15.6	action suggested
10.0	250	13.7	action suggested
9.0	215	11.9	action suggested
8.0	180	10.0	good
7.0	150	8.2	good
6.0	115	6.3	excellent
5.0	80	4.7	excellent
4.0	50	2.6	excellent

WHO Diagnostic criteria of DM

Plasma Glucose	Normal	Impaired Fasting Glucose	Impaired Glucose Tolerance	Diabetes Mellitus
Fasting	<110 (6.1)	≥110 and <126	-	≥126 (7.0)
2-Hour postload	<140 (7.8)	-	≥140 and <200	≥200 (11.1)
Random	-	-	-	≥200 with symptoms

Note: When a person has symptoms of diabetes, the diagnosis can be confirmed with either a fasting glucose ≥ 7.0 mmol/L (126 mg/dL) or a random glucose ≥ 11.1 mmol/L (200 mg/dL). Asymptomatic individuals should have a second confirmatory test (2 reading).

Management

The aims of management are to:

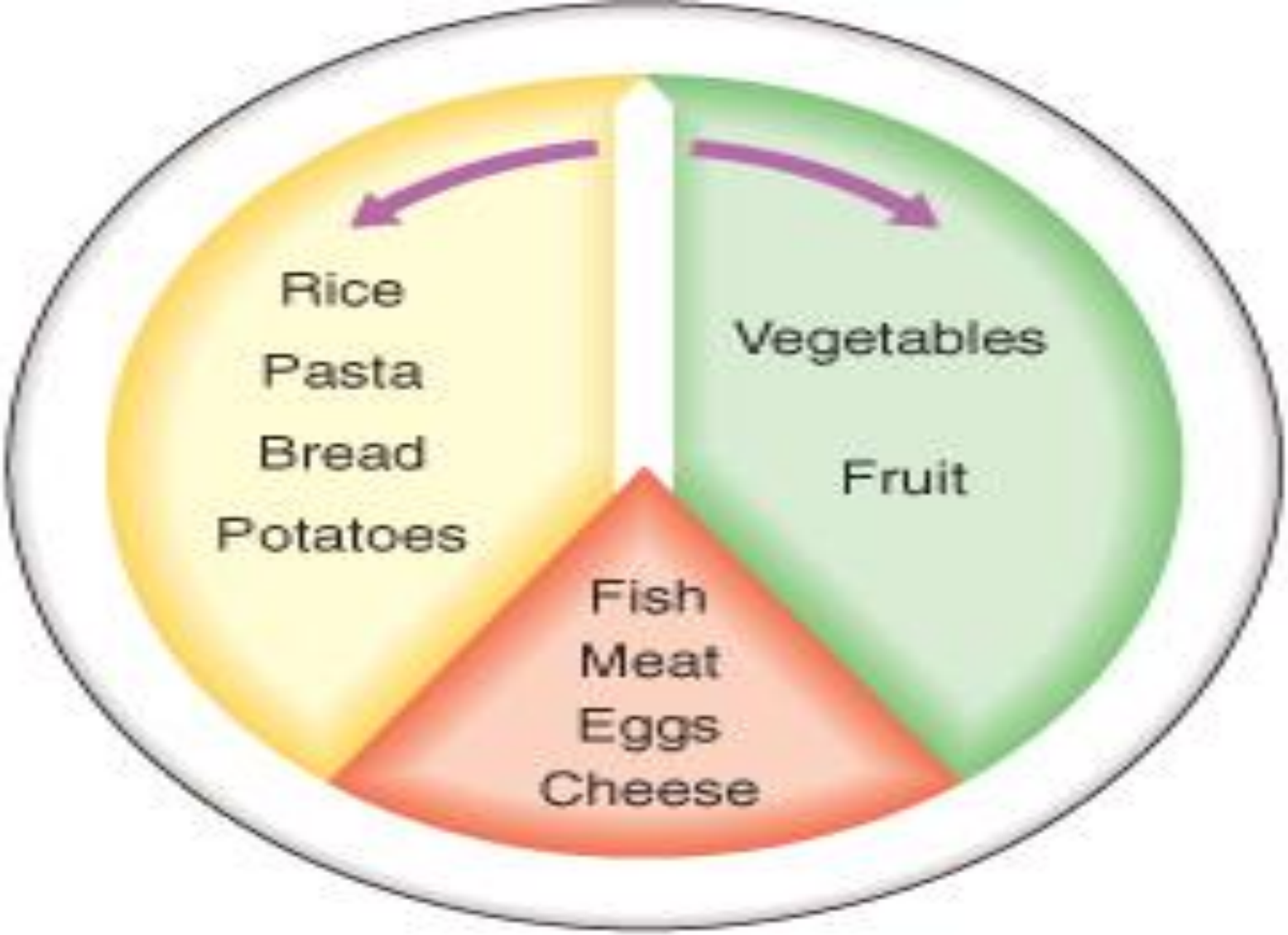
1. Improve symptoms of hyperglycaemia
2. Minimise the risks of complications.

Treatment methods for diabetes include:

1. Dietary/lifestyle modification
2. Oral anti-diabetic drugs
3. Injected therapies
4. Others: treatment of hypertension and dyslipidaemia and advice on smoking cessation

EDUCATING PATIENTS:

- Understand their condition.
- Those requiring insulin need to learn how to measure their dose of insulin accurately with an insulin syringe or pen device, to give their own injections and to adjust the dose themselves on the basis of blood glucose values and other factors such as exercise, illness and episodic hypoglycaemia.
- Familiar with the symptoms of hypoglycaemia.
- Self-assessment of glycaemic control.
- Diet= decrease saturated fat, decrease sugar intake, increase starch, moderate protein intake.
- Smoking cessation.
- Foot care.
- Preconception advice.
- Regular exercise: such as walking, gardening, swimming or cycling.



A 'plate model' for meal planning. The plate is divided into three sections. The smallest section (one-fifth of total area) is for the meat, fish, eggs or cheese, and the remainder divided in roughly equal proportions between the staple food (rice, pasta, potatoes, bread etc.) and vegetables or fruit.

ORAL ANTI-DIABETIC DRUGS

1- Biguanides

Metformin is the only biguanide now available and it is now widely used as first-line therapy for type 2 diabetes, irrespective of body weight. Metformin is also given increasingly as an adjunct to insulin therapy in obese patients with type 1 diabetes.

The main side-effects are diarrhoea, abdominal cramps, bloating and nausea.

The mechanism of action: Improve insulin sensitivity, increase peripheral glucose uptake and reduces hepatic glucose production. It does not cause hypoglycaemia.

It is contraindicated in renal impairment (eGFR of 30 mL/min), hepatic impairment and in those who drink excess alcohol, because there is a significant risk of lactic acidosis.

2- Sulphonylureas:

Mechanism of action: Stimulate the release of insulin from the pancreatic β cell.

Clinical use: Sulphonylureas are an effective therapy for lowering blood glucose and used as an add-on to metformin, if glycaemia is inadequately controlled on metformin alone.

The main adverse effects: are weight gain and hypoglycaemia.

The first-generation: Tolbutamide, Chlorpropamide.

The second-generation: gliclazide and glipizide cause few side-effects, but glibenclamide is prone to induce severe hypoglycaemia and should be avoided in the elderly.

Newer long-acting preparations such as glimepiride and a modified-release form of gliclazide can be administered once daily with no apparent increased risk of hypoglycaemia.

3- Alpha-glucosidase inhibitors:

which delay carbohydrate absorption in the gut by selectively inhibiting disaccharidases. Acarbose or miglitol is available and is taken with each meal. Both lower post-prandial blood glucose and modestly improve overall glycaemic control. They can be combined with a sulphonylurea.

The main side-effects are flatulence, abdominal bloating and diarrhoea.

4- Thiazolidinediones: (glitazones: Rosiglitazone or Pioglitazone) work by enhancing the actions of endogenous insulin.

Recently, rosiglitazone, was reported to increase the risk of myocardial infarction and was withdrawn in 2010.

Pioglitazone, exacerbate cardiac failure by causing fluid retention, and recent data show that it increases the risk of bone fracture, and possibly bladder cancer. These observations have reduced the use of pioglitazone dramatically.

Pioglitazone is usually added to metformin with or without sulphonylurea therapy

5- Meglitinides and amino acid derivatives: Repaglinide and Nateglinide.

The mechanism of action is similar to that of the sulfonylureas in stimulating insulin secretion from the pancreas. The advantages of these classes over the sulfonylureas are the rapid onset and short duration of action. These drugs are taken immediately before food. These drugs are less likely to cause hypoglycaemia than sulphonylureas.

6- Incretin-based therapies: Dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 analogues:

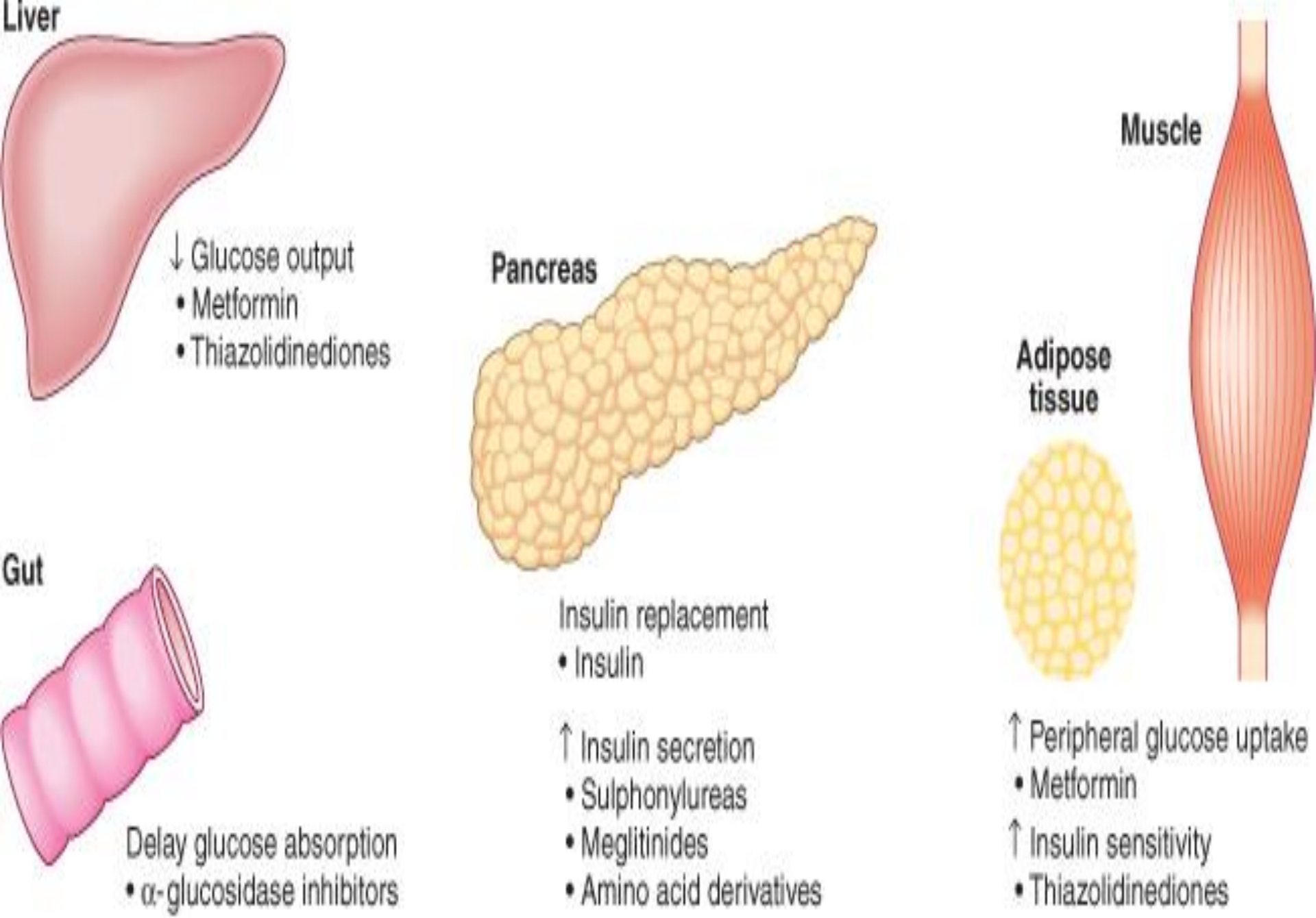
The incretin effect is the augmentation of insulin secretion seen when a glucose stimulus is given orally rather than intravenously, and reflects the release of incretin peptides from the gut.

The incretin hormones are primarily glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP). These are rapidly broken down by the peptidase DPP-4.

Unlike sulphonylureas, both incretin-based therapies only promote insulin secretion when there is a glucose 'trigger' for insulin secretion. Thus, when the blood glucose is normal, the insulin secretion is not augmented and so these agents do not cause hypoglycaemia.

- DPP-4 inhibitors, or **gliptins**: increase the level of endogenous GLP-1 and GIP. The first drug marketed was **sitagliptin**. Others include vildagliptin, saxagliptin and linagliptin. It taken orally in type 2 diabetes.
- The GLP-1 receptor agonists it given by subcutaneous injection. advantage over the DPP-4 inhibitors as it delays gastric emptying and, at the level of the hypothalamus, decreases appetite and result in weight loss. So it indicated in obese patients with type 2 diabetes. It include **exenatide** (twice daily), **exenatide MR** (once weekly) and **liraglutide** (once daily).

7- SGLT2 inhibitors: The sodium and glucose transporter 2 (SGLT2) inhibitor, **dapagliflozin**. Which inhibit glucose reabsorbed in the proximal tubules. Dapagliflozin, was licensed for use in 2012.



INSULIN

Manufacture and formulation:

Insulin was discovered in 1921, and obtained from animal sources (bovine and porcine insulin).

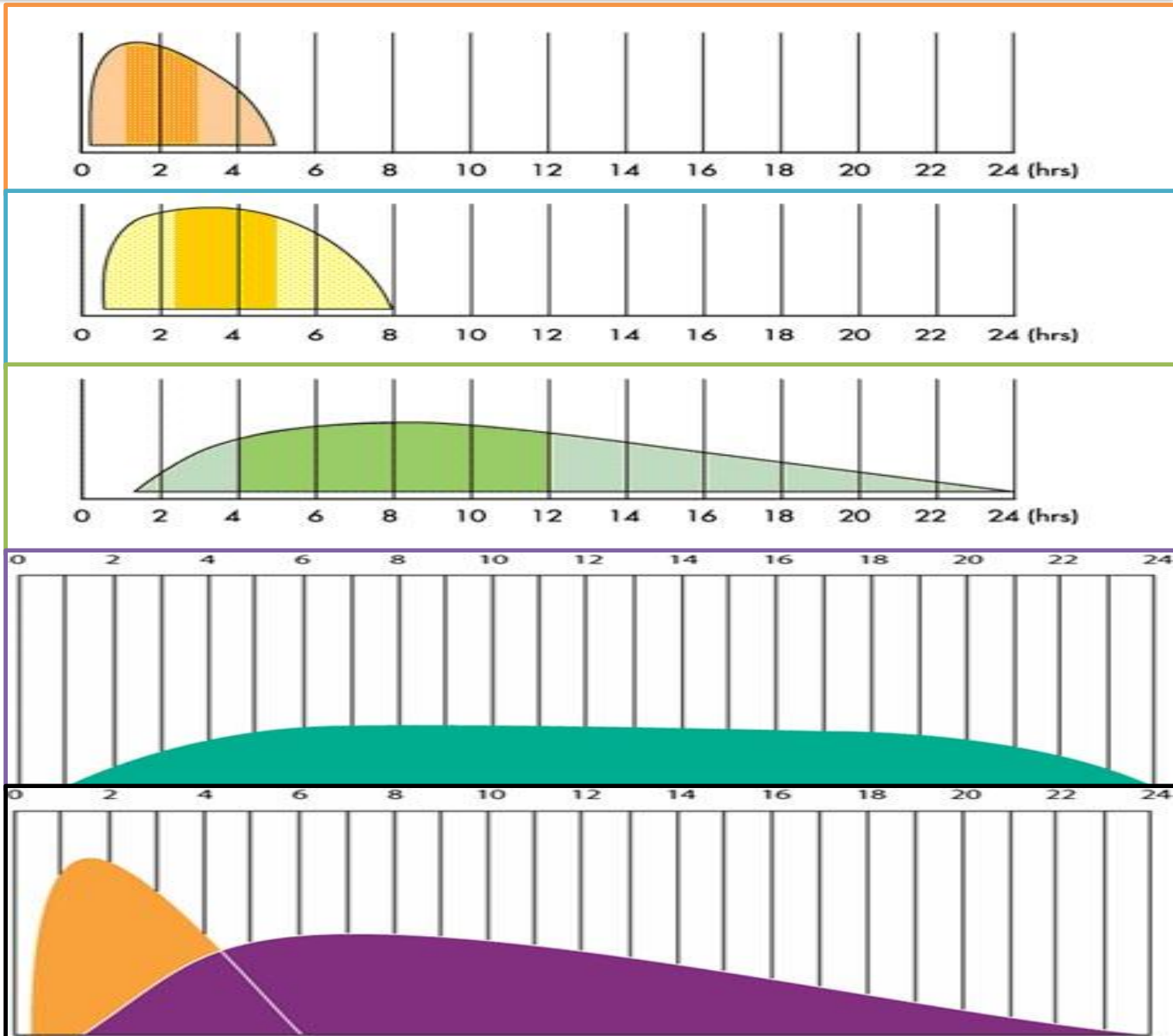
After 1980, the use of recombinant DNA technology has enabled large-scale production of human insulin.

Recently, rDNA and protein engineering techniques that alter the amino acid sequence of insulin have been used to produce 'monomeric' analogues of insulin, which are more rapidly absorbed from the site of injection (e.g. insulin lispro or aspart).

Duration of action (in hours) of insulin preparations

Insulin	Onset	Peak	Duration
Rapid-acting (insulin analogues-lispro, aspart, glulisine)	< 0.5	0.5-2.5	3-4.5
Short-acting (soluble (regular))	0.5-1	1-4	4-8
Intermediate-acting (isophane (NPH), lente)	1-3	3-8	7-14
Long-acting (bovine ultralente)	2-4	6-12	12-30
Long-acting (insulin analogues- glargine, detemir, degludec)	1-2	None	18-24

Duration of action (in hours) and types of insulin

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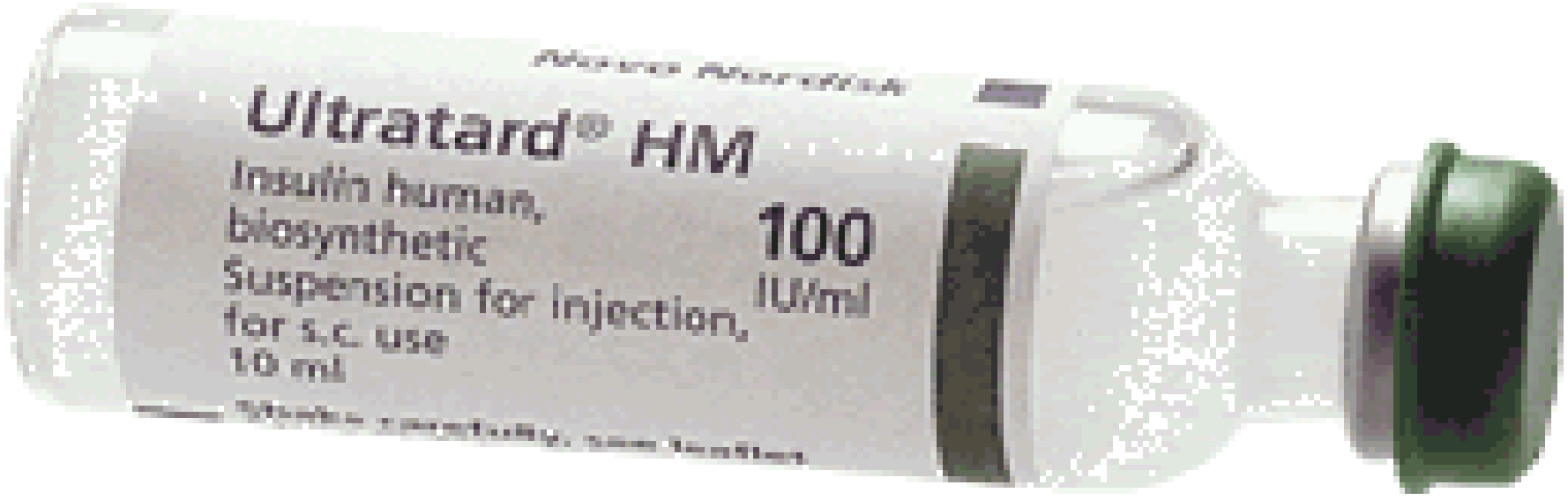
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Insulin human,
biosynthetic
Suspension for injection,
for s.c. use
10 ml
100
IU/ml

Insulin delivery

The strength of insulin is 100 u/ml.

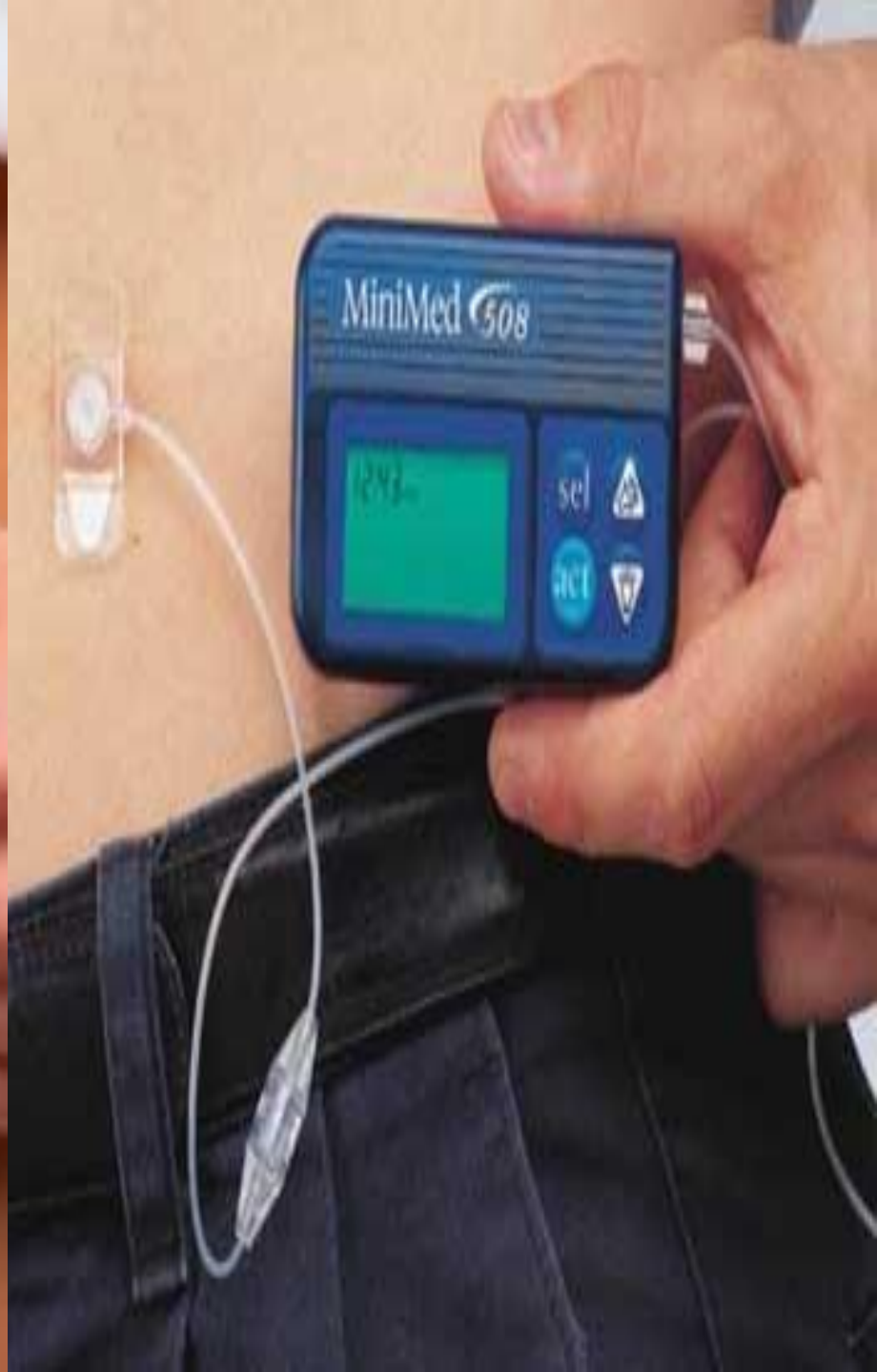
1-Subcutaneous injection: the most common rout, into the anterior abdominal wall, upper arms, outer thighs and buttocks. Used in:

- **Type 1 DM**
- **Type 2 DM: in combination with OHA, pregnant woman, or sever illness or major surgery require hospital admission.**
- **Gestational DM.**

By using a battery-powered portable insulin pump or a disposable plastic syringe with a fine needle (which can be reused several times), or pen device.

2-Intramuscular injection or I.V. infusion: use just soluble insulin or rapidly acting insulin analogue, by using infusion pump providing continuous intravenous infusion of insulin. Use in treatment of DKA or NKHDC.

3-Other rout: intraperitoneal inj. in patient on peritoneal dialysis.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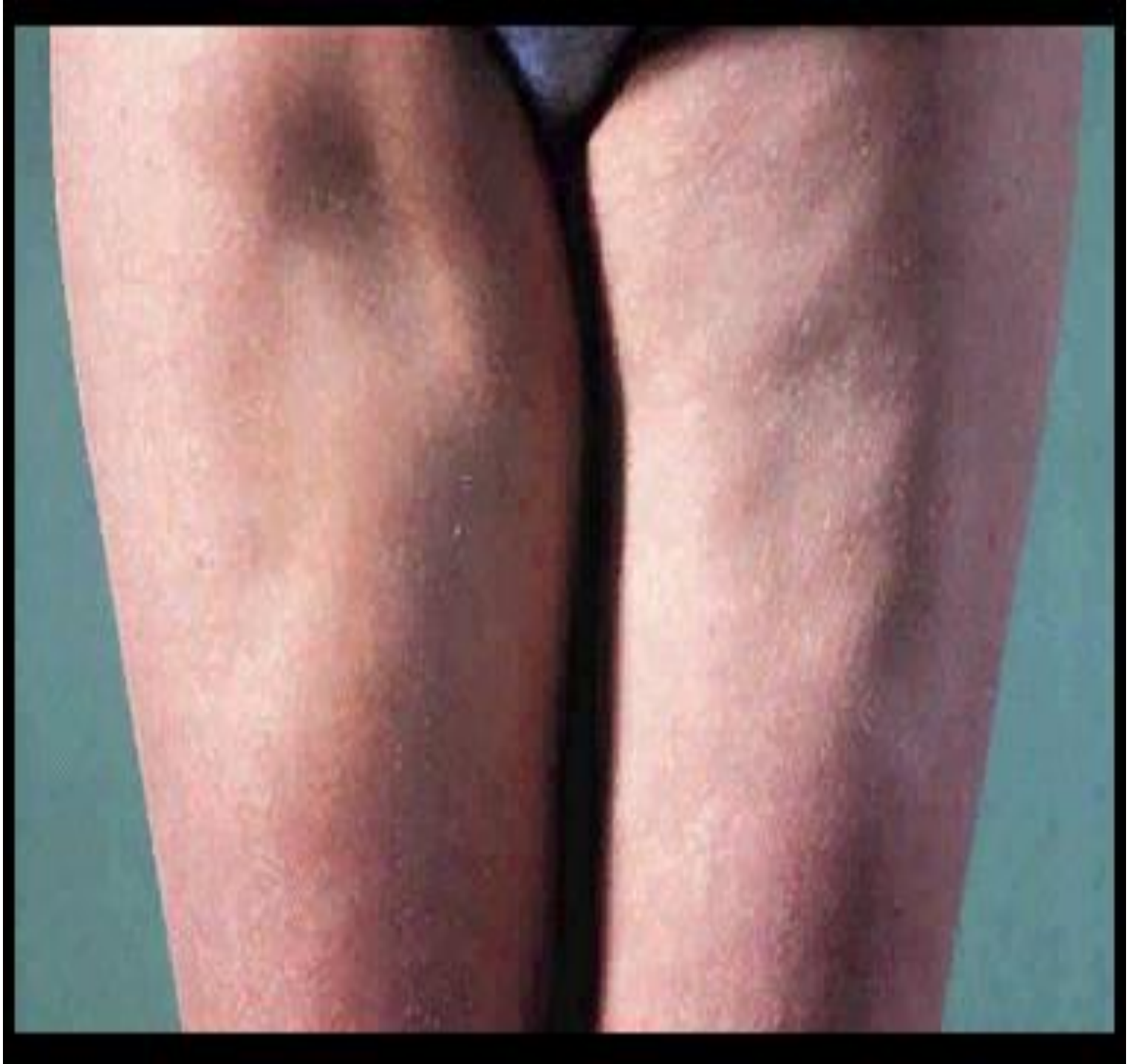
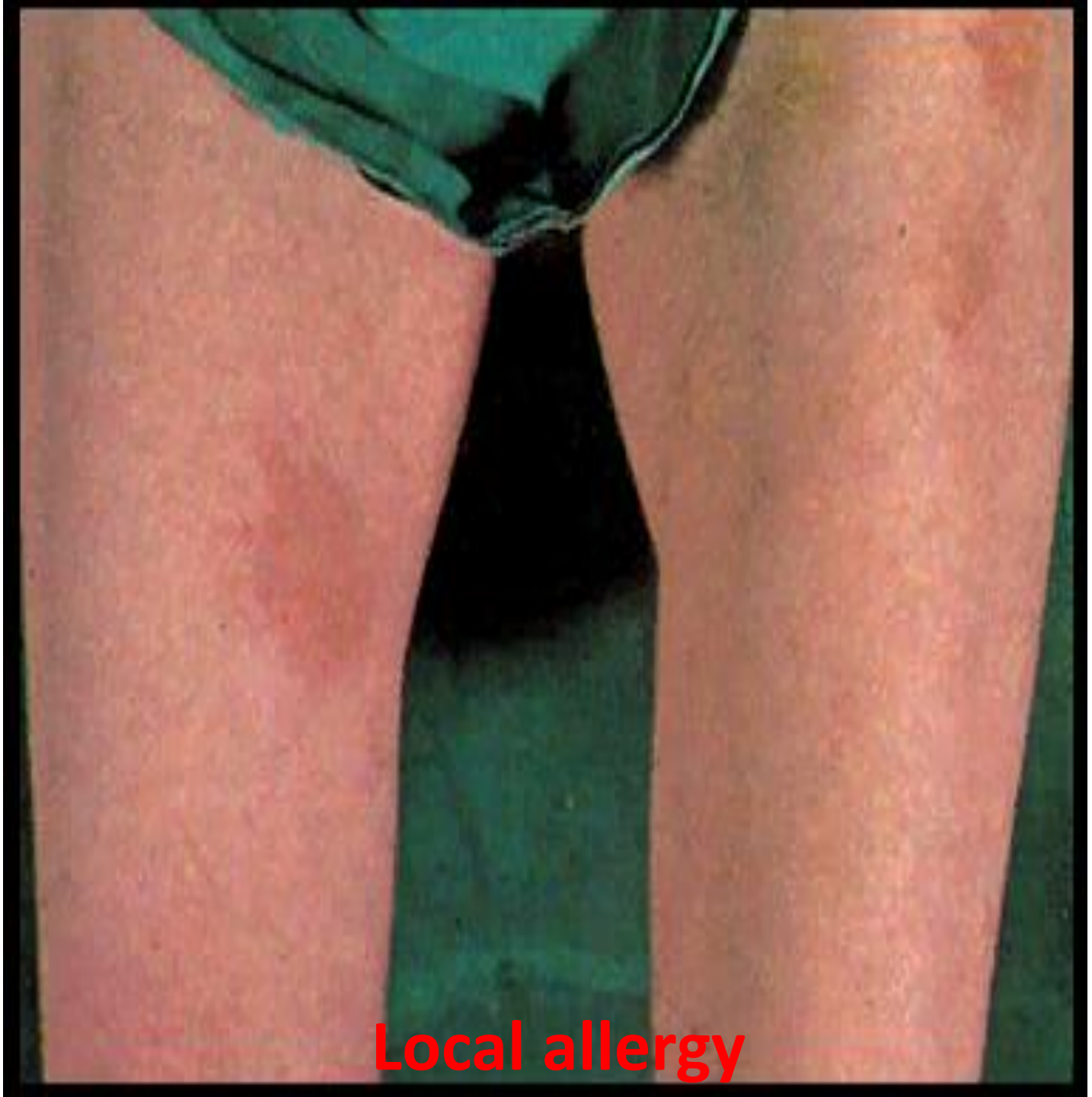
SIDE-EFFECTS OF INSULIN THERAPY

- Hypoglycaemia
- Weight gain
- Peripheral oedema (insulin treatment causes salt and water retention in the short term)
- Insulin antibodies (animal insulins)
- Local allergy (rare)
- Lipodystrophy at injection sites




Local allergy

Insulin regimens

- Twice-daily administration of a short-acting and intermediate-acting insulin (usually soluble and isophane insulins), given in combination before breakfast and the evening meal, is the simplest regimen and is still commonly used. Individual requirements vary considerably but usually two-thirds of the total daily requirement of insulin is given in the morning in a ratio of 1:2, short:intermediate-acting insulins. The remaining third is given in the evening, and doses are adjusted according to blood glucose monitoring.

- **Multiple injection regimens are popular, with short-acting insulin being taken before each meal, and intermediate-acting insulin being injected at bedtime (basal-bolus regimen). This type of regimen allows greater freedom of timing of meals and is of value to individuals with variable day-to-day activities, but snacks may have to be taken between meals to prevent hypoglycaemia.**

- Once-daily injections rarely achieve satisfactory glycaemic control and are reserved either for some elderly patients or for those who retain substantial endogenous insulin secretion and have a low insulin requirement.

Honey moon period:

The pancreas of patient with type 1 DM may partially recover after the initial diagnosis resulting in decrease insulin requirement.

Gestational diabetes

Gestational diabetes is defined as diabetes with first onset or recognition during pregnancy, due to an inability to increase insulin secretion adequately to compensate for pregnancy-induced insulin resistance and most women return to normal after pregnancy.

If treatment is necessary, metformin or glibenclamide is considered safe to use in pregnancy.

Glibenclamide should be used rather than other sulphonylureas because it does not cross the placenta.

Insulin may be required, especially in the later stages of pregnancy.

If the maternal blood glucose is not well controlled prior to, and during, delivery, the resulting fetal hyperinsulinaemia leads to neonatal hyperinsulinaemia, which in turn can cause neonatal hypoglycaemia.

Complications of diabetes mellitus

A- ACUTE COMPLICATIONS

1. Hypoglycemia
2. Diabetic Ketoacidosis
3. Hyperosmolar Nonketotic Syndrome (HNKS)
4. Lactic Acidosis

B- CHRONIC COMPLICATIONS

1- Microvascular:

- Retinopathy
- Neuropathy
- Nephropathy

2- Macrovascular:

- Coronary artery disease
- Peripheral arterial disease
- Cerebrovascular disease


Thanks