

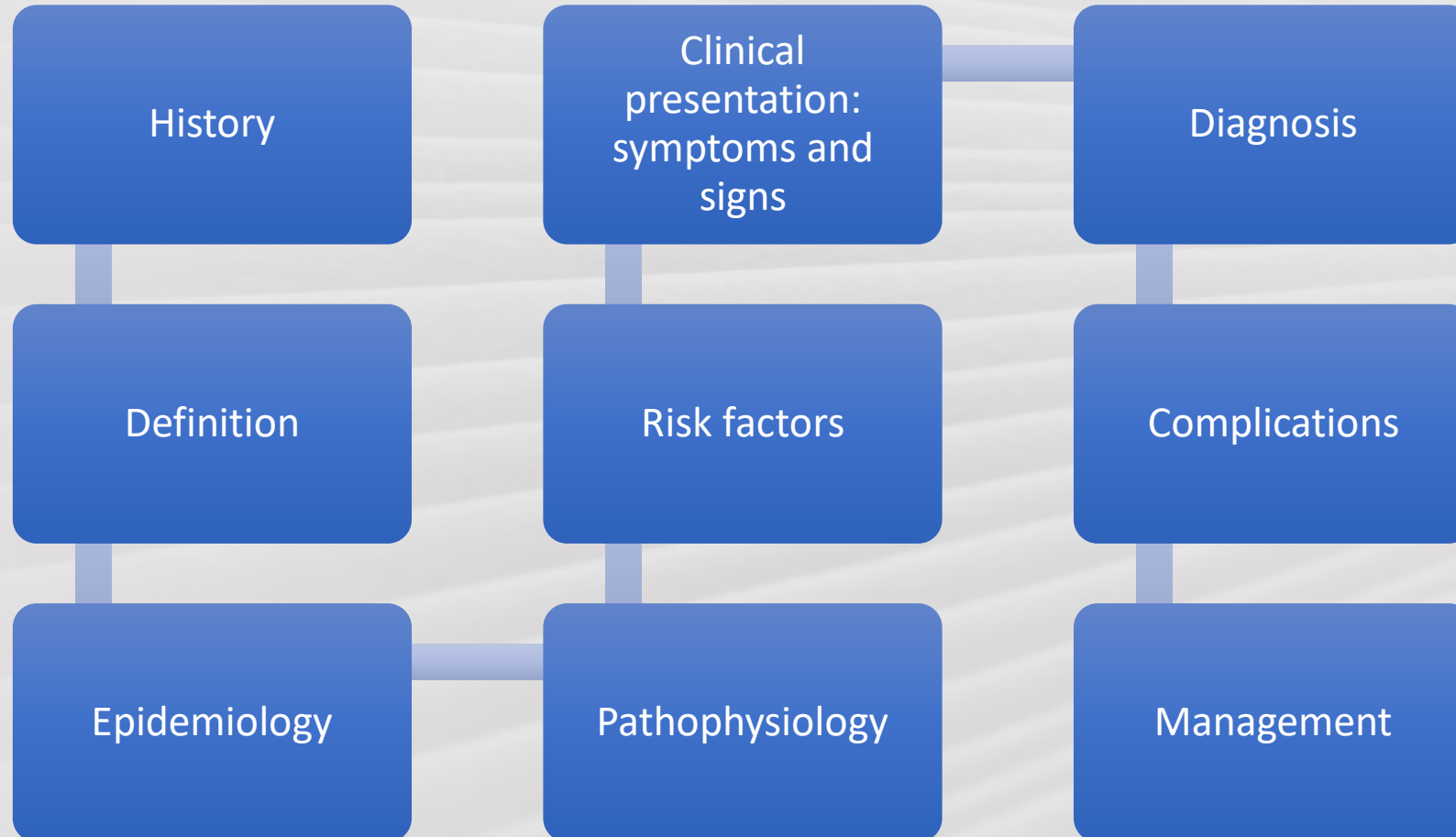
Diabetes

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Endocrinology and diabetes



Objectives



DIABETES THROUGH THE YEARS

In conjunction with World Diabetes Day on Nov 14, take a trip through time and discover the history behind one of the world's most prevalent diseases.

THE BEGINNINGS, IN ANCIENT EGYPT

1552 BC

The earliest known record of diabetes was written on papyrus by Egyptian physician Hesy-Ra, who mentioned frequent urination as a symptom.

1500 BC

Ancient Indians tested for diabetes by determining if ants were attracted to a person's urine.

250 BC

Apollonius of Memphis came up with the term "diabetes"; meaning to go through, referring to a disease that drains patients of more fluid than they can consume.

"diabetes"

DIFFERENTIATING TYPE 1 AND TYPE 2 DIABETES

1776

Type 1

Type 2

English physician Matthew Dobson, makes the distinction between Type 1 and Type 2 diabetes for the first time.



Early 1800's

The first chemical tests were developed by researchers to indicate and measure the presence of sugar in urine.

THE FIRST DIABETES CHEMICAL TEST

1889



The link between diabetes and the pancreas was established when Oskar Minkowski discovered that a dog from which he removed the pancreas had developed the illness.



THE MIRACULOUS DISCOVERY OF INSULIN

THE FIRST HOME SUGAR TESTING KIT

1925

The first home testing for sugar in the urine is introduced.

The connection between diabetes and long-term complications such as kidney and eye disease is made.

1940's

Canadian surgeon Frederick Banting's work leads to the discovery of insulin. On July 30, Dog 410 is the first to receive the extract. On August 4, the extract is called 'Isletin' for the first time. News of the miraculous discovery began to spread across the world.

Before the discovery of insulin, being diagnosed with diabetes was equivalent to a death sentence with patients lasting no more than three or four years at most.

1921 BC

Dog 410

INNOVATIONS IN THE TREATMENT OF DIABETES

1944



Diabetes management becomes more standardized with the development of the insulin syringe.

1964



Development of strips for testing of blood glucose.

1955



The introduction of oral drugs that help lower blood glucose levels.

TRANSFORMATION OF DIABETES CARE

1970



Insulin pumps and the first blood glucose meter are first developed for use in doctors' offices. The insulin pump was made to imitate the body's usual release of insulin. The first glucose meters were large in size before being shrunk to the portable glucose meters which we know of today. 1970 also marks the year laser therapy was introduced to help prevent blindness resulting from diabetes.

2006



Diabetes is recognised as a global threat by the United Nations and November 14 is designated as World Diabetes Day – in honour of Frederick Banting's birthday.



The World Health Organization (WHO) reported that the number of people with diabetes around the world continues to increase from 108 million in 1980 to 422 million in 2014. Diabetes is especially prevalent in low and middle-income countries compared to high-income countries due to poor management of the diseases and lack of access to medical care.

NOW A WORLDWIDE EPIDEMIC

2014

2012



The World Health Organization (WHO) reported that diabetes was the direct cause of close to 1.5 million deaths in the world.

Sources:

<http://www.diabetes.ca/about-diabetes/history-of-diabetes#sthash.NkWjqZRL.dpuf>

<http://www.defeatdiabetes.org/diabetes-history/>

<http://www.diabetes.ca/about-diabetes/history-of-diabetes>

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<http://www.diabete.qc.ca/en/understand-diabetes/all-about-diabetes/history-of-diabetes/treating-diabetes-1921-to-the-present-day>

<http://www.diabetes.org/research-and-practice/student-resources/history-of-diabetes.html?referrer=https://www.google.com.sg/>

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Definition

Diabetes Mellitus is a clinical syndrome characterized by an increase in plasma blood glucose (Hyperglycemia)

Epidemiology

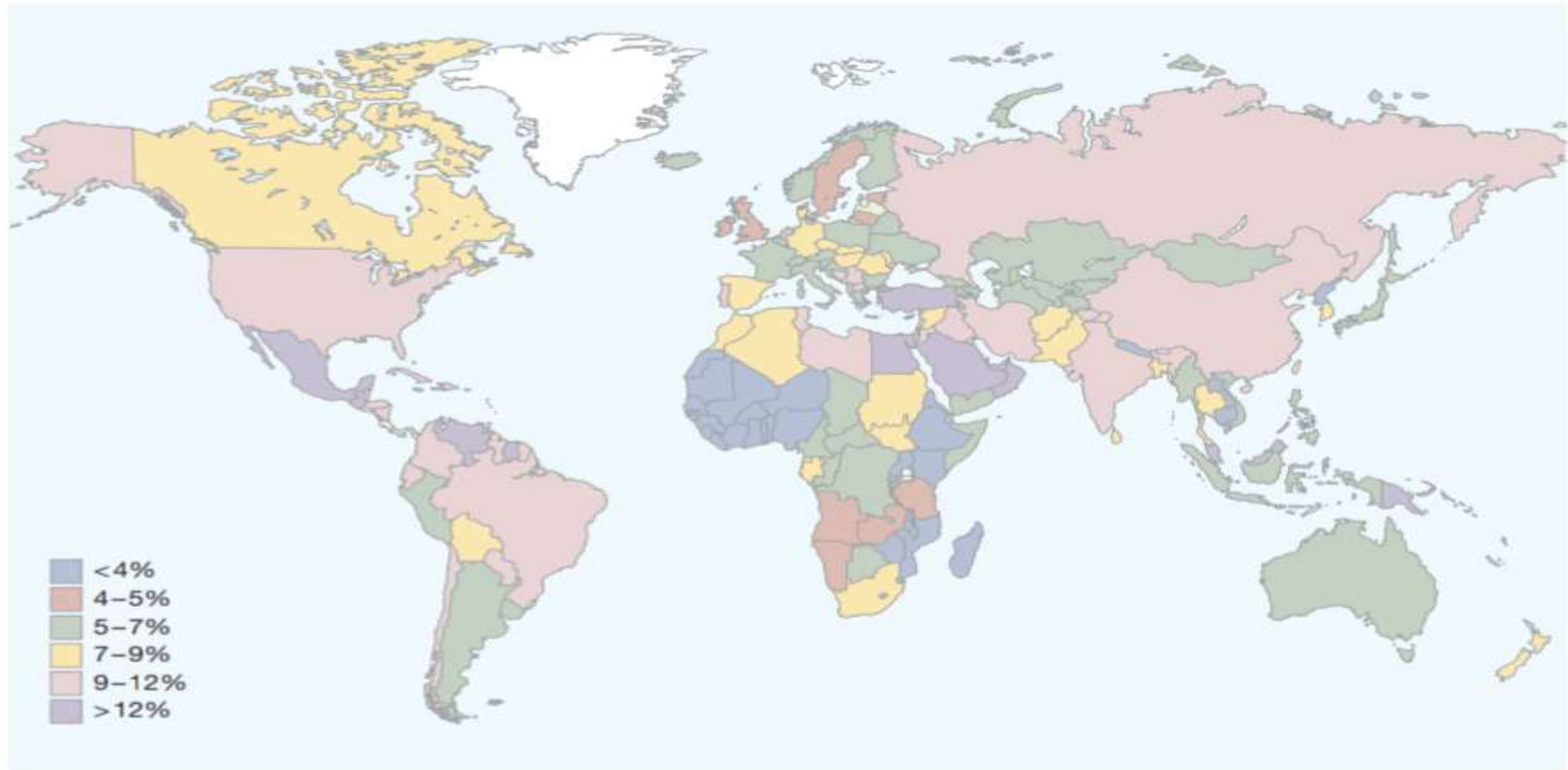


Fig. 20.1 Prevalence (%) of diabetes in those aged 20–79 years, 2015. Based on estimates from the International Diabetes Federation. *IDF Diabetes Atlas, 7th edn.* Brussels, Belgium: International Diabetes Federation, 2015. <http://www.diabetesatlas.org>.

- The number of people with diabetes rose from 108 million in 1980 to 422 million in 2014. Prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries.
- Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation.
- Between 2000 and 2019, there was a 3% increase in diabetes mortality rates by age.
- In 2019, diabetes and kidney disease due to diabetes caused an estimated 2 million deaths.

Glucose metabolism

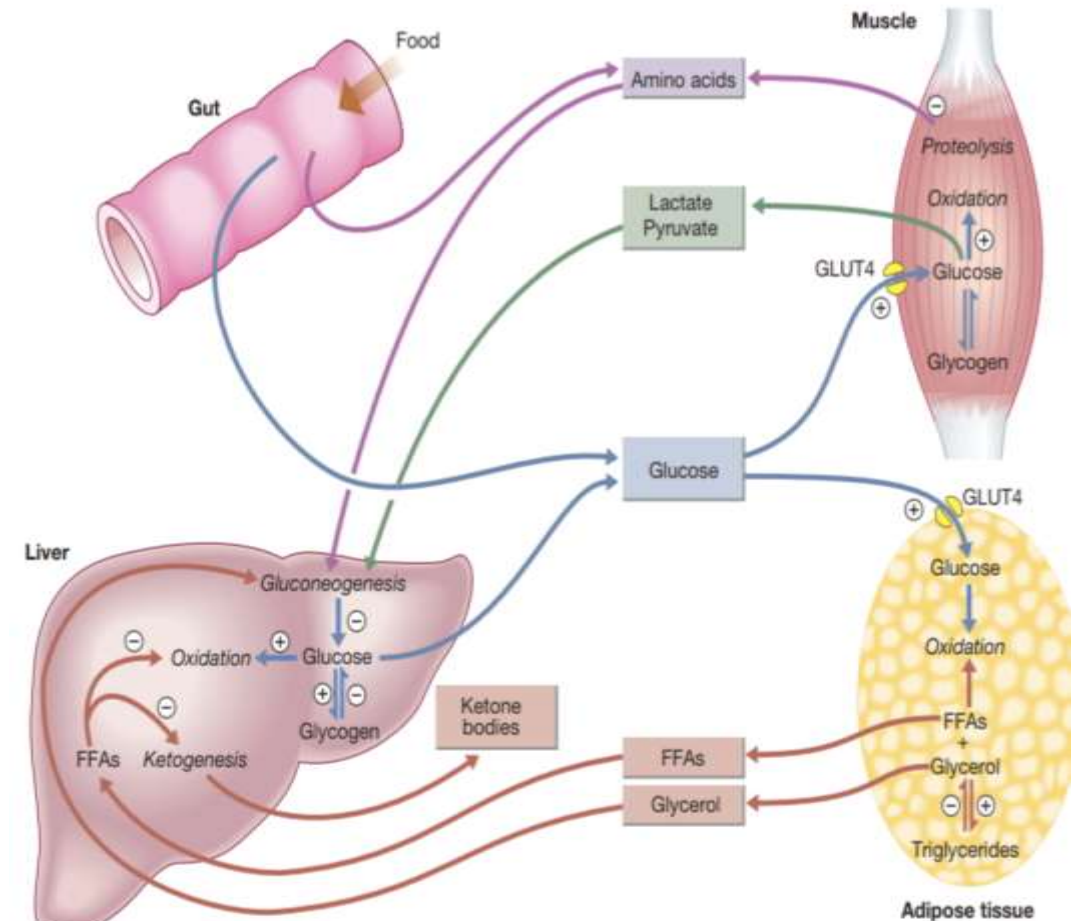
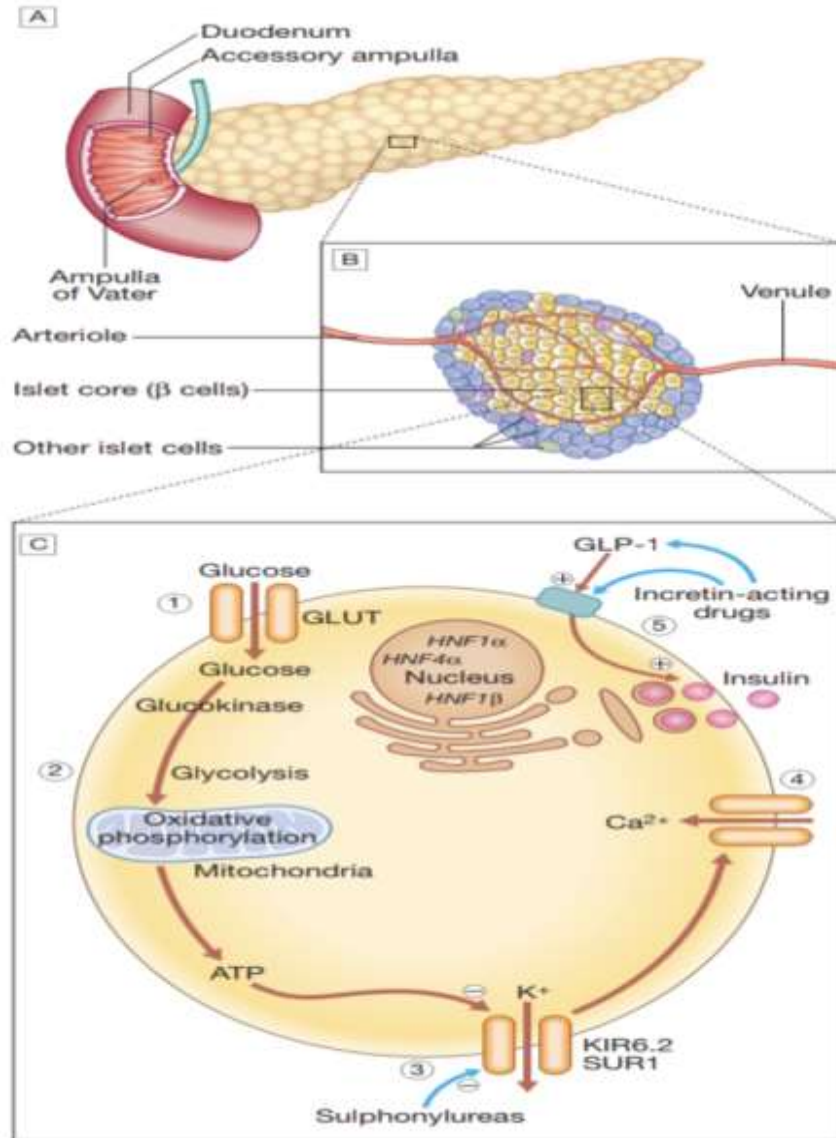
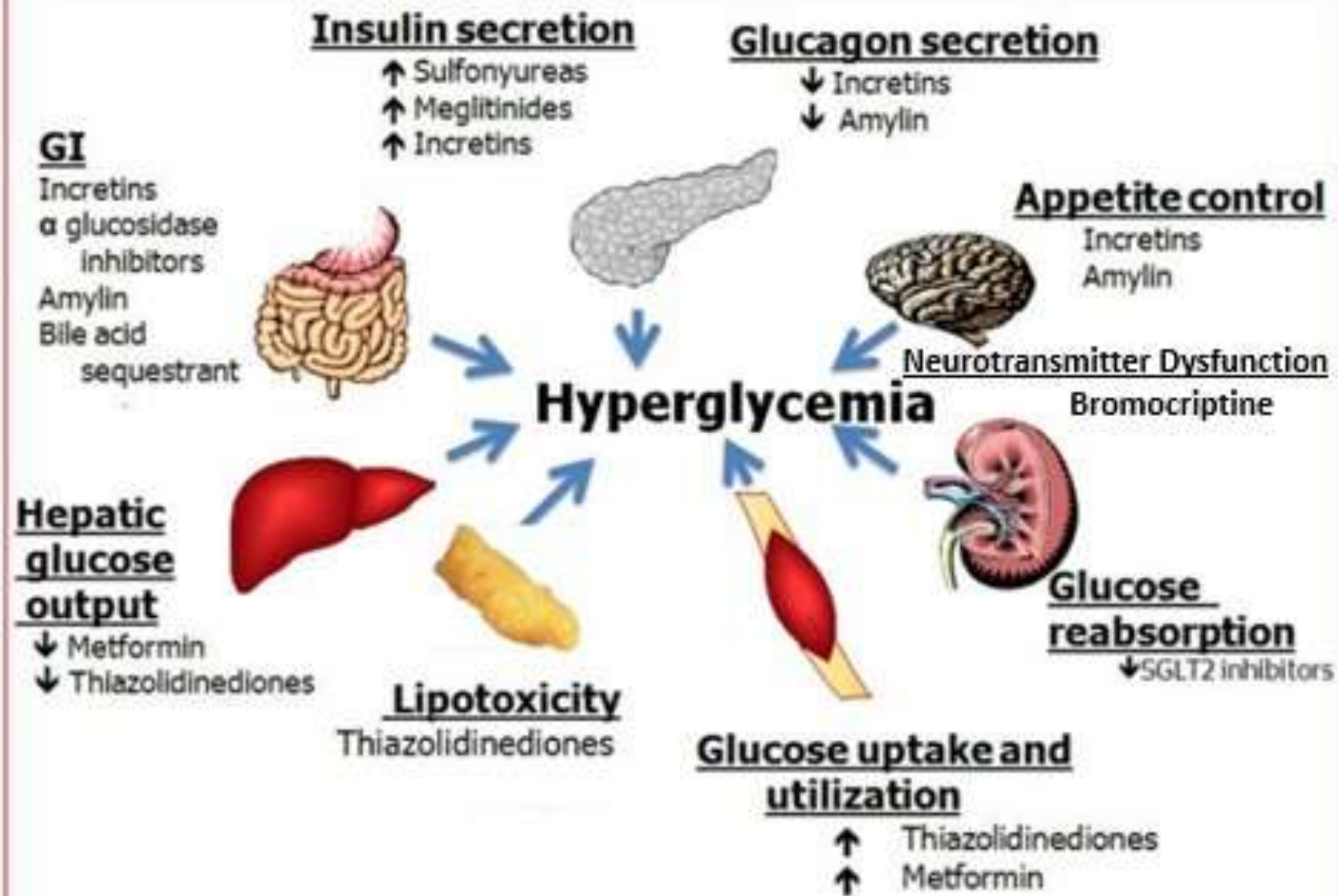


Fig. 20.5 Major metabolic pathways of fuel metabolism and the actions of insulin. ⊕ indicates stimulation and ⊖ indicates suppression by insulin. In response to a rise in blood glucose, e.g. after a meal, insulin is released, suppressing gluconeogenesis and promoting glycogen synthesis and storage. Insulin promotes the peripheral uptake of glucose, particularly in skeletal muscle, and encourages storage (as muscle glycogen). It also promotes protein synthesis and lipogenesis, and suppresses lipolysis. The release of intermediate metabolites, including amino acids (glutamine, alanine), 3-carbon intermediates in oxidation (lactate, pyruvate) and free fatty acids (FFAs), is controlled by insulin. In the absence of insulin, e.g. during fasting, these processes are reversed and favour gluconeogenesis in liver from glycogen, glycerol, amino acids and other 3-carbon precursors.



i**20.1 Metabolic actions of insulin****Increase****Decrease****Carbohydrate metabolism**

Glucose transport (muscle, adipose tissue)
Glucose phosphorylation
Glycogen synthesis
Glycolysis
Pyruvate dehydrogenase activity
Pentose phosphate shunt

Gluconeogenesis
Glycogenolysis

Lipid metabolism

Triglyceride synthesis
Fatty acid synthesis (liver)
Lipoprotein lipase activity (adipose tissue)

Lipolysis
Lipoprotein lipase (muscle)
Ketogenesis
Fatty acid oxidation (liver)

Protein metabolism

Amino acid transport
Protein synthesis

Protein degradation

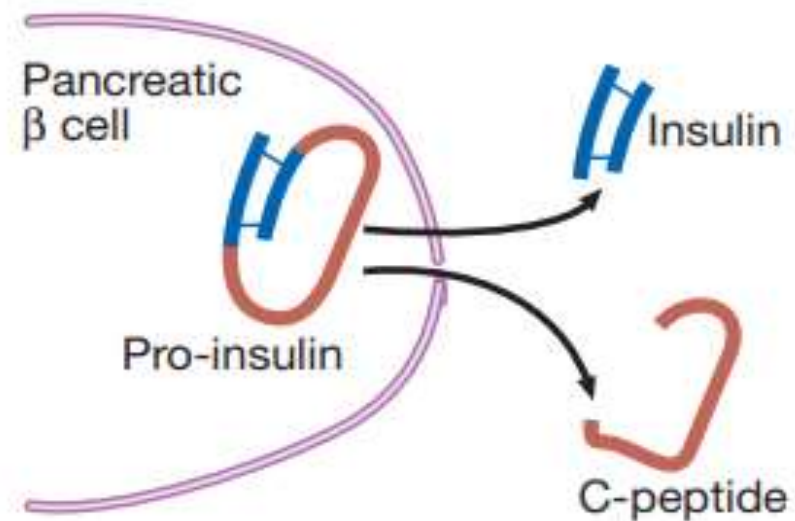
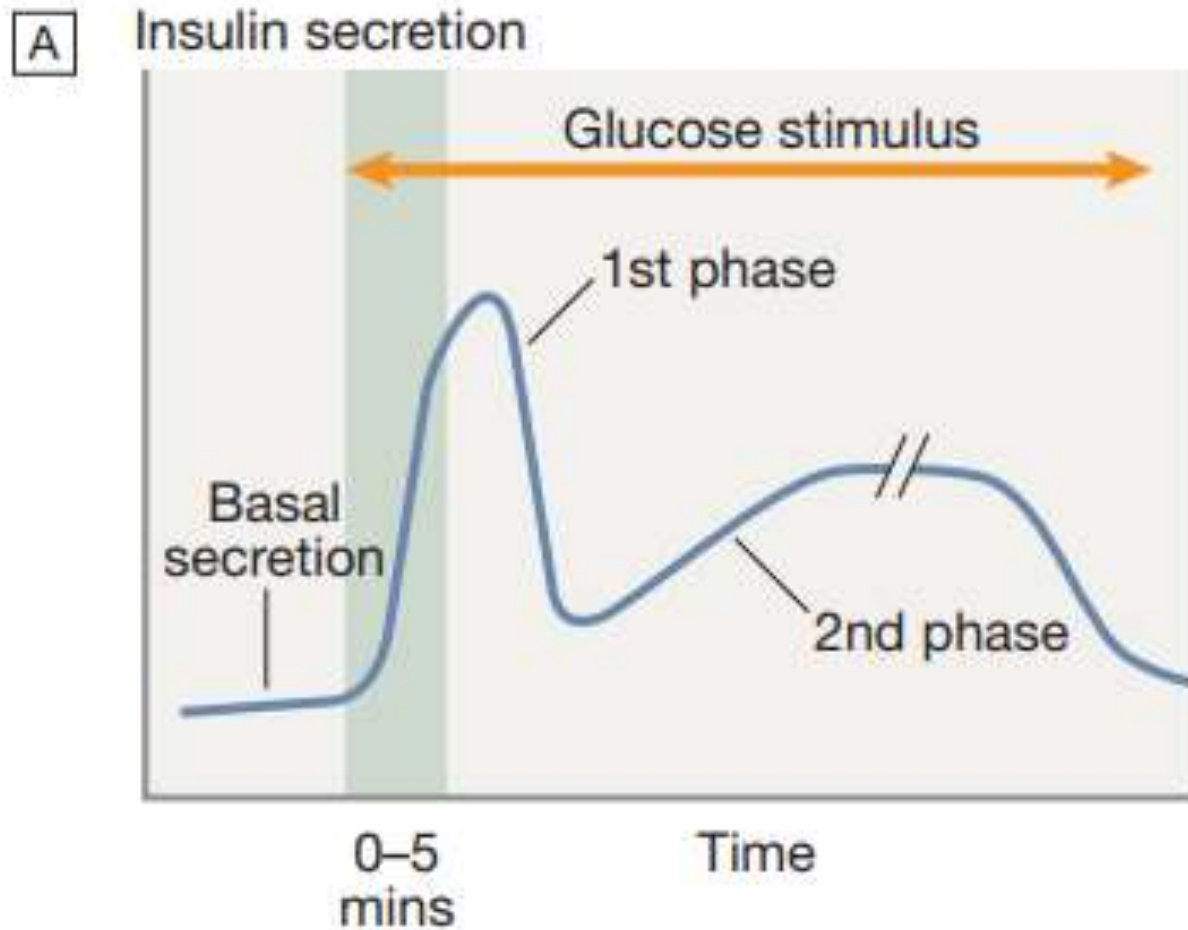


Fig. 20.4 Processing of pro-insulin into insulin and C-peptide. Pro-insulin in the pancreatic β cell is cleaved to release insulin and equimolar amounts of inert C-peptide (connecting peptide). Measurement of C-peptide can be used to assess endogenous insulin secretory capacity.

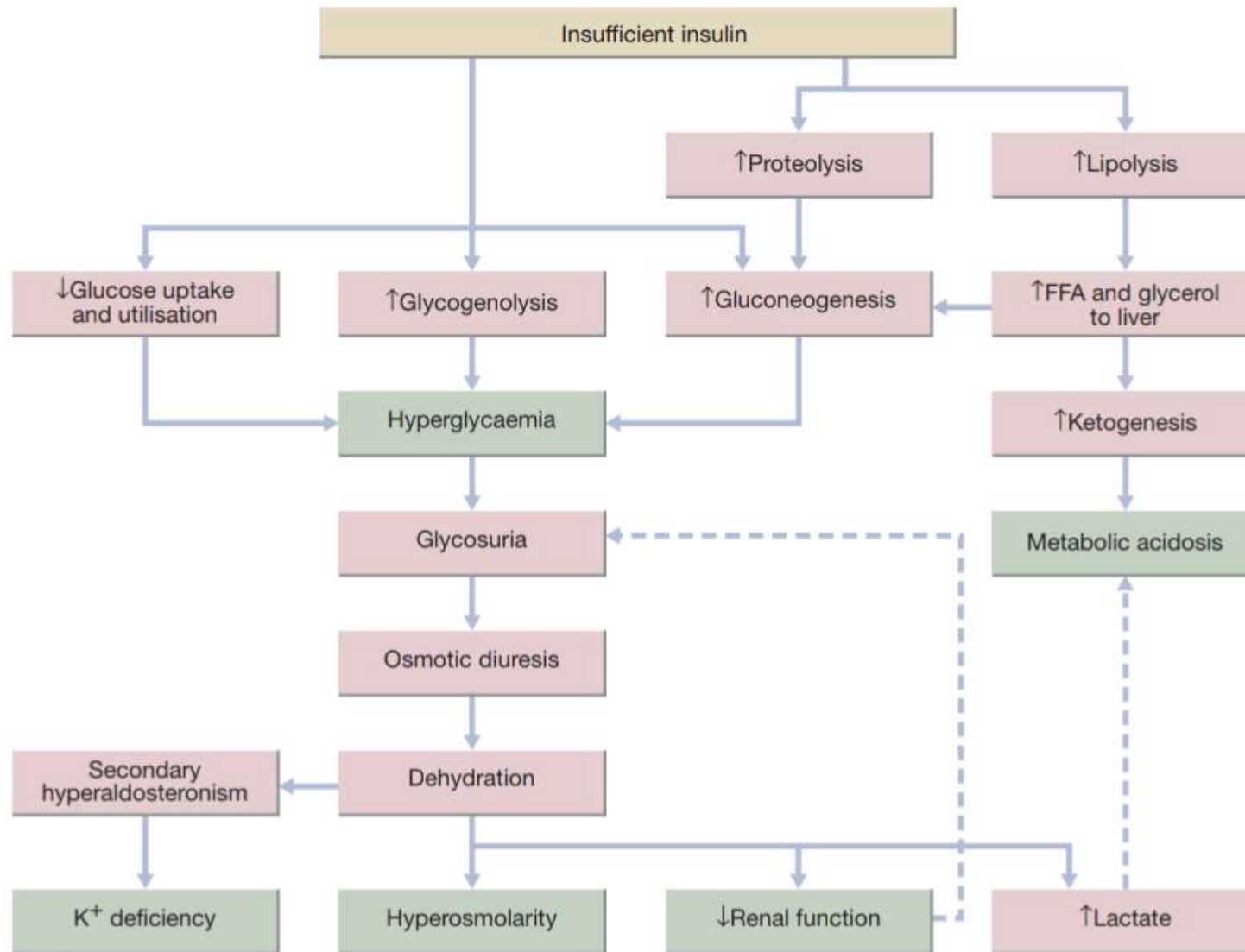


Fig. 20.7 Acute metabolic complications of insulin deficiency. (FFA = free fatty acid)

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20.12 Classical features of type 1 and type 2 diabetes

	Type 1	Type 2
Typical age at onset	<40 years	>50 years
Duration of symptoms	Weeks	Months to years
Body weight	Normal or low	Obese
Ketonuria	Yes	No
Rapid death without treatment with insulin	Yes	No
Autoantibodies	Positive in 80–90%	Negative
Diabetic complications at diagnosis	No	25%
Family history of diabetes	Uncommon	Common
Other autoimmune disease	Common	Uncommon

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20.9 Aetiological classification of diabetes mellitus

Type 1 diabetes

- Immune-mediated
- Idiopathic

Type 2 diabetes

Other specific types

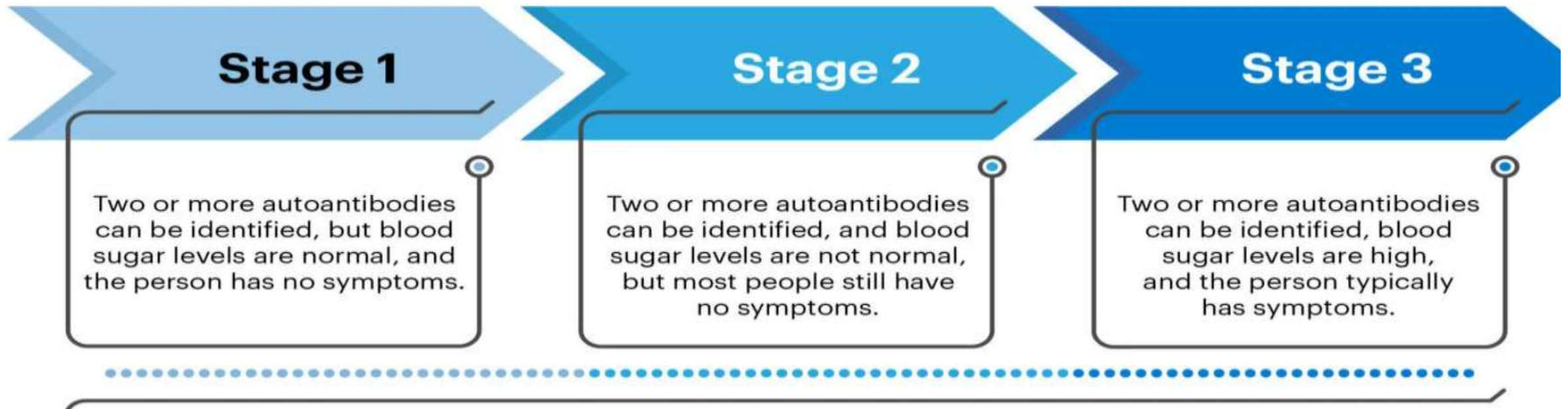
- Genetic defects of β -cell function (see Box 20.10)
- Genetic defects of insulin action (e.g. leprechaunism, lipodystrophies)
- Pancreatic disease (e.g. pancreatitis, pancreatectomy, neoplastic disease, cystic fibrosis, haemochromatosis, fibrocalculous pancreatopathy)
- Excess endogenous production of hormonal antagonists to insulin, e.g.:
 - Growth hormone – acromegaly
 - Glucocorticoids – Cushing's syndrome
 - Glucagon – glucagonoma
 - Catecholamines – pheochromocytoma
 - Thyroid hormones – thyrotoxicosis
- Drug-induced (e.g. glucocorticoids, thiazide diuretics, phenytoin)
- Uncommon forms of immune-mediated diabetes (e.g. IPEX syndrome)
- Associated with genetic syndromes (e.g. Down's syndrome, Klinefelter's syndrome, Turner's syndrome, DIDMOAD (Wolfram's syndrome), Friedreich's ataxia, myotonic dystrophy)

Gestational diabetes

(DIDMOAD = diabetes insipidus, diabetes mellitus, optic atrophy, nerve deafness; IPEX = immunodysregulation polyendocrinopathy X)

Type 1 diabetes

- T-cell mediated autoimmune disease
- Genetic susceptibility (complex and multifactorial) + environmental trigger → B-cell autoimmunity (progressive process; months to years)
- Marked hyperglycemia; when 80-90% of B-cells are destroyed
- Stages of type 1 diabetes



- Auto-antibodies are present in around 80 %
- Presence of antibodies can predict disease risk
- Associated with other autoimmune diseases:
Celiac disease, thyroid disease, Addison's disease
Vitiligo, and pernicious anemia

i 20.6 Risk of type 1 diabetes among first-degree relatives of patients with type 1 diabetes	
Relative with type 1 diabetes	% overall risk
Identical twin	30–50
Non-identical twin	6–10
HLA-identical sibling	16
Non-HLA-identical sibling	5
Father	10
Mother	1–4
Both parents	Up to 30

Type 1 in adults; LADA

- More common in children (5-7) years but can happen at any age
- Half of the cases develop in adults
- More insidious onset in adults
- LADA; the presence of islet autoantibodies in high titer (anti-GAD), without rapid progression to insulin therapy
- LADA patients often present and are managed initially as type 2 but with rapid progression to insulin

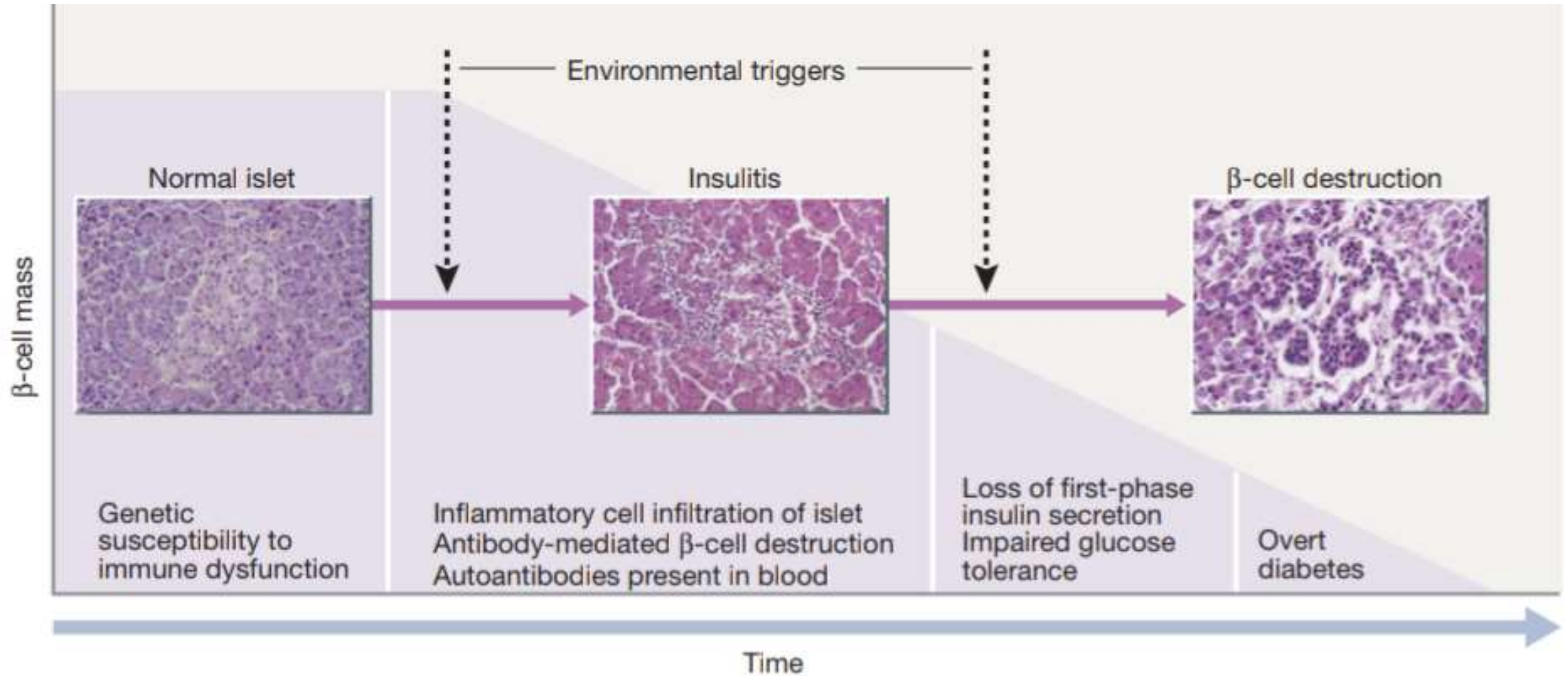


Fig. 20.6 Pathogenesis of type 1 diabetes. Proposed sequence of events in the development of type 1 diabetes. Environmental triggers are described in the text. *Insets (normal islet, β -cell destruction)* Courtesy of Dr A. Foulis, Dept of Pathology, University of Glasgow.

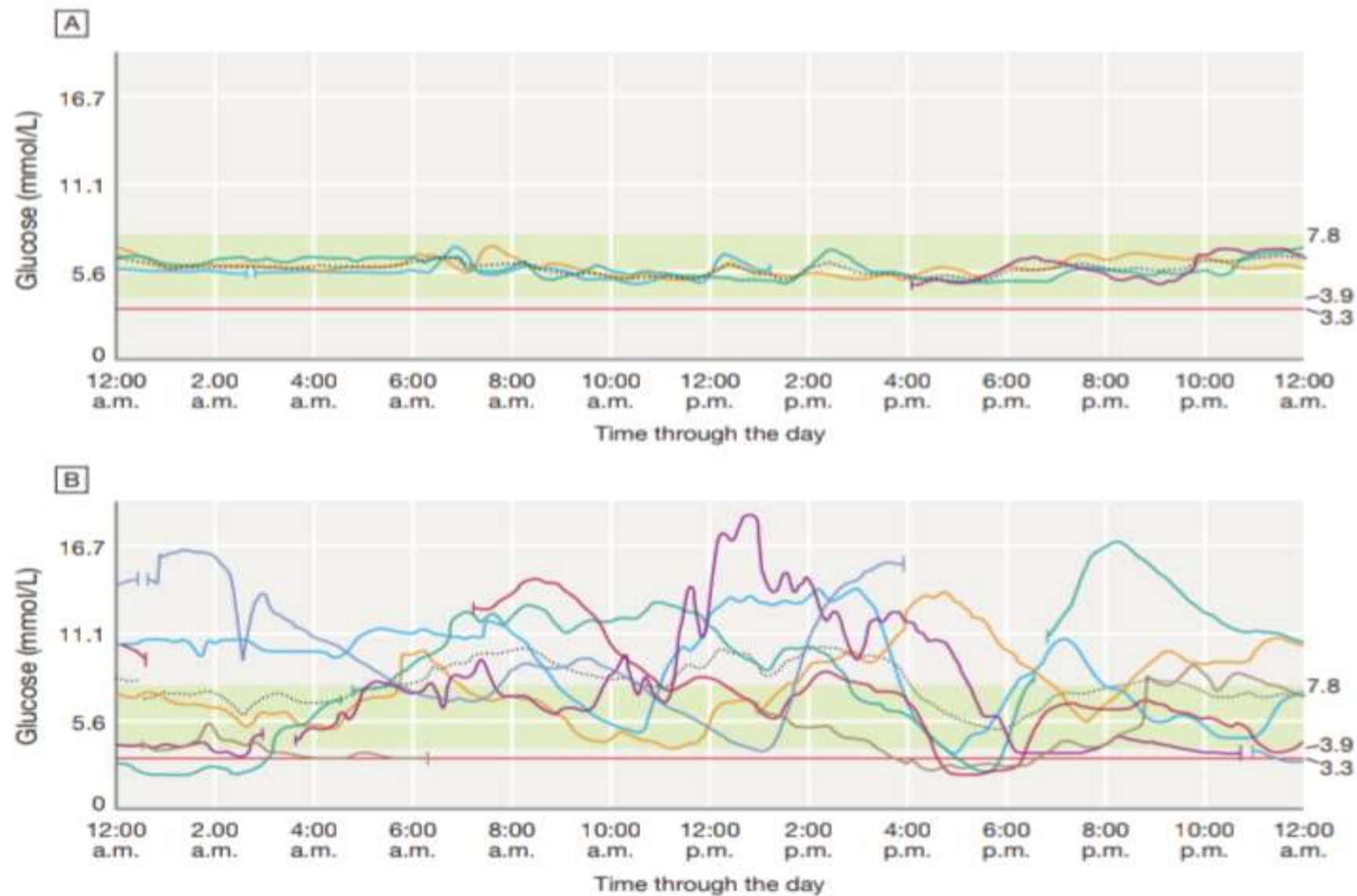


Fig. 20.17 Continuous glucose monitoring (CGM) profiles: sensor data. **A** CGM profile from an individual without diabetes. **B** CGM profile from an individual with type 1 diabetes. The green box shows the reference range. CGM devices may be worn for 7–14 days and the glucose profile of each day illustrated by a different colour. Based on this, the person with diabetes and their health-care team can review overall profiles and adjust treatment as necessary to improve control and avoid hypoglycaemia.

Type 2 diabetes

- Insulin resistance and/or relative insulin deficiency
- Increased insulin resistance → increased insulin secretion
- In susceptible individuals B-cells fail to sustain this response → slow development of insulin deficiency
- Reduced insulin sensitivity:
 1. Obesity → Adipocytes: release FFA and Adipokines → insulin resistance
 2. Decreased physical activity

-
- Loss of 50% of B-cell function at time of diagnosis
 - Deposition of amyloid in the islets
 - FFA and hyperglycemia are toxic to the B-cells
 - Genetic predisposition is more evident; polygenic (> 70 genes or gene regions; mainly affect B-cell function or cell regulation and turnover)
 - Concordance in monozygotic twins can approach 100%
 - Ethnic variations (high risk ethnicities)
 - Ketosis prone diabetes (Flatbush syndrome)

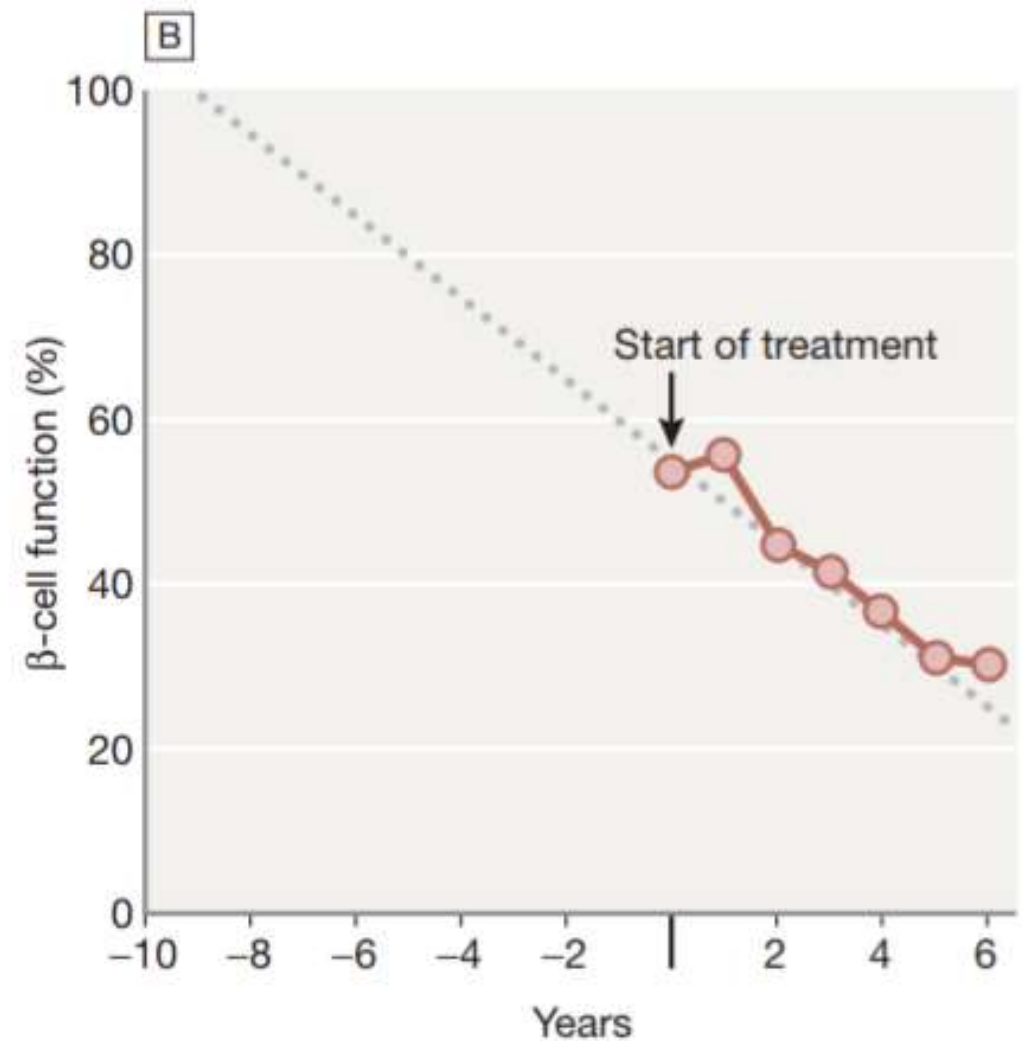
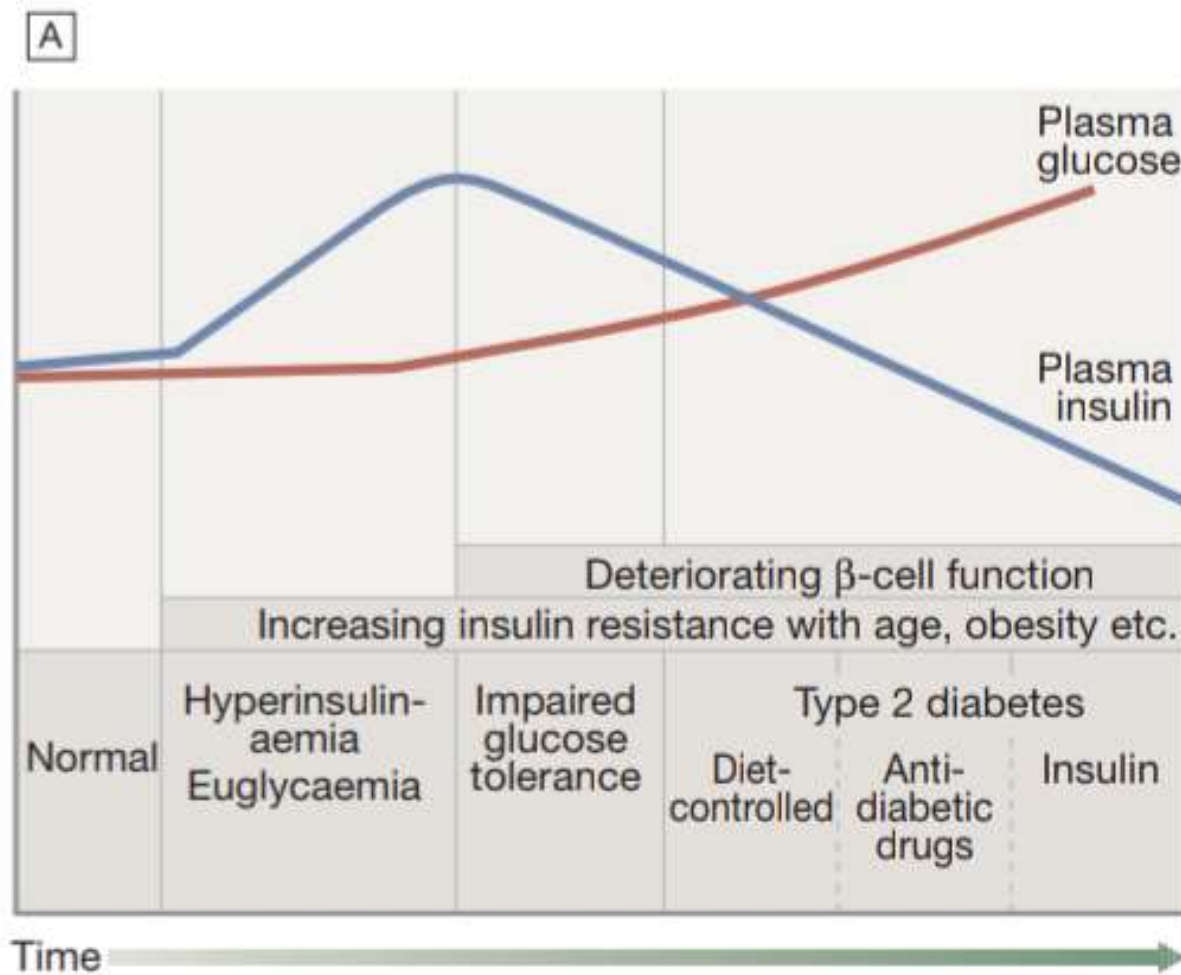


Fig. 20.8 Natural history of type 2 diabetes. **A** In the early stage of the disorder, the response to progressive insulin resistance is an increase in insulin secretion by the pancreatic cells, causing hyperinsulinaemia. Eventually, the β cells are unable to compensate adequately and blood glucose rises, producing hyperglycaemia. With further β -cell failure, glycaemic control deteriorates and treatment requirements escalate. **B** Progressive pancreatic β -cell failure in patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS). Beta-cell function was estimated using the homeostasis model assessment (HOMA) and was already below 50% at the time of diagnosis. Thereafter, long-term incremental increases in fasting plasma glucose were accompanied by progressive β -cell dysfunction. If the slope of this progression is extrapolated, it appears that pancreatic dysfunction may have been developing for many years before diagnosis of diabetes. *B, Adapted from Holman RR. Diabetes Res Clin Pract 1998; 40 (Suppl.):S21–S25.*

Metabolic syndrome; insulin resistance syndrome

- Elevated BP or hypertension
- Hyperglycemia or diabetes
- Hypertriglyceridemia
- Low HDL
- Increased waist circumference
- PCOS
- NAFLD
- Hyperuricemia



Risk factors of diabetes

Other forms of diabetes

- Genetic disorders
 1. Monogenic diabetes
 2. Diabetes as part of a syndrome
- Endocrinopathies
- Pancreatic diseases
- Medications

Monogenic diabetes

- MODY is defined as non-insulin-requiring diabetes that develops under the age of 25 years in one family member
- AD inheritance
- Strong FH

i 20.10 Monogenic diabetes mellitus: maturity-onset diabetes of the young (MODY)		
Functional defect	Main type*	Gene mutated*
β -cell glucose sensing	MODY2	<i>GCK</i>
The set point for basal insulin release is altered, causing a high fasting glucose, but sufficient insulin is released after meals. As a result, the HbA _{1c} is often normal and microvascular complications are rare. Treatment is rarely required		
β -cell transcriptional regulation	MODY3 MODY5 MODY1	<i>HNF1α</i> <i>HNF1β</i> <i>HNF4α</i>
Diabetes develops during adolescence/early adulthood and can be managed with diet and tablets for many years, but ultimately, insulin treatment is required. The HNF1 α and 4 α forms respond particularly well to sulphonylurea drugs. All types are associated with microvascular complications. <i>HNF1β</i> mutations also cause renal cysts and renal failure		
*Other gene mutations have been found in rare cases. For further information, see diabetesgenes.org .		

Gestational diabetes

- Diabetes that occurs in the second half of pregnancy
- Diagnosis
- Whom to screen?
- Risk factor for future development of Type 2 diabetes
- HbA1c is not used for diagnosis
- Complications of gestational diabetes
- Treatment

Clinical presentation



Symptoms of
hyperglycemia



Acute diabetes
complications



Chronic complications
(mainly in type 2 diabetes)



Nocturnal enuresis

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20.11 Symptoms of hyperglycaemia

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

6 Head
Xanthelasma
Cranial nerve palsy/eye movements/ptosis

5 Neck
Carotid pulse
Bruit
Thyroid enlargement

4 Axillae

▲ Acanthosis nigricans in insulin resistance

3 Blood pressure

2 Skin
Bullae
Pigmentation
Granuloma annulare
Vitiligo

1 Hands
(see opposite)

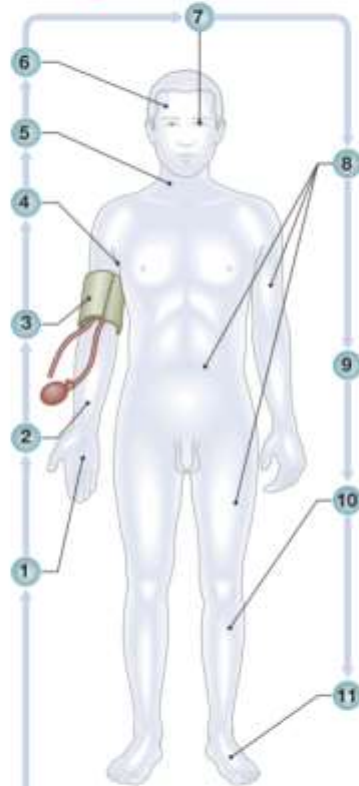


▲ 'Prayer sign'

7 Eyes (see opposite)
Visual acuity
Cataract/lens opacity
Fundoscopy



▲ Exudative maculopathy



Observation

- Weight loss in insulin deficiency
- Obesity in type 2 diabetes
- Mucosal candidiasis
- Dehydration—dry mouth, ↓tissue turgor
- Air hunger—Kussmaul breathing in ketoacidosis

8 Insulin injection sites
(see opposite)

9 Abdomen
Hepatomegaly
(fatty infiltration of liver)

10 Legs
Muscle-wasting
Sensory abnormality
Hair loss
Tendon reflexes



▲ Necrobiosis lipidica

11 Feet (see opposite)
Inspection
Peripheral pulses
Sensation



▲ Neuropathic foot ulcer



▲ Charcot neuroarthropathy

Diabetes can affect every system in the body. In routine clinical practice, examination of the patient with diabetes is focused on hands, blood pressure, axillae, neck, eyes, insulin injection sites and feet.

7 Examination of the eyes

Visual acuity

- Check distance vision using Snellen chart at 6 m
- Check near vision using standard reading chart
- Note that visual acuity can alter reversibly with acute hyperglycaemia due to osmotic changes affecting the lens. Most patients with retinopathy do not have altered visual acuity, except after a vitreous haemorrhage or in some cases of maculopathy

Lens opacification

- Look for the red reflex using the ophthalmoscope held 30 cm from the eye

Fundal examination

- Either use a three-field retinal camera or dilate pupils with a mydriatic (e.g. tropicamide) and examine with an ophthalmoscope in a darkened room
- Note features of diabetic retinopathy (p. 1174), including photocoagulation scars from previous laser treatment



Background retinopathy. Courtesy of Dr A.W. Patrick and Dr I.W. Campbell.



Proliferative retinopathy. Courtesy of Dr A.W. Patrick and Dr I.W. Campbell.

8 Examination of the hands

Several abnormalities are more common in diabetes:

- Limited joint mobility ('cheiroarthropathy') causes painless stiffness. The inability to extend (to 180°) the metacarpophalangeal or interphalangeal joints of at least one finger bilaterally can be demonstrated in the 'prayer sign'
- Dupuytren's contracture (p. 1059) causes nodules or thickening of the skin and knuckle pads
- Carpal tunnel syndrome (p. 1139) presents with wrist pain radiating into the hand
- Trigger finger (flexor tenosynovitis) may be present
- Muscle-wasting/sensory changes may be present in peripheral sensorimotor neuropathy, although this is more common in the lower limbs

8 Insulin injection sites

Main areas used

- Anterior abdominal wall
- Upper thighs/buttocks
- Upper outer arms

Inspection

- Bruising
- Subcutaneous fat deposition (lipohypertrophy)
- Subcutaneous fat loss (lipoatrophy; associated with injection of unpurified animal insulins – now rare)
- Erythema, infection (rare)



Lipohypertrophy of the upper arm.

11 Examination of the feet

Inspection

- Look for evidence of callus formation on weight-bearing areas, clawing of the toes (in neuropathy), loss of the plantar arch, discoloration of the skin (ischaemia), localised infection and ulcers
- Deformity may be present, especially in Charcot neuroarthropathy
- Fungal infection may affect skin between toes, and nails

Circulation

- Peripheral pulses, skin temperature and capillary refill may be abnormal

Sensation

- This is abnormal in stocking distribution in typical peripheral sensorimotor neuropathy
- Testing light touch with monofilaments is sufficient for risk assessment; test other sensation modalities (vibration, pain, proprioception) only when neuropathy is being evaluated

Reflexes

- Ankle reflexes are lost in typical sensorimotor neuropathy
- Test plantar and ankle reflexes



Monofilaments. The monofilament is applied gently until slightly deformed at five points on each foot. Callus should be avoided as sensation is reduced. If the patient feels fewer than 8 out of 10 touches, the risk of foot ulceration is increased 5–10-fold.

Diagnosis



20.2 Diagnosis of diabetes and pre-diabetes

Diabetes is confirmed by:

- *either* plasma glucose in random sample or 2 hrs after a 75 g glucose load ≥ 11.1 mmol/L (200 mg/dL) *or*
- fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) *or*
- $\text{HbA}_{1c} \geq 48$ mmol/mol

In asymptomatic patients, two diagnostic tests are required to confirm diabetes; the second test should be the same as the first test to avoid confusion

'Pre-diabetes' is classified as:

- impaired fasting glucose = fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dL) and < 7.0 mmol/L (126 mg/dL)
- impaired glucose tolerance = fasting plasma glucose < 7.0 mmol/L (126 mg/dL) *and* 2-hr glucose after 75 g oral glucose drink 7.8–11.1 mmol/L (140–200 mg/dL)

HbA_{1c} criteria for pre-diabetes vary. The National Institute for Health and Care Excellence (NICE) guidelines (UK) recommend considering an HbA_{1c} range of 42–47 mmol/mol to be indicative of pre-diabetes; the American Diabetes Association (ADA) guidelines suggest a range of 39–47 mmol/mol. The ADA also suggests a lower fasting plasma glucose limit of ≥ 5.6 mmol/L (100 mg/dL) for impaired fasting glucose.

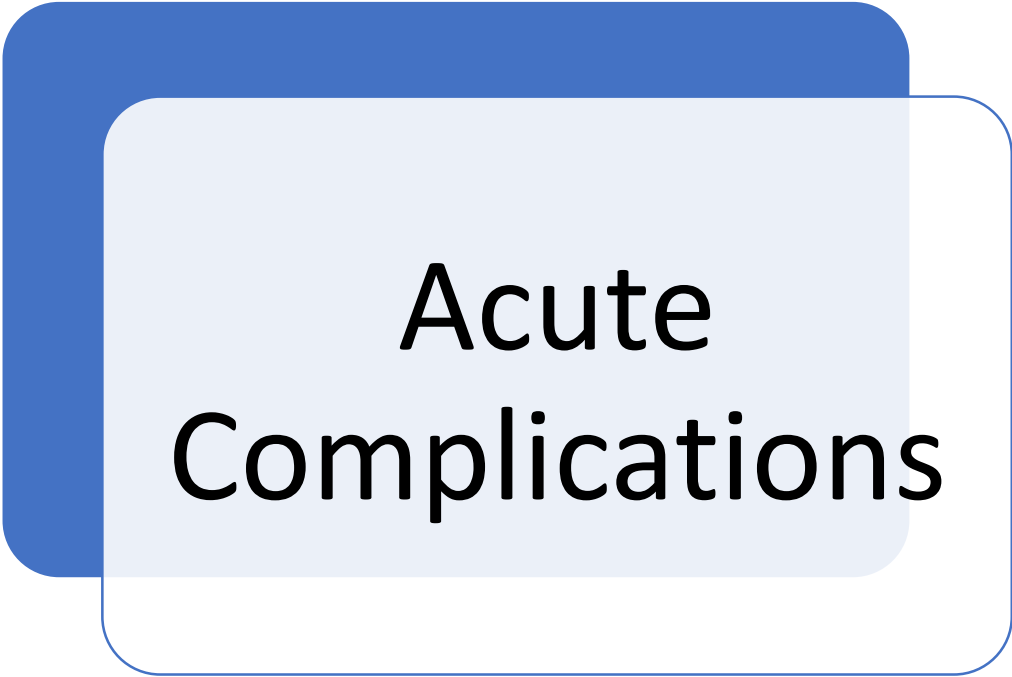
Investigations

- Urine glucose
- Blood glucose
- Interstitial glucose
- Glycated hemoglobin
- Islet auto-antibodies
- C-peptide
- Urine and blood ketones
- Urine protein

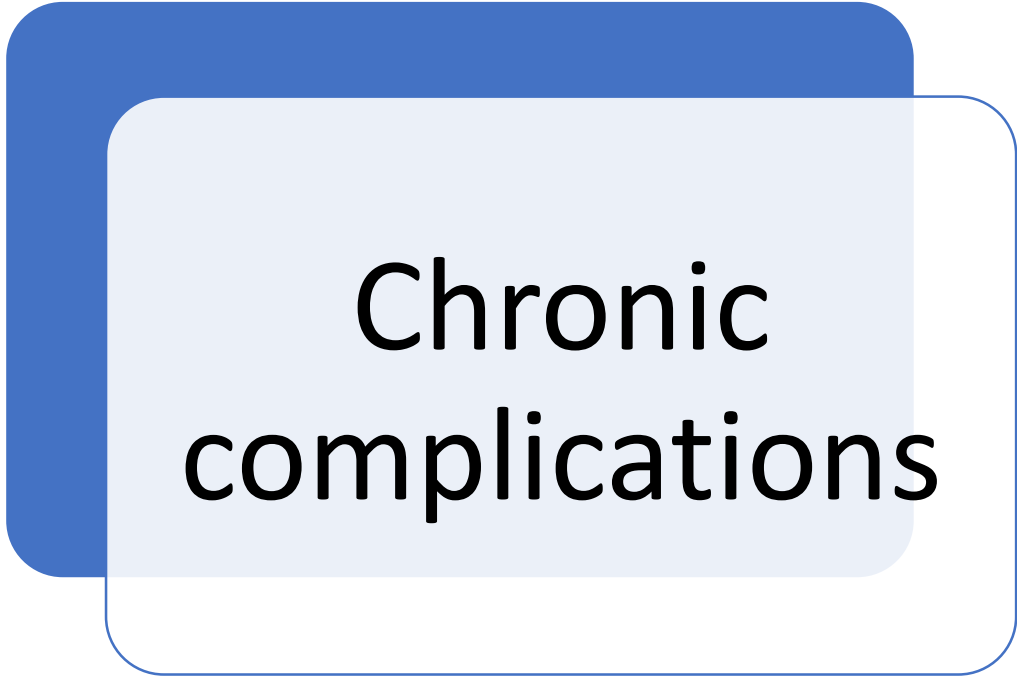




Complications of diabetes



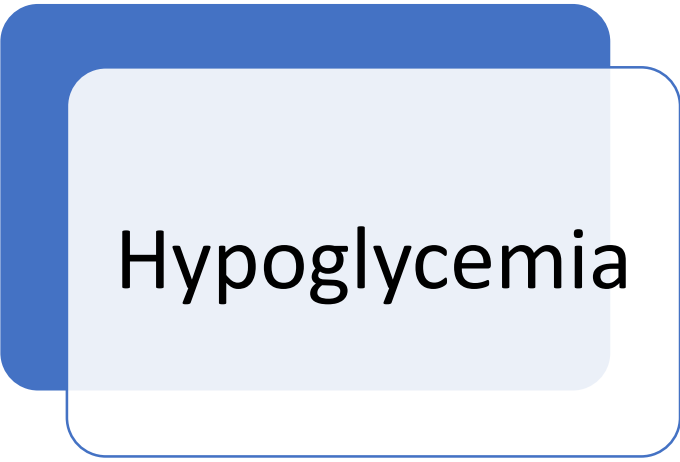
**Acute
Complications**



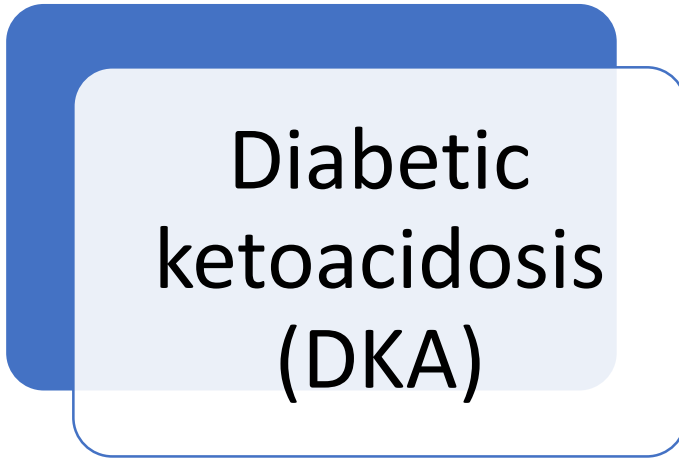
**Chronic
complications**



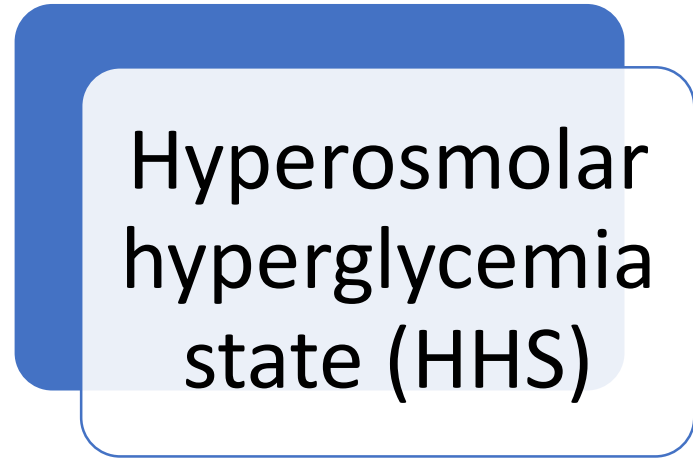
Acute complications



Hypoglycemia



Diabetic
ketoacidosis
(DKA)



Hyperosmolar
hyperglycemia
state (HHS)

Chronic complications

i 20.35 Complications of diabetes

Microvascular/neuropathic

Retinopathy, cataract

- Impaired vision

Nephropathy

- Renal failure

Peripheral neuropathy

- Sensory loss
- Pain
- Motor weakness

Autonomic neuropathy

- Gastrointestinal problems (gastroparesis; altered bowel habit)
- Postural hypotension

Foot disease

- Ulceration
- Arthropathy

Macrovascular

Coronary circulation

- Myocardial ischaemia/infarction

Cerebral circulation

- Transient ischaemic attack
- Stroke

Peripheral circulation

- Claudication
- Ischaemia

i 20.36 Mortality in diabetes

Risk versus non-diabetic controls (mortality ratio)

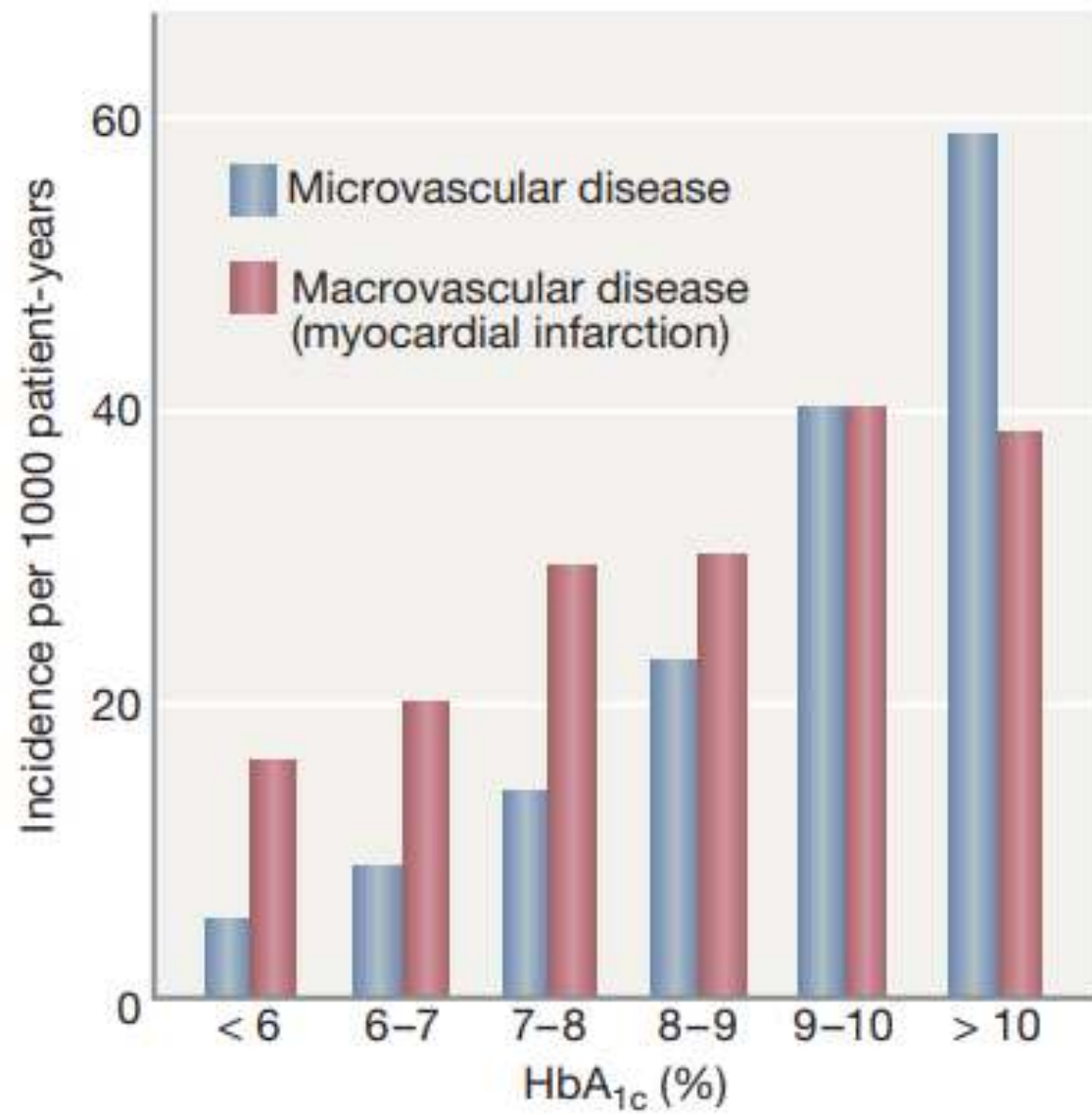
- | | |
|---|-------|
| • Overall | 2.6 |
| • Coronary heart disease | } 2.8 |
| • Cerebrovascular disease | |
| • Peripheral vascular disease | |
| • All other causes, including renal failure | 2.7 |

Causes of death in diabetes (approximate proportion)

- | | |
|--------------------------|-----|
| • Cardiovascular disease | 70% |
| • Renal failure | 10% |
| • Cancer | 10% |
| • Infections | 6% |
| • Diabetic ketoacidosis | 1% |
| • Other | 3% |

Risk factors for increased morbidity and mortality in diabetes

- | | |
|--|---------------------------------|
| • Duration of diabetes | • Raised blood pressure |
| • Early age at onset of disease | • Proteinuria; microalbuminuria |
| • High glycated haemoglobin (HbA _{1c}) | • Dyslipidaemia |
| | • Obesity |





20.38 Risk factors for diabetic nephropathy

- Poor glycaemic control
- Long duration of diabetes
- Presence of other microvascular complications
- Ethnicity (e.g. Asians, Pima Indians)
- Pre-existing hypertension
- Family history of diabetic nephropathy
- Family history of hypertension

Cardiovascular

- Postural hypotension
- Resting tachycardia
- Fixed heart rate

Gastrointestinal

- Dysphagia, due to oesophageal atony
- Abdominal fullness, nausea and vomiting, unstable glycaemia, due to delayed gastric emptying ('gastroparesis')
- Nocturnal diarrhoea $\pm$ faecal incontinence
- Constipation, due to colonic atony

Genitourinary

- Difficulty in micturition, urinary incontinence, recurrent infection, due to atonic bladder
- Erectile dysfunction and retrograde ejaculation

Sudomotor

- Nocturnal sweats without hypoglycaemia
- Gustatory sweating
- Anhidrosis; fissures in the feet

Vasomotor

- Feet feel cold, due to loss of skin vasomotor responses
- Dependent oedema, due to loss of vasomotor tone and increased vascular permeability
- Bulla formation

Pupillary

- Decreased pupil size
- Resistance to mydriatics
- Delayed or absent reflexes to light

Management of diabetes

- Lifestyle modifications
- Pharmacotherapy:
 1. Non-insulin agents
 2. Insulin
- Islet cell transplantation
- Pancreatic transplantation
- Diabetes technologies

Peripheral neuropathy



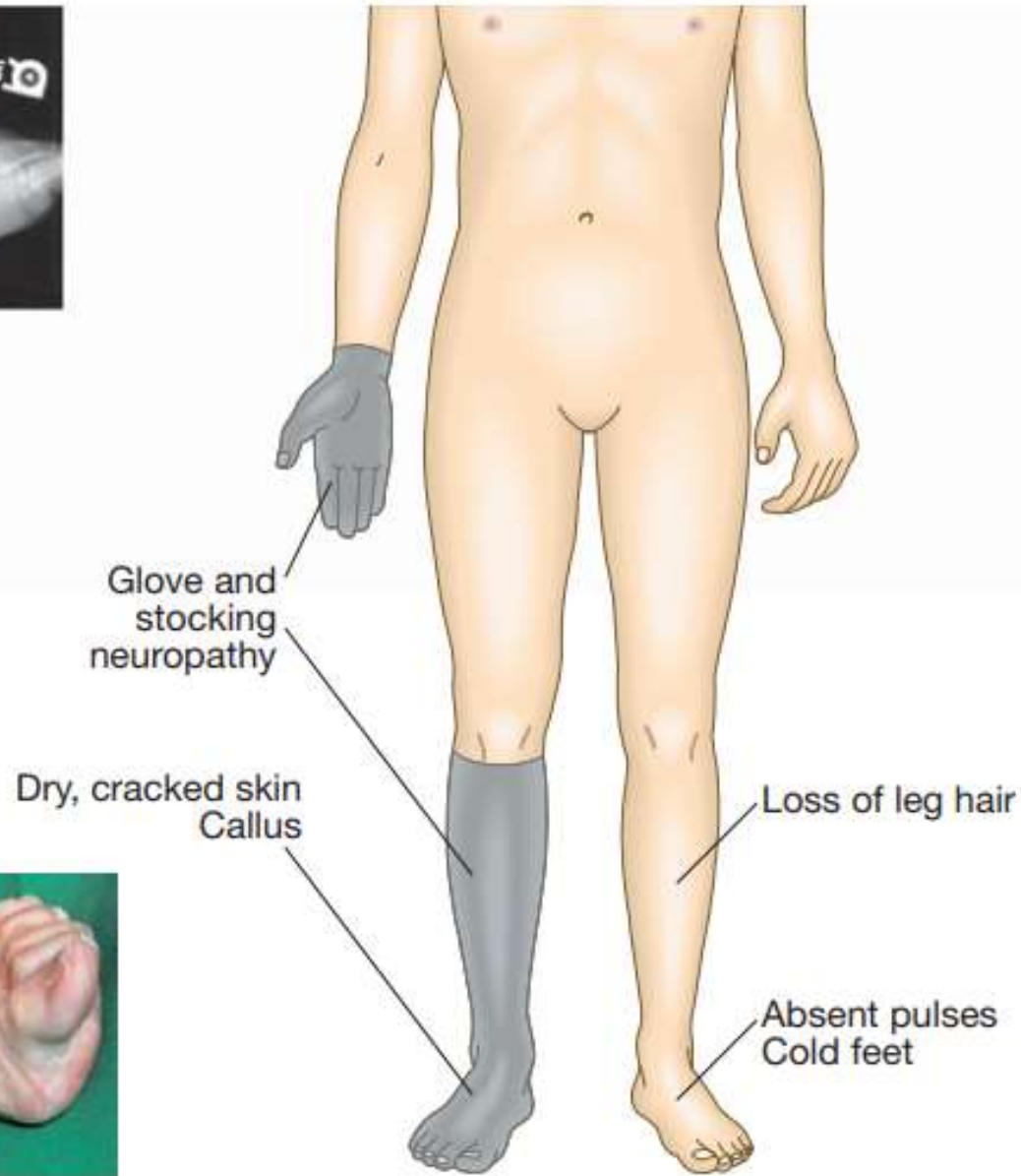
▲ Charcot foot



▲ Neuropathic ulcer



▲ Clawing of toes



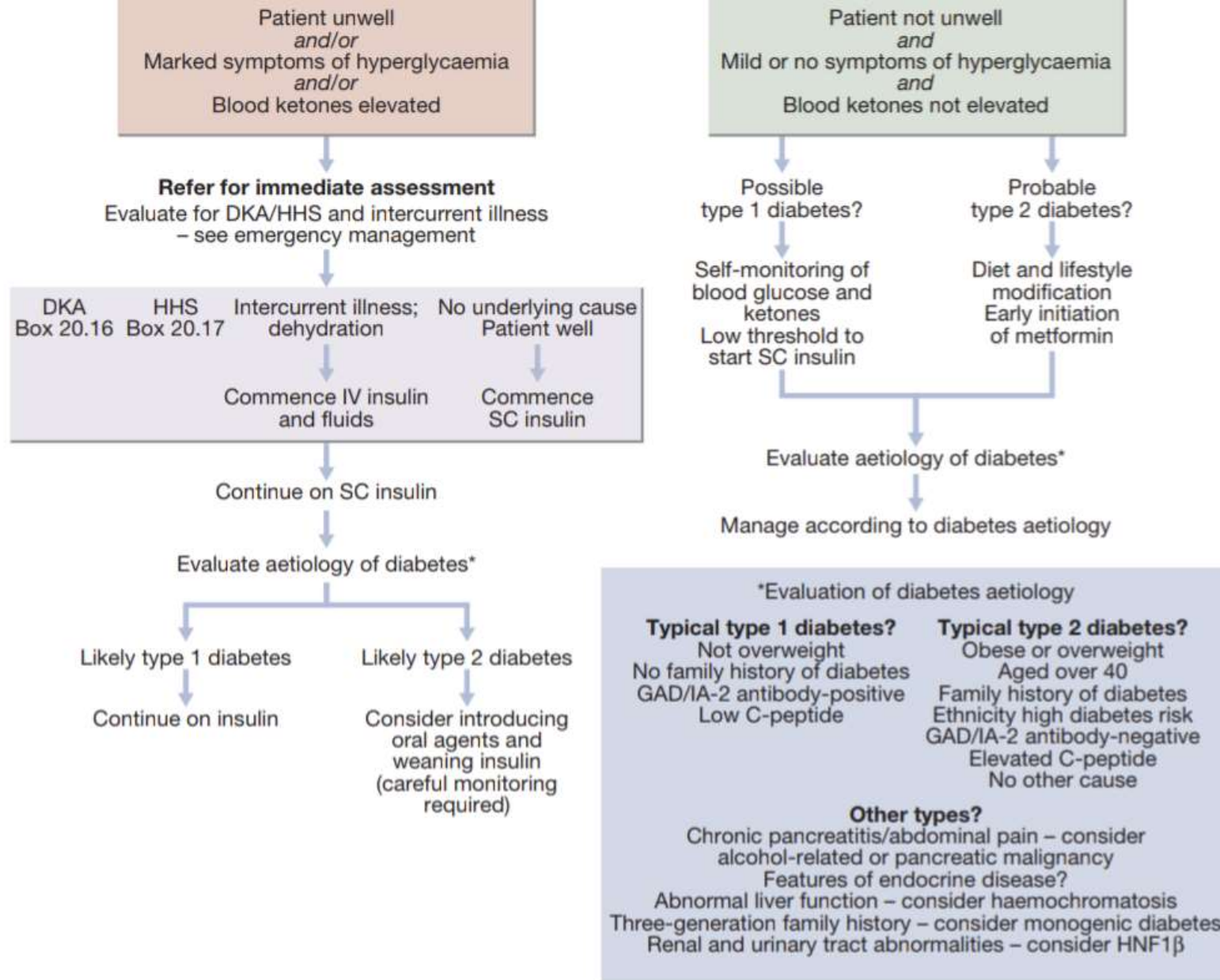
Peripheral vascular disease



▲ Proximal arterial occlusion



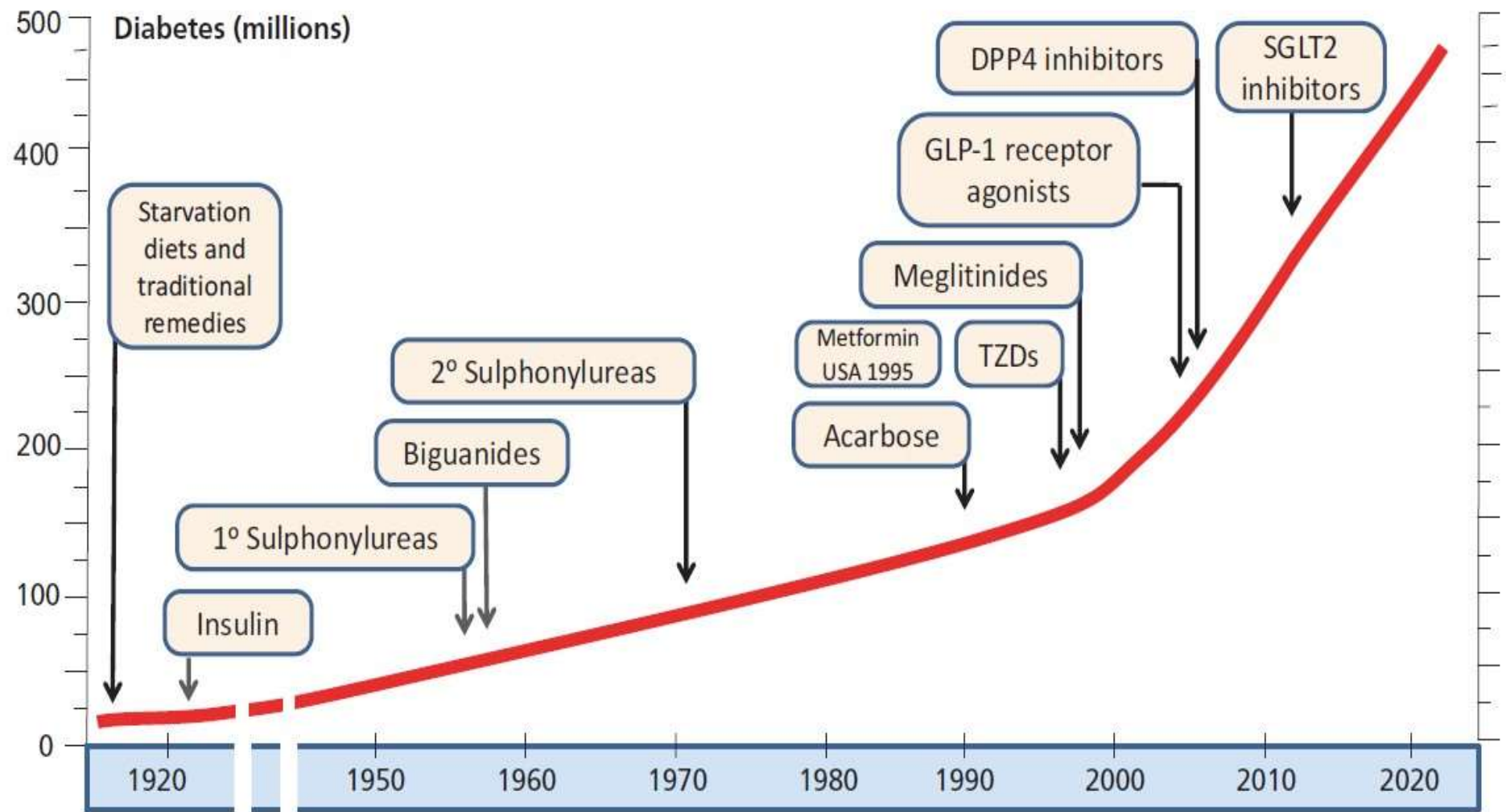
▲ Digital gangrene



Management of diabetes: Acute management

Fig. 20.9 New-onset hyperglycaemia. (DKA = diabetic ketoacidosis; GAD = glutamic acid decarboxylase; HHS = hyperosmotic hyperglycaemic state; IA-2 = islet antigen 2; IV = intravenous; SC = subcutaneous)

Figure 1. Timeline showing the introduction of different classes of glucose-lowering agents. The red line indicates the estimated global prevalence of people with diabetes (in millions), >90% of whom are believed to have T2DM



DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter-2; TZD, thiazolidinedione; 1°, first; 2°, second.

ORAL ANTIDIABETIC DRUGS

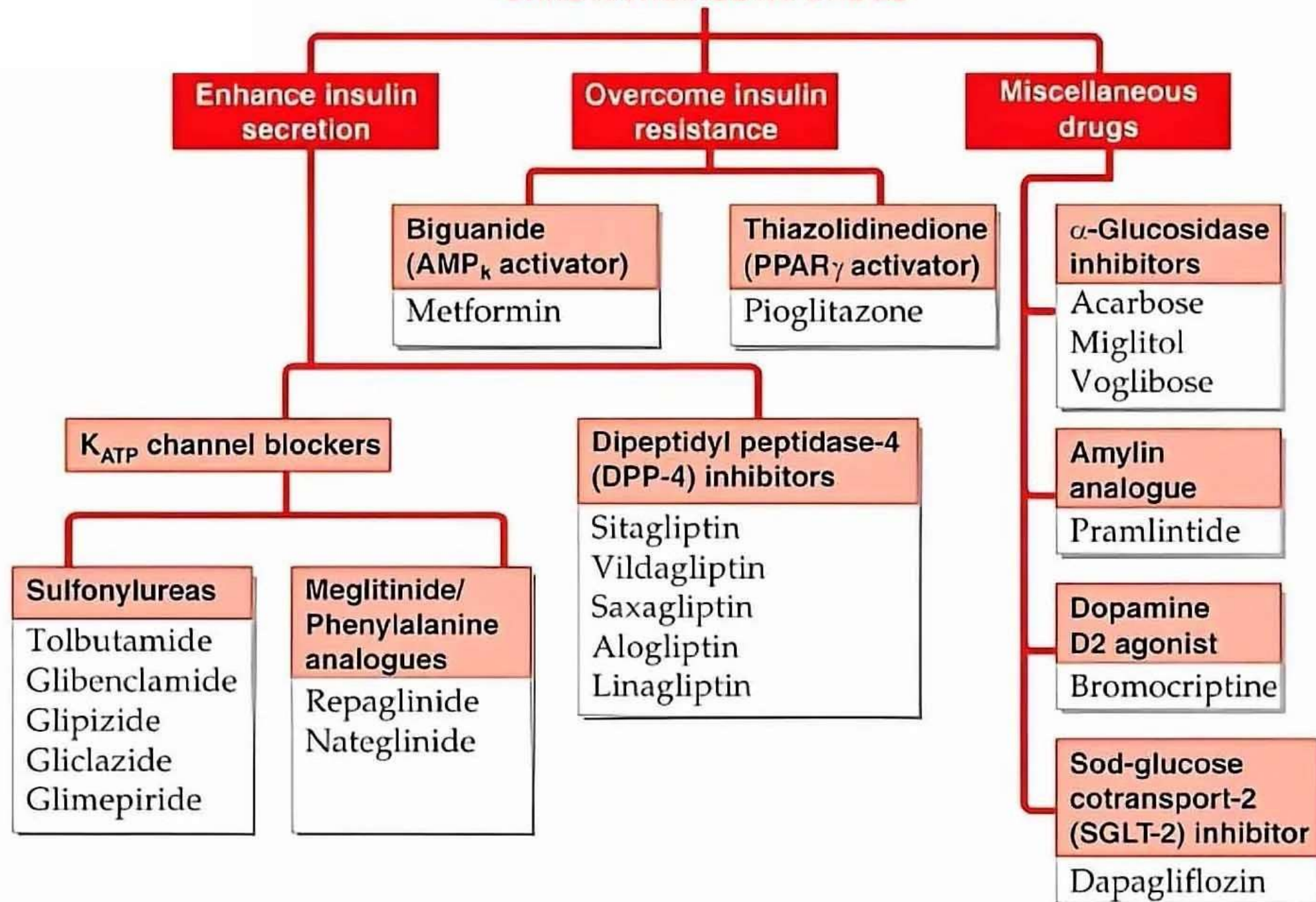


Table 1. Blood glucose-lowering agents used in the UK.*

Class with examples	Dose range mg/day (unless stated)	a. Glucose-lowering efficacy^ b. Hypo risk^ c. Weight^	Mode of action	Cautions, limitations and additional benefits
Oral				
Biguanide <i>Metformin</i> (IR, SR/XR formulations)	500-3000	a. High efficacy b. Low hypo risk c. Weight neutral	Counter insulin resistance ↓ hepatic glucose output ↑ glucose uptake and cycling	Check renal function. Interrupt if using contrast media. Avoid in renal or liver impairment, or any hypoxaemic state and history of lactic acidosis. Rare risk of lactic acidosis. Glucose-independent effects to reduce CV risk.
Sulphonylureas <i>Glibenclamide</i> <i>Gliclazide</i> <i>Gliclazide MR</i> <i>Glimepiride</i> <i>Glipizide</i> <i>Tolbutamide</i>	2.5-20 40-320 30-100 1-6 2.5-20 500-3000	a. High efficacy b. Moderate hypo risk c. Weight gain	Initiate and potentiate insulin secretion (effect lasts 6-24 h depending on agent and dose)	Initial efficacy may wear-off after 6-12 months in some patients. Avoid in renal or liver impairment depending on agent. Risk of hypoglycaemia.
Meglitinides <i>Nateglinide</i> <i>Repaglinide</i>	60-540 0.5-16	a. Intermediate efficacy b. Moderate hypo risk c. Weight gain	Initiate and potentiate insulin secretion (rapid effect, typically lasts < 6 h)	Avoid in liver impairment. Take with main meals
DPP4 inhibitors <i>Alogliptin</i> <i>Linagliptin</i> <i>Saxagliptin</i> <i>Sitagliptin</i> <i>Vildagliptin</i>	6.25-25 5 2.5-5 25-100 50-100	a. Intermediate-high efficacy b. Low hypo risk c. Weight neutral	Prolong circulating half-lives of incretin hormones such as GLP-1	Discontinue if acute pancreatitis. Dose adjustment in renal impairment except linagliptin
Thiazolidinedione <i>Pioglitazone</i>	15-45	a. High efficacy b. Low hypo risk c. Weight gain	↑ insulin sensitivity mainly via activation of PPARγ	Slow onset of action, risk of oedema. Increased risk of heart failure and bone fractures. Check liver enzymes and CV risk.
SGLT2 inhibitors <i>Canagliflozin</i> <i>Dapagliflozin</i> <i>Empagliflozin</i> <i>Ertugliflozin</i>	100-300 5-10 10-25 5-15	a. Intermediate-high efficacy b. Low hypo risk c. Weight reduction	Inhibit renal SGLT2 to eliminate glucose via the urine.	Check for adequate renal function and hydration. Glucosuric effect: risk of genital and urinary infections. Can reduce blood pressure: evidence of reduced heart failure and chronic kidney disease.
Alpha-glucosidase inhibitors <i>Acarbose</i>	50-600	a. Intermediate efficacy b. Low hypo risk c. Weight neutral	Slow carbohydrate digestion by competitive inhibition of intestinal glucosidases	Avoid if gastro-intestinal disorders. Side effect of flatulence

Subcutaneous injection

GLP-1 receptor agonists

<i>Dulaglutide</i>	0.75-1.5 QW	a. High efficacy	Activate GLP-1 receptors to potentiate prandial insulin secretion, ↓ prandial glucagon secretion, delay gastric emptying and exert satiety effect	Initial nausea, titrate as appropriate. Discontinue if acute pancreatitis. Can reduce blood pressure: evidence of reduced CV risk and albuminuria.
<i>Exenatide BD</i>	5-10 ug BD	b. Low hypo risk		
<i>Exenatide QW</i>	2 QW	c. Weight reduction		
<i>Liraglutide</i>	0.6-1.8 OD			
<i>Lixisenatide</i>	10-20 ug OD			
<i>Semaglutide</i>	0.25-2 QW			
<i>Semaglutide oral</i>	3-14 mg/day			

Insulin

Ultra-rapid acting: <i>Fiasp, Lyumjev</i>	For basal sc injections usually start at 0.1 or 0.2 units/kg body weight daily (ie 10 or 20 units per day for a person weighing 100kg). Titrate up dose to achieve target glycaemic control. For MDI give ~30-50% as basal, and remainder divided between meals	a. Very high efficacy b. High hypo risk c. Weight gain	↓ hepatic glucose output ↑ peripheral glucose uptake ↑ glucose metabolism ↓ lipolysis ↑ lipogenesis ↑ protein anabolism	Select regimen consistent with patient lifestyle and needs. Glucose monitoring required. Appropriate lifestyle adjustments. High risk of hypoglycemia
Rapid-acting: <i>Aspart, Glulisine, Lispro</i>				
Short-acting: <i>Actrapid, Humulin S, Insuman Rapid</i>				
Intermediate: <i>Insulatard, Humulin I</i>				
Long-acting: <i>Degludec, Detemir, Glargine</i>				
Biphasic (pre-mixed): <i>Humalog, Humulin M3, Novomix</i>				

Continued on following page



20.22 How to review a patient in the diabetes clinic

Lifestyle issues

- General health
- Work or school
- Smoking
- Alcohol intake
- Stress or depression
- Sexual health
- Exercise

Body weight and BMI

Blood pressure

- Individualised target of 130–140/70–80 mmHg, depending on risk factors and presence of nephropathy

Urinalysis

- Analyse fasting specimen for glucose, ketones, albumin (both macro- and micro-albuminuria)

Biochemistry

- Renal, liver and thyroid function
- Lipid profile and estimated 10-year cardiovascular risk to guide need for lipid-lowering therapy (p. 487)

Glycaemic control

- Glycated haemoglobin (HbA_{1c}); individualised target between 48 and 58 mmol/mol
- Inspection of home blood glucose monitoring record (if carried out by patient)

Hypoglycaemic episodes

- Number and cause of severe (requiring assistance for treatment) events and frequency of mild (self-treated) episodes and biochemical hypoglycaemia
- Awareness of hypoglycaemia
- Driving advice

Assessment of injection sites if insulin-treated

Eye examination

- Visual acuities (near and distance)
- Ophthalmoscopy (with pupils dilated) or digital photography

Examination of lower limbs and feet

- Assessment of foot risk (p. 721)

i

20.23 Dietary management of diabetes

Aims of dietary management

- Achieve good glycaemic control
- Reduce hyperglycaemia and avoid hypoglycaemia
- Assist with weight management:
 - Weight maintenance for type 1 diabetes and non-obese type 2 diabetes
 - Weight loss for overweight and obese type 2 diabetes
- Reduce the risk of micro- and macrovascular complications
- Ensure adequate nutritional intake
- Avoid 'atherogenic' diets or those that aggravate complications, e.g. high protein intake in nephropathy

Dietary constituents and recommended % of energy intake

- Carbohydrate: 50%:
 - Sucrose: up to 10%
- Fat (total): <35%:
 - n-6 Polyunsaturated: <10%
 - n-3 Polyunsaturated: eat 1 portion (140 g) oily fish once or twice weekly
 - Monounsaturated: 10–20%
 - Saturated: <10%
- Protein: 10–15% (do not exceed 1 g/kg body weight/day)
- Fruit/vegetables: 5 portions daily

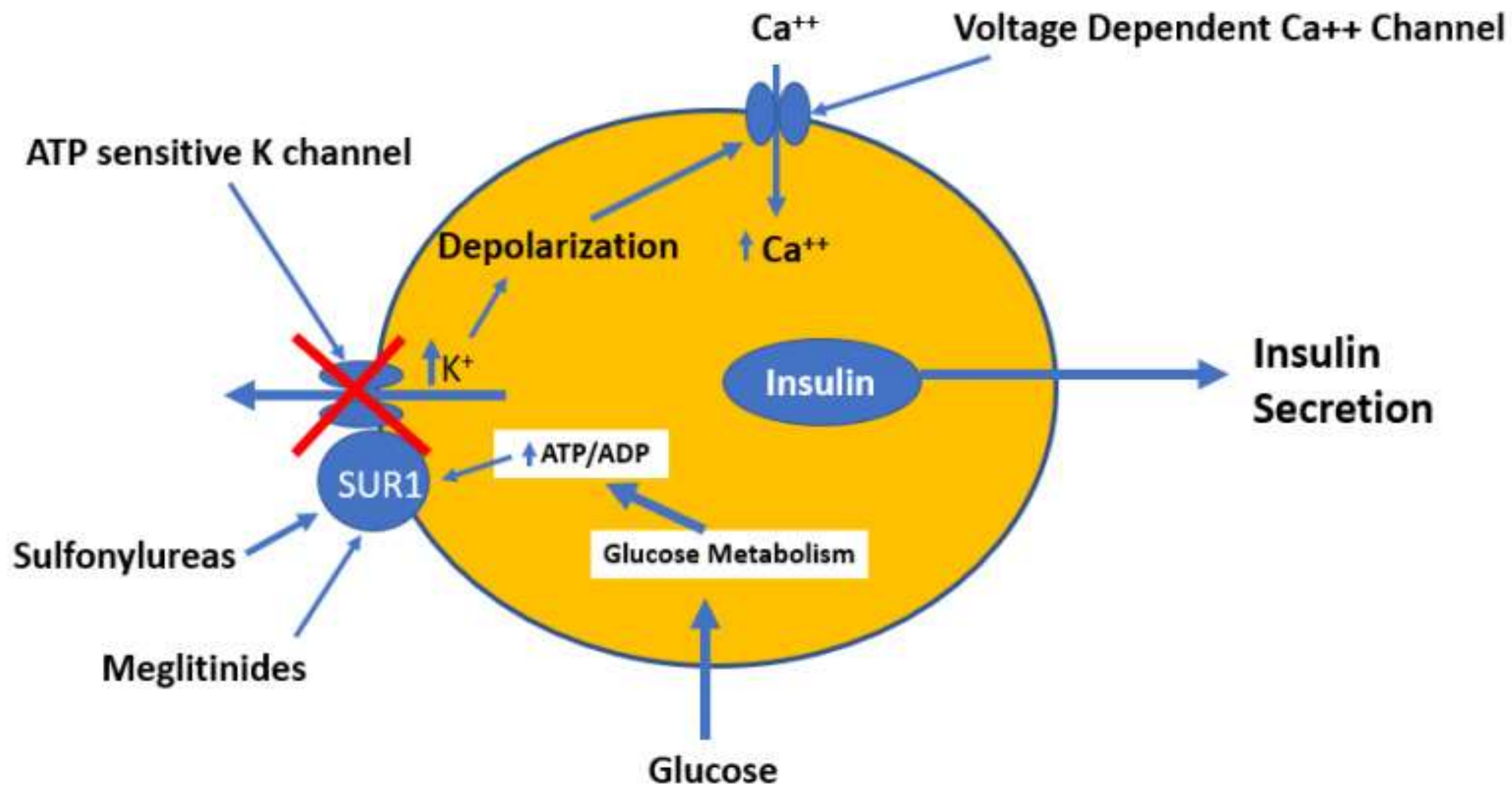


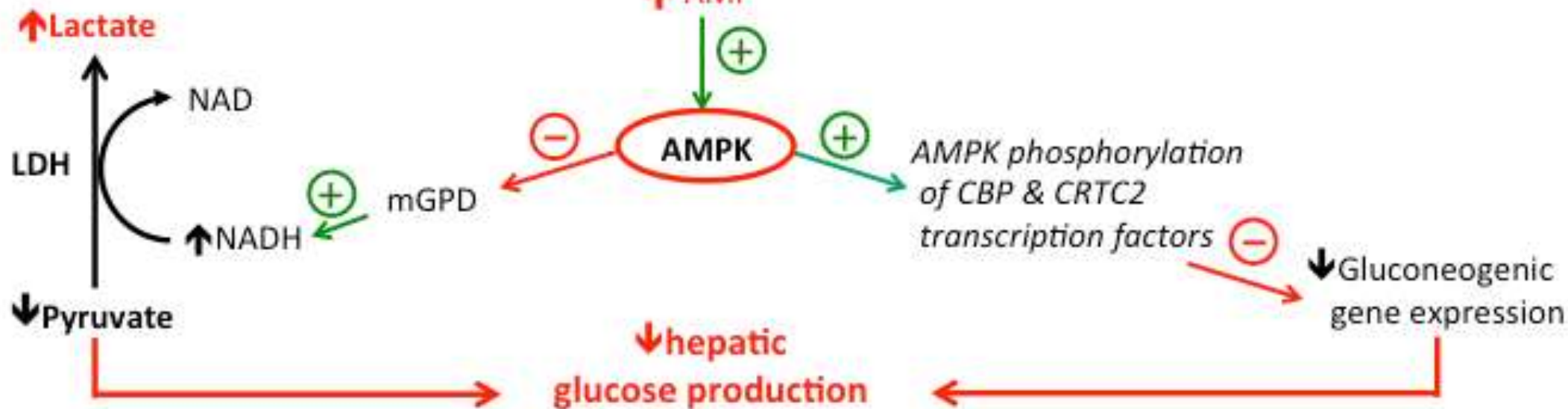
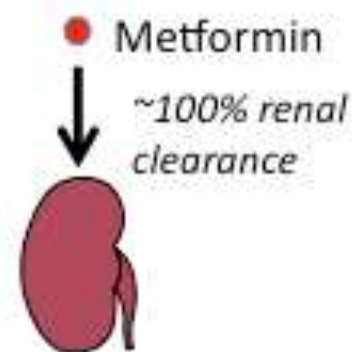
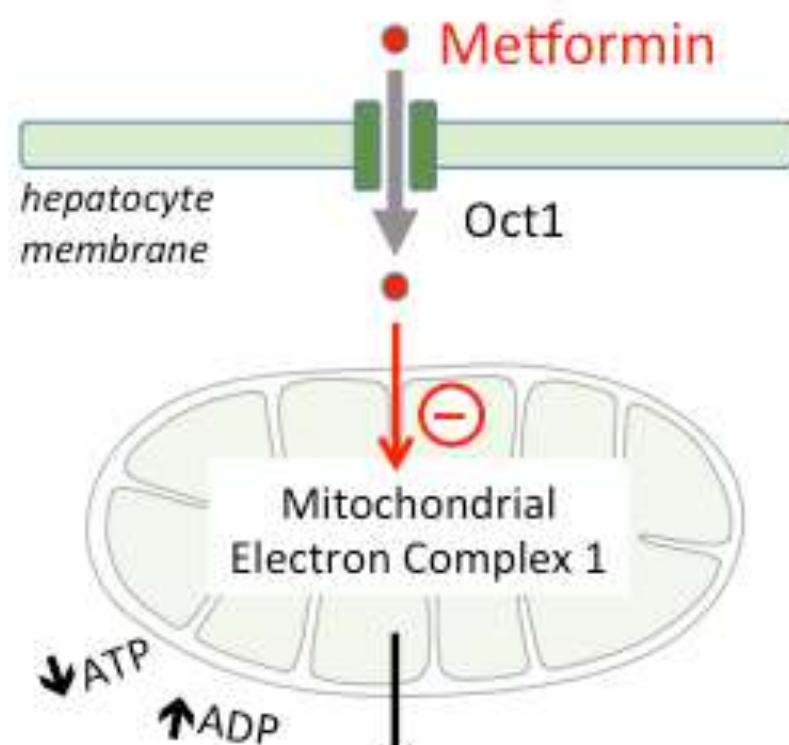
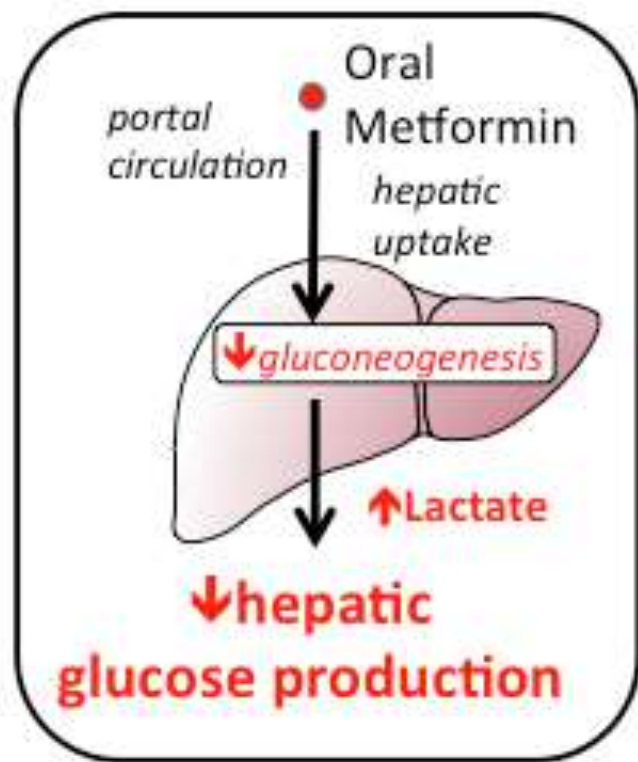
20.26 Effects of drugs used in the treatment of type 2 diabetes

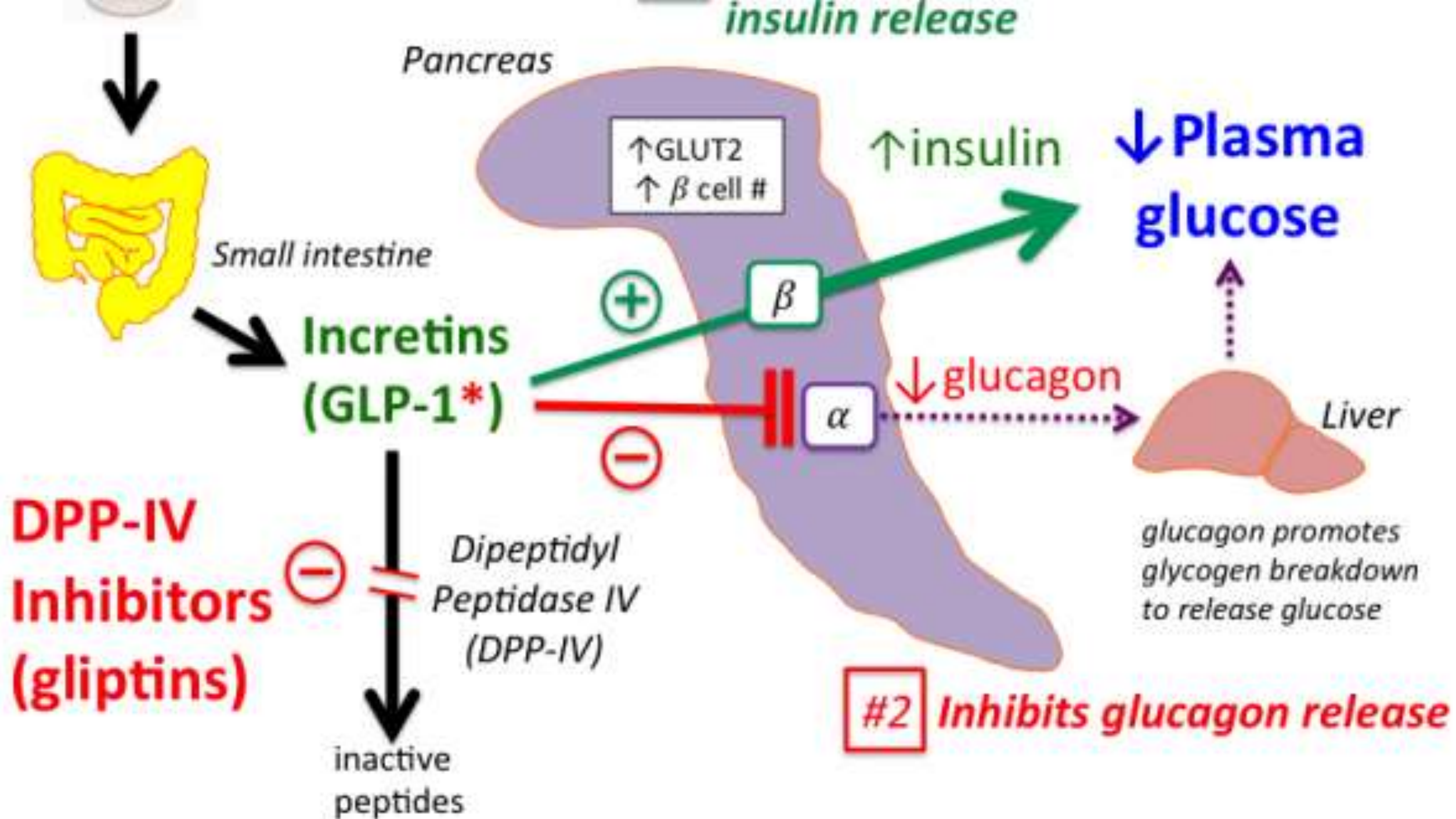
	Insulin	Sulphonylureas and meglitinides	Metformin	Alpha- glucosidase inhibitors	Thiazolidinediones (glitazones)	DPP-4 inhibitors (gliptins)	GLP-1 receptor agonists	SGLT2 inhibitors
Fasting blood glucose	↓	↓	↓	↘	↓	↓	↓	↓
Post-prandial blood glucose	↓	↓	↓	↓	↓	↓	↓	↓
Plasma insulin	↑	↑	↓	↓	↓	↑	↑	↓
Body weight	↑	↑	→	→	↑	→	↓	↓
Cardiovascular benefit?	No	No	Possible	No	Probable (pioglitazone)	No	Yes	Yes
Risk of hypoglycaemia	++	+	–	–	–	–	–	–
Tolerability	Good	Good	Moderate	Moderate	Moderate	Good	Moderate	Limited experience

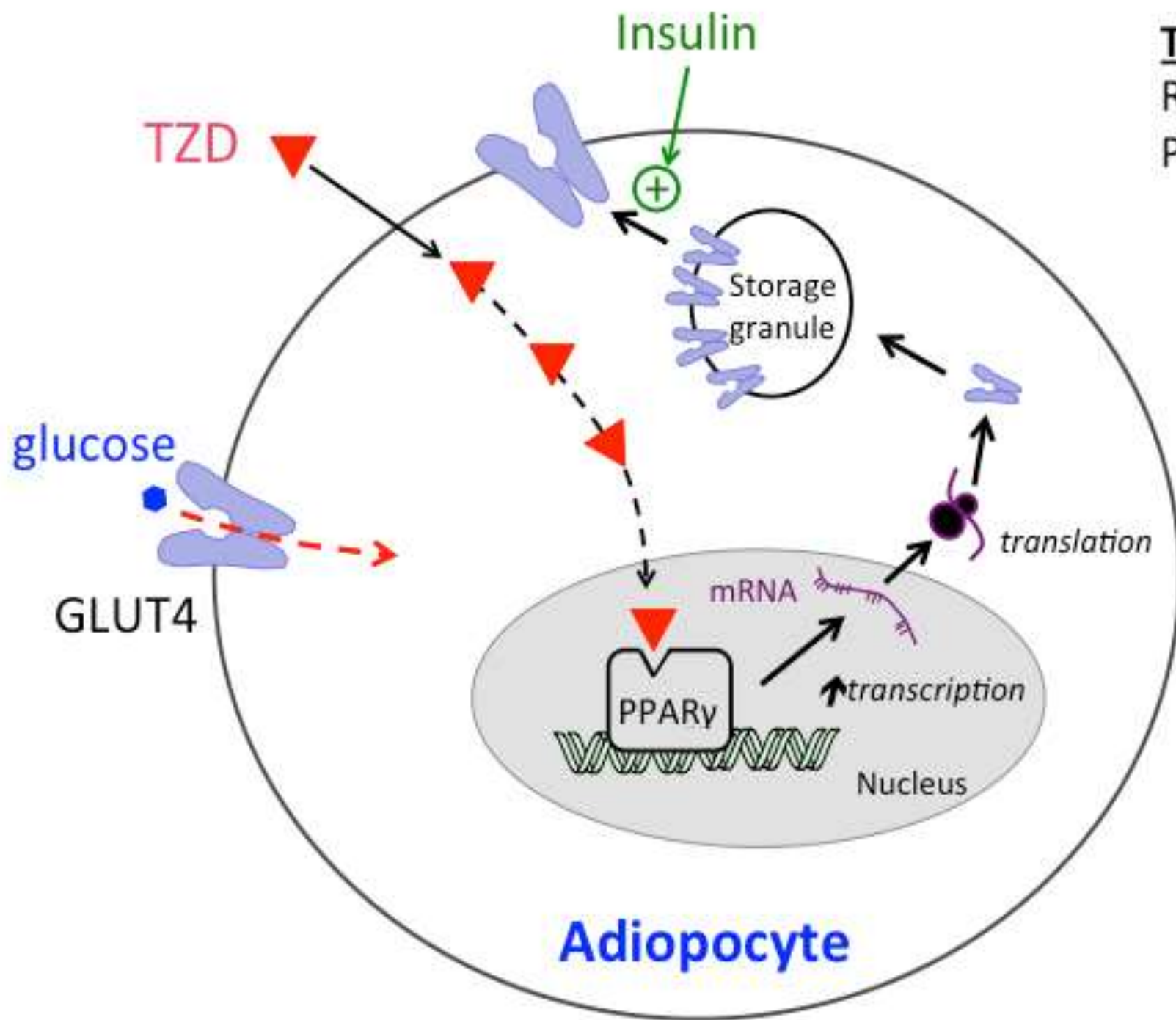
(↘ = small reduction; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; SGLT2 = sodium and glucose transporter 2)

		Efficacy¹	Hypoglycemia	Weight change²	CV effects		Renal effects		Oral/SQ	Cost	Clinical considerations
					Effect on MACE	HF	Progression of DKD	Dosing/use considerations*			
Metformin		High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min per 1.73 m²	Oral	Low	• GI side effects common; to mitigate GI side effects, consider slow dose titration, extended release formulations, and administration with food • Potential for vitamin B12 deficiency; monitor at regular intervals
SGLT2 inhibitors		Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	Oral	High	• DKA risk, rare in T2DM: discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic DKA); discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting to mitigate potential risk • Increased risk of genital mycotic infections • Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports: institute prompt treatment if suspected • Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable
GLP-1 RAs		High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ)	Neutral	Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	• See labels for renal dose considerations of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ; oral (semaglutide)	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
					Neutral: exenatide once weekly, lixisenatide						
GIP and GLP-1 RA		Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See label for renal dose considerations • No dose adjustment • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
DPP-4 inhibitors		Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	Oral	High	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Joint pain • Bullous pemphigoid (postmarketing): discontinue if suspected
Thiazolidinediones		High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	Oral	Low	• Congestive HF (pioglitazone, rosiglitazone) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Weight gain: consider lower doses to mitigate weight gain and edema
Sulfonylureas (2nd generation)		High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in chronic kidney disease • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	Oral	Low	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text) • Use with caution in persons at risk for hypoglycemia
Insulin	Human	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	SQ; inhaled	Low (SQ)	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
	Analog								SQ	High	









Thiazolidinediones (TZDs):

Rosiglitazone - PPAR γ

Pioglitazone - PPAR γ > PPAR α

PPAR γ expression:

Adipose tissue

Skeletal muscle ($\uparrow$ in obesity)

Pancreatic β cells

Vascular endothelium

Macrophages

CNS

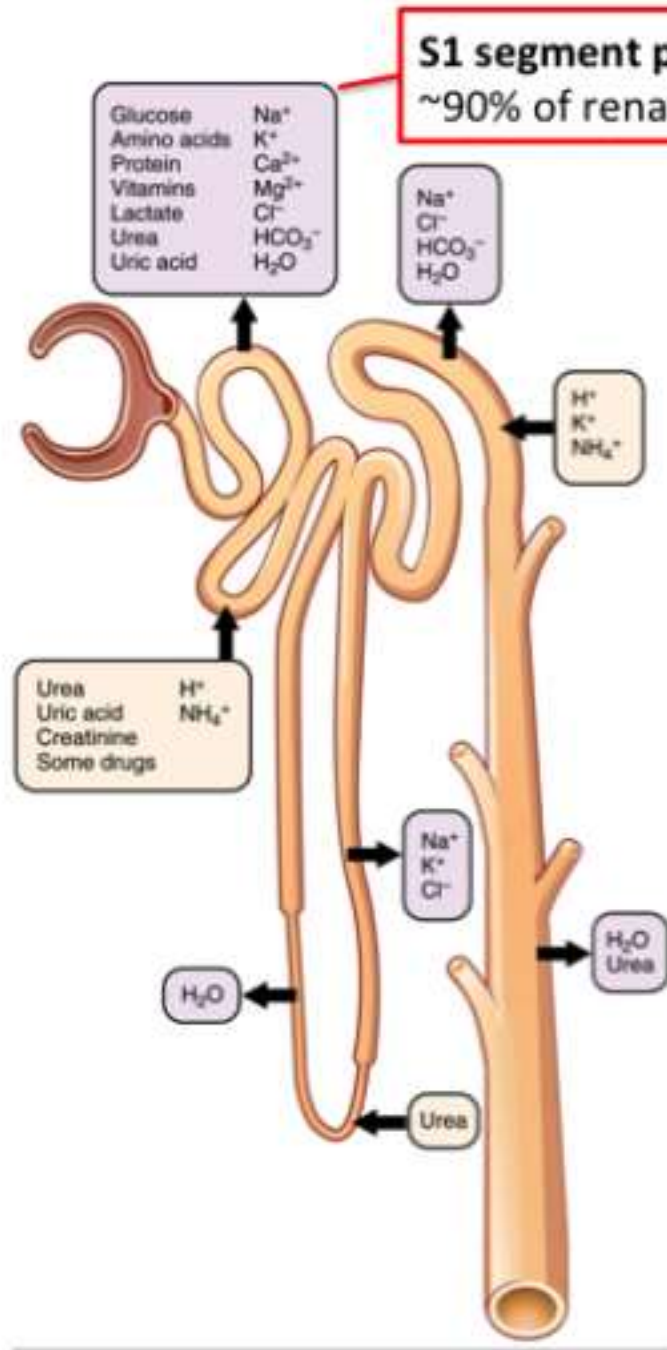
PPAR α expression:

Liver

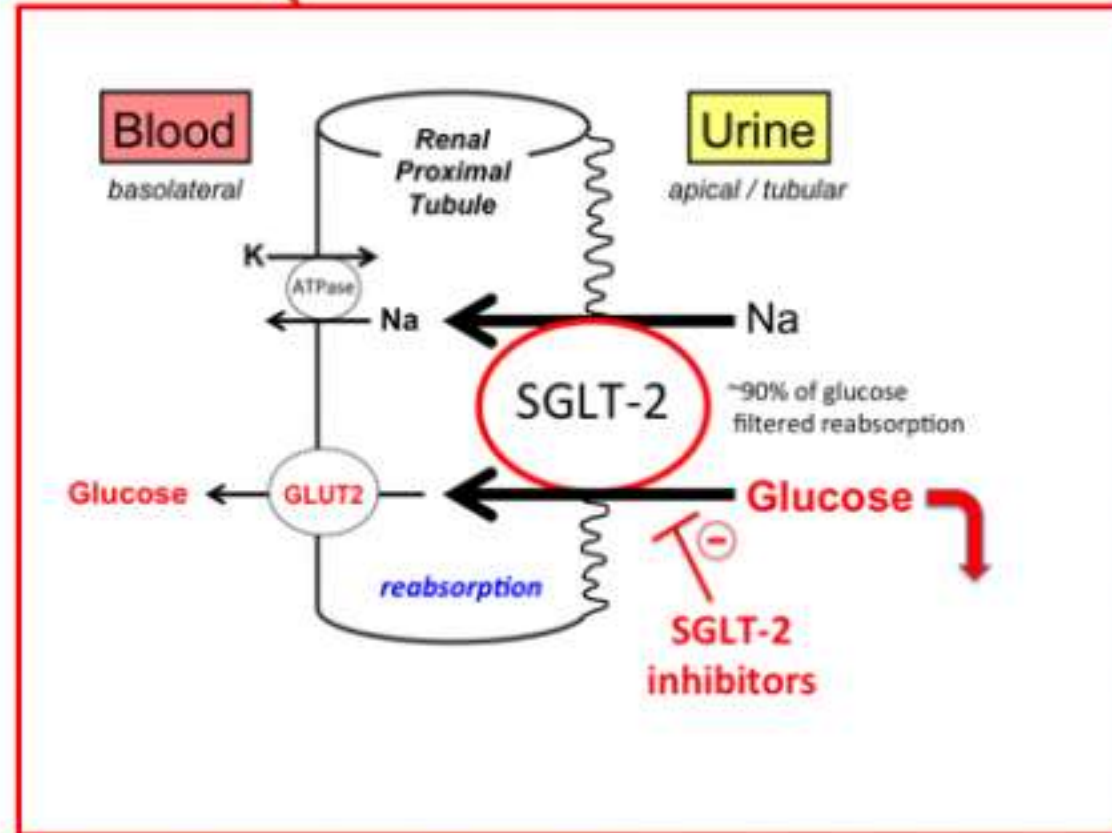
Heart

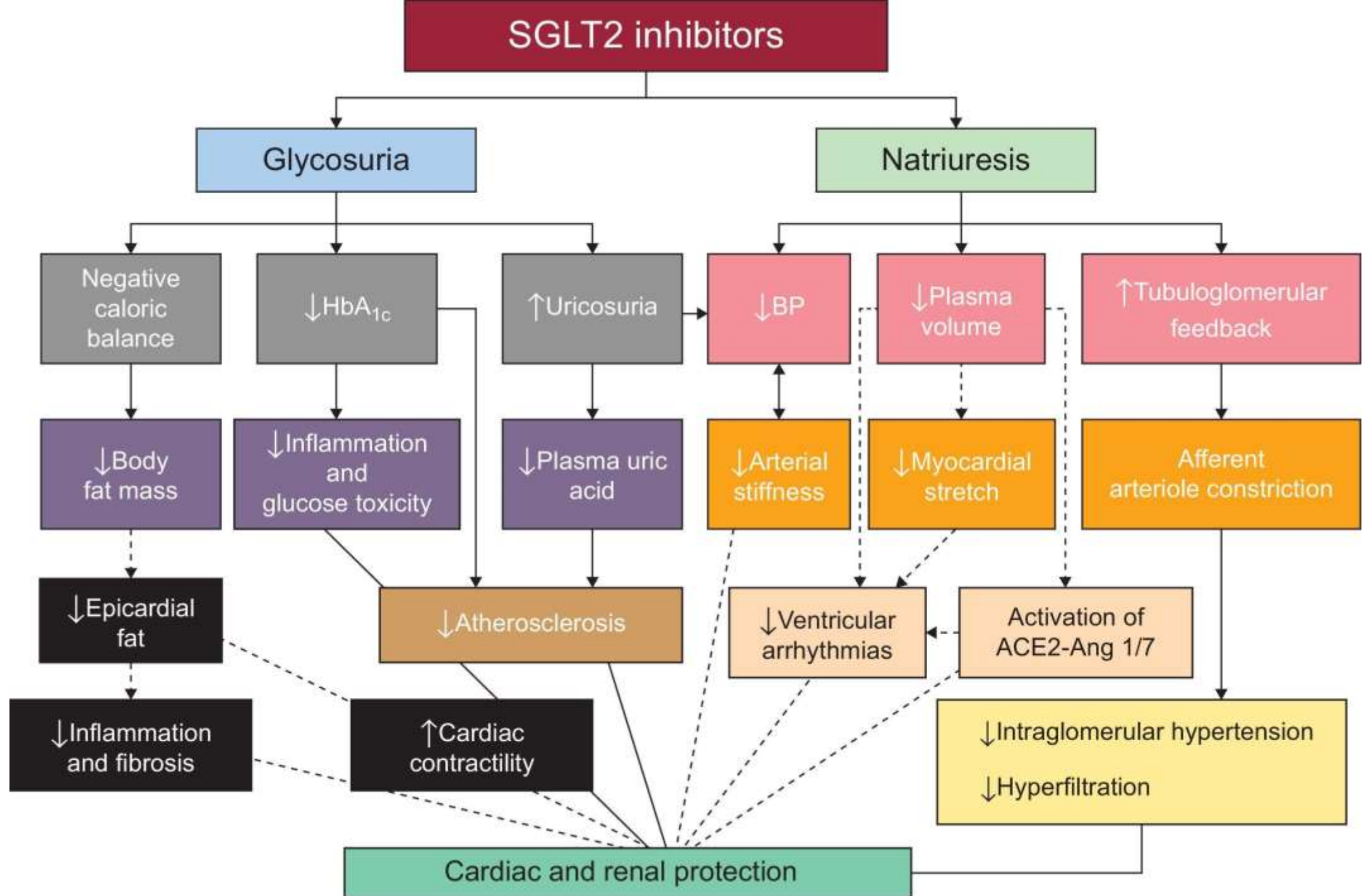
Skeletal muscle

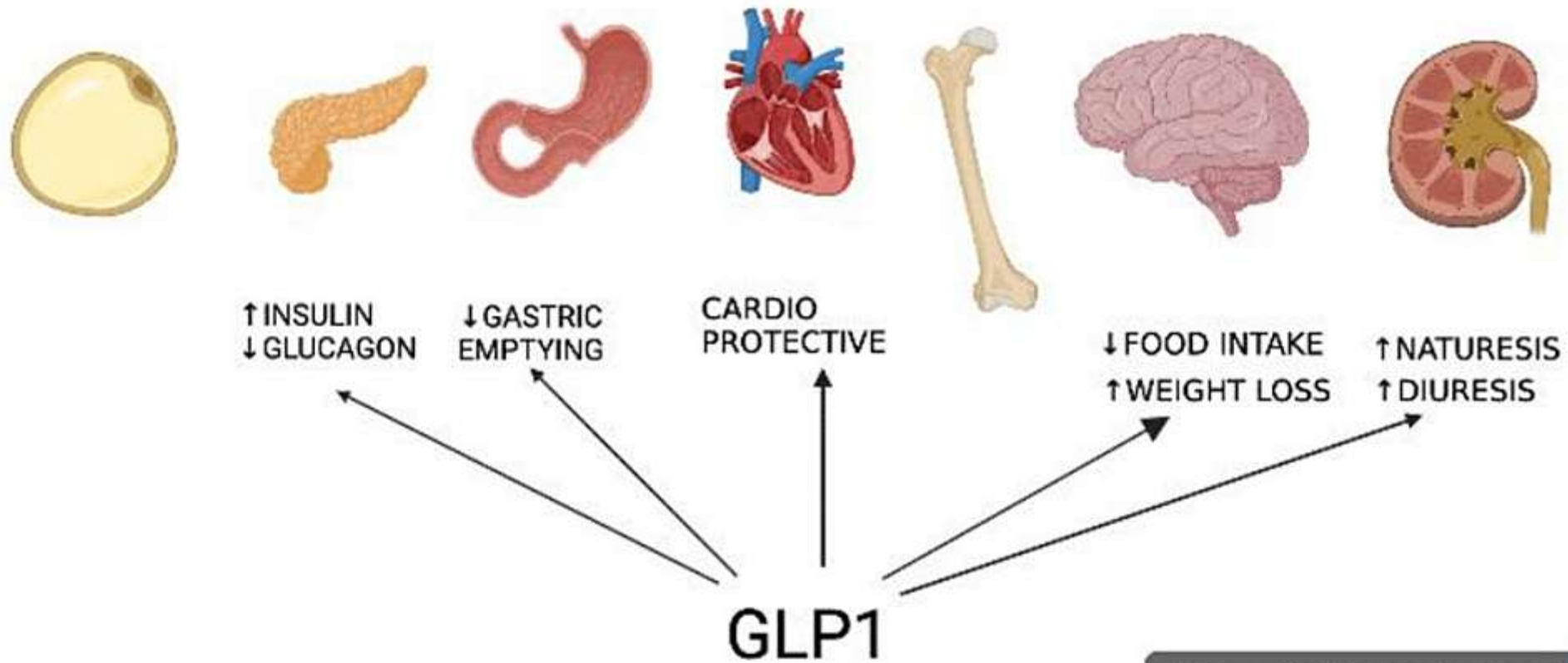
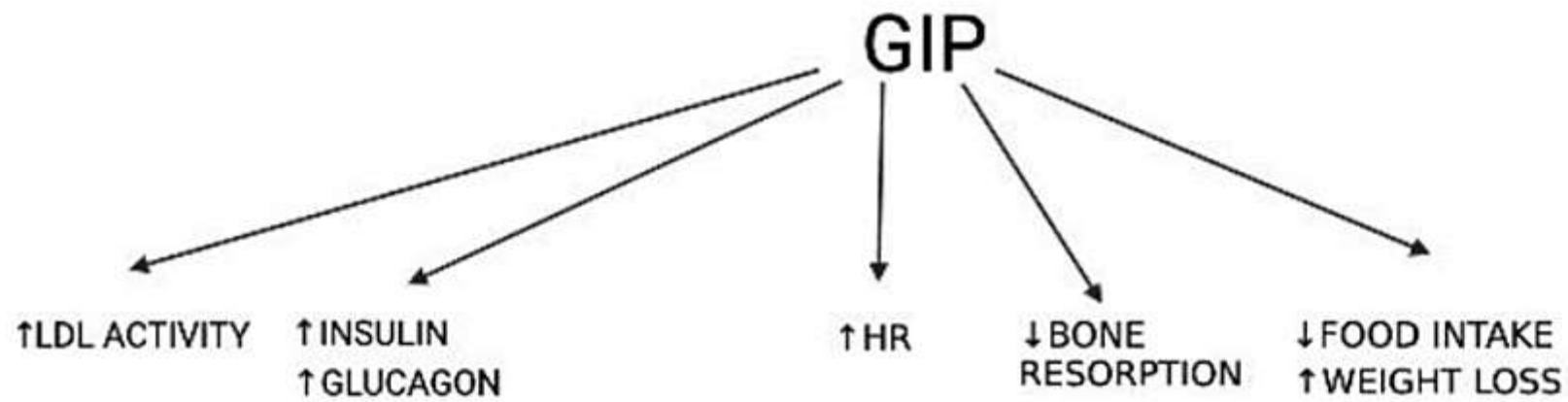
Vascular wall

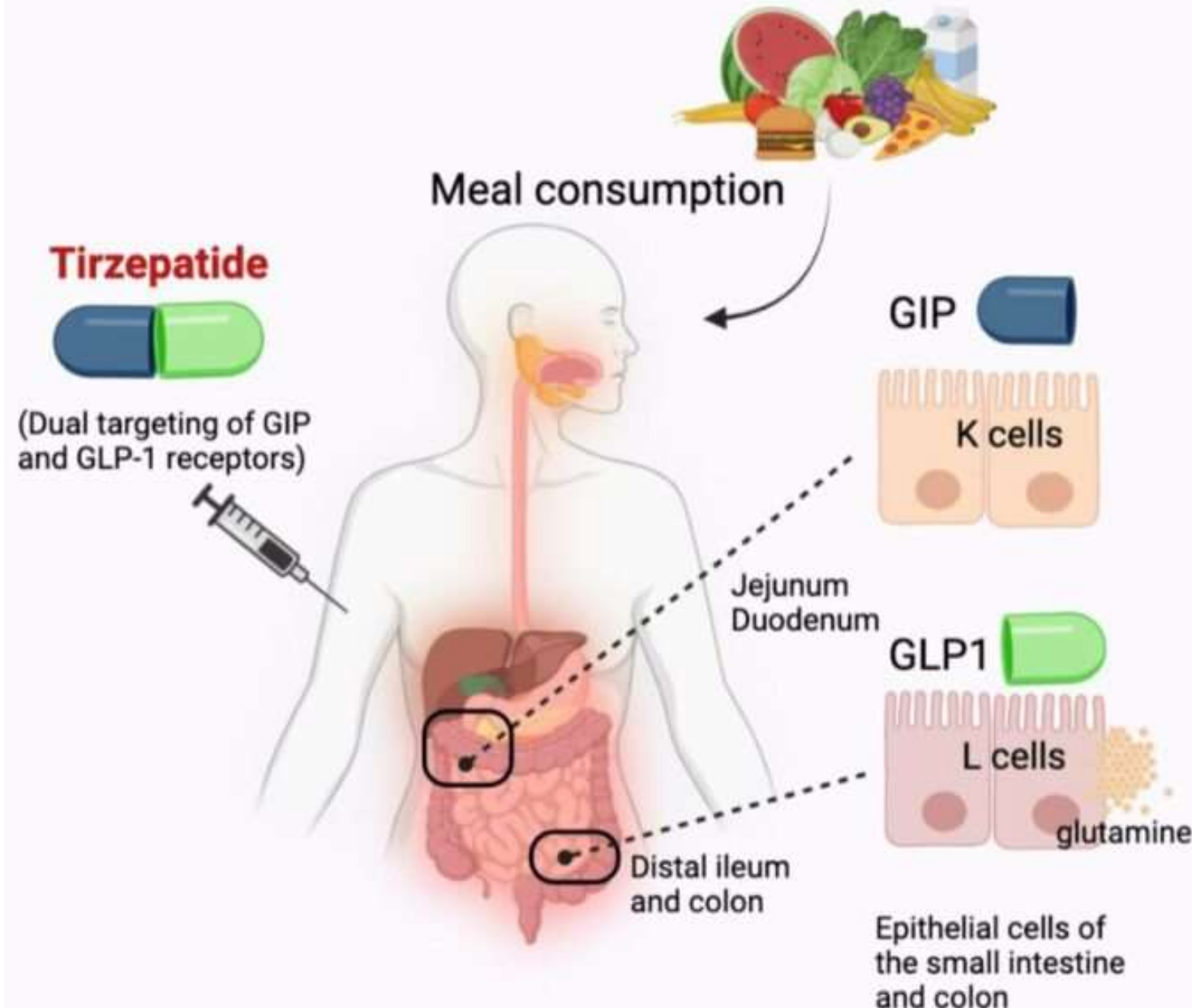


S1 segment proximal tubule:
~90% of renal glucose reabsorption









Tirzepatide actions

Decrease appetite
Decreases food consumption
Increases production of insulin
Increases beta-cell survival

increases lipolysis (GLP-1)
Increases cardio-protection (GLP-1)
Increases lipogenesis (GIP)
Reduces bone reabsorption

Type-2 diabetes management
Weight loss



Insulin

- Mainstay of treatment for type 1 diabetes
- Might be used for type 2 diabetes; initially or later on
- First extracted from the pancreas of a dog in 1921
- Porcine and bovine insulins
- Human insulins
- Insulin analogues



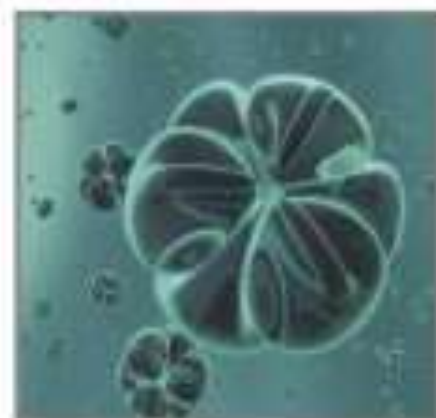
Isolation of insulin.
Banting & Macleod



Hagedorn
protamine-
retarded
insulin NPH



Recombinant
human insulin



Basal insulin analogues

Time

1922

1923

1946

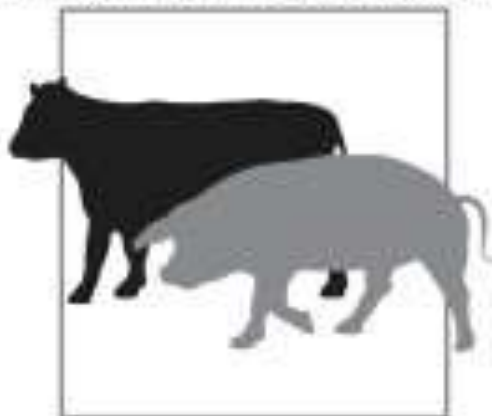
1950s

1977

1990s

2000s

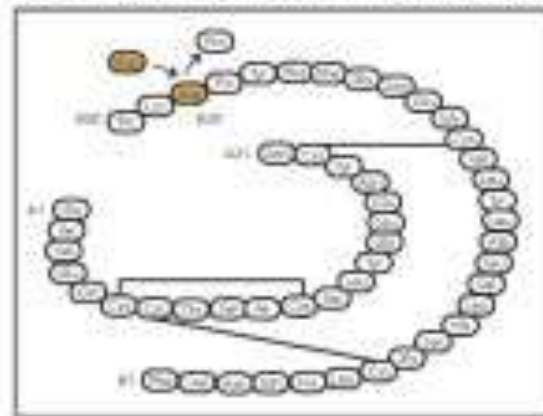
Animal insulin preparations



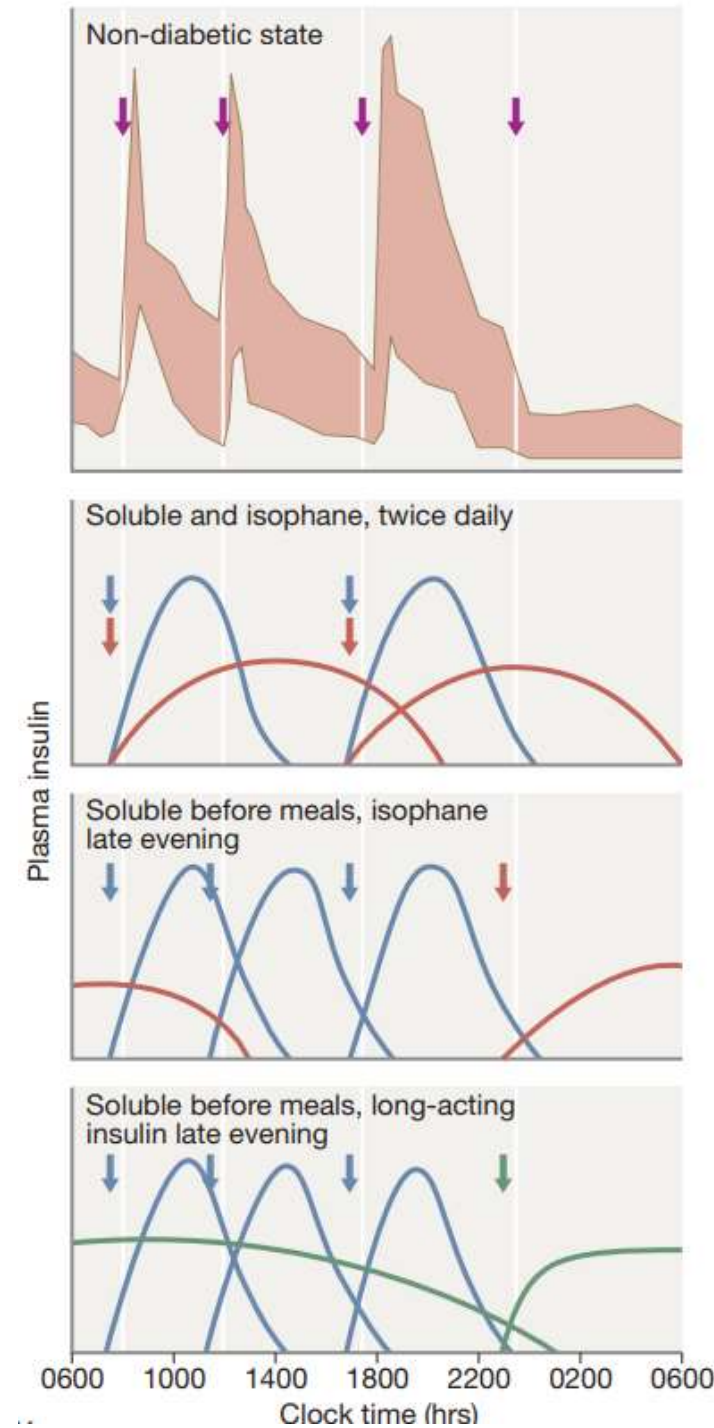
Lente[®] insulin series



Rapid-acting insulin analogues



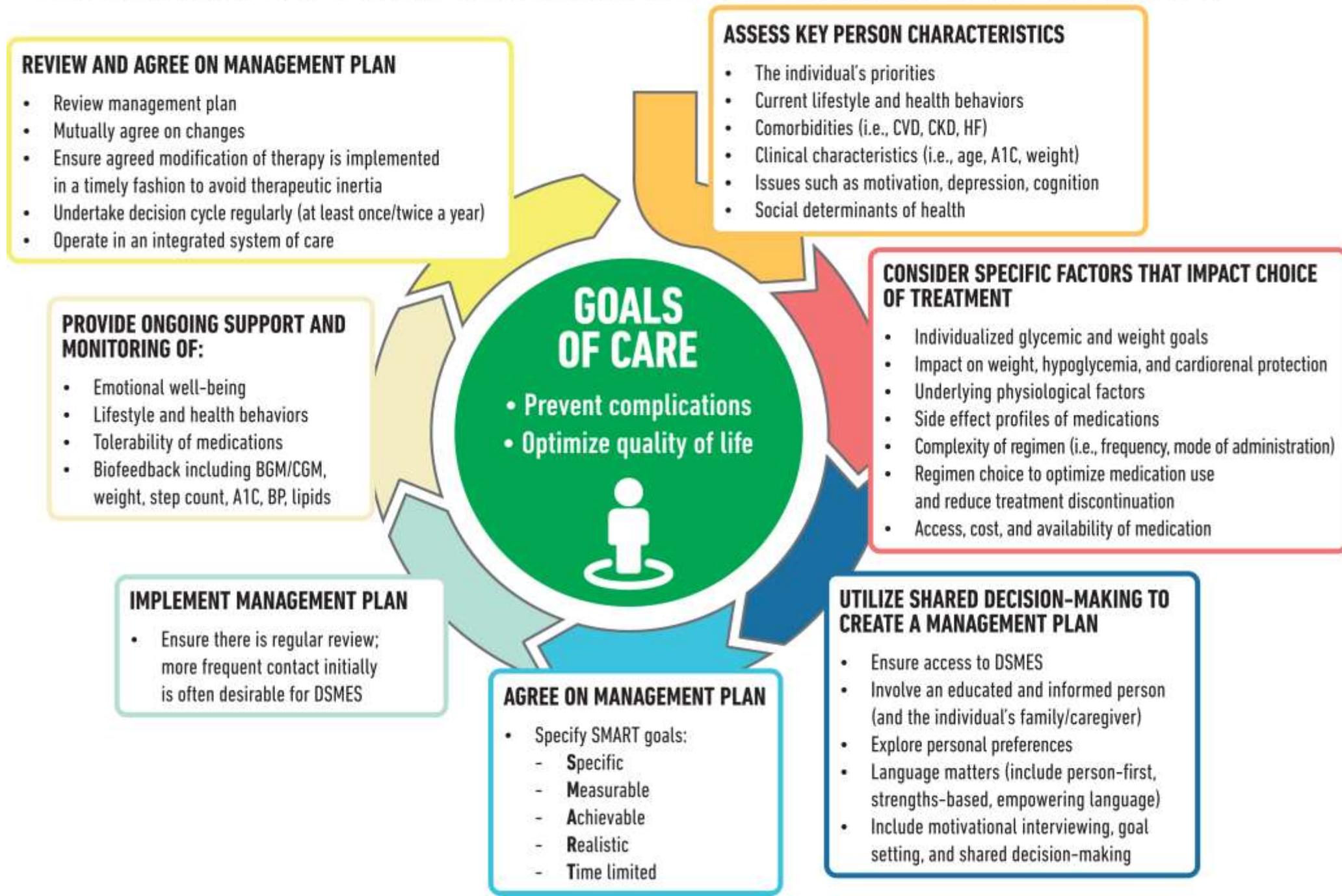
i 20.27 Duration of action (in hours) of insulin preparations			
Insulin	Onset	Peak	Duration
Rapid-acting (insulin analogues: lispro, aspart, glulisine)	<0.5	0.5–2.5	3–4.5
Short-acting (soluble (regular))	0.5–1	1–4	4–8
Intermediate-acting (isophane (NPH), lente)	1–3	3–8	7–14
Long-acting (bovine ultralente)	2–4	6–12	12–30
Long-acting (insulin analogues: glargine, detemir, degludec)	1–2	None	18–26



Insulin regimens

- Type 2 diabetes:
 1. Basal insulin
 2. Pre-mixed insulin
 3. Basal bolus insulin
- Type 1 diabetes
 1. Basal bolus insulin
 2. Subcutaneous insulin infusion pumps

DECISION CYCLE FOR PERSON-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES



PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS

	MET	GLP-1 RA	DUAL GIP/ GLP-1 RA	SGLT2i	TZD	INSULIN (basal & basal bolus)	DPP-4i	SU	GLN	AGi	COLSVL	BRC	PRAML
EFFICACY FOR GLUCOSE LOWERING	++	+++	+++	++	++	+++/++++	+	++	+	+	+	+	+
ASCVD	MACE	Benefit ^{1,3}	Safe	Benefit ²	Neutral ³	Neutral	Neutral	Possible Increased Risk	Neutral	Insufficient Evidence	Neutral ³	Safe	Insufficient Evidence
	CHF	Unclear		Reduced Risk	Moderate to Severe ⁴	Moderate	Moderate ⁴						
	STROKE	Benefit ⁵		Possible Benefit ²	Benefit	Neutral	Neutral						
CKD	CKD3a/3b ⁶	Benefit ⁷	Insufficient Evidence	Benefit	Neutral	Increased hypoglycemia risk with impaired renal function	Neutral	Increased hypoglycemia risk with impaired renal function	Not recommended SCR >2 mg/dL or CrCl <25	Neutral	Neutral	Neutral	Neutral
RENAL ADJUSTMENT	Not with CKD4 eGFR <30 ⁶	Exenatide not recommended eGFR <45		Check medication- specific eGFR thresholds ⁸			Adjust Dose ⁹						
HYPOGLYCEMIA RISK ¹⁴	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate to Severe	Neutral	Moderate to Severe	Mild	Neutral	Neutral	Neutral	Neutral
WEIGHT	Slight loss	Loss	Loss	Loss	Gain ⁴	Gain	Neutral	Gain	Neutral	Neutral	Neutral	Neutral	Loss
NAFLD	Neutral	Benefit	Benefit	Potential Benefit	Benefit	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Benefit
GI ADVERSE SYMPTOMS	Mild to Moderate	Moderate ¹⁰	Moderate ¹⁰	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Mild	Moderate	Moderate
OTHER CONSIDERATIONS		Medullary Thyroid Carcinoma/ MEN2	Medullary Thyroid Carcinoma/ MEN2	GU infections DKA ¹¹ Fracture Risk ¹²	Fracture Risk		Rare Arthralgias/ Myalgias						
ACCESS/COST	\$	\$\$\$	\$\$\$	\$\$\$	\$	\$ - \$\$\$ ¹³	\$-\$	\$	\$-\$	\$-\$	\$\$\$	\$\$\$	\$\$\$

■ Possible benefits
 ■ Use with caution
 ■ Likelihood of adverse events
 ■ Neutral, not studied, insufficient evidence

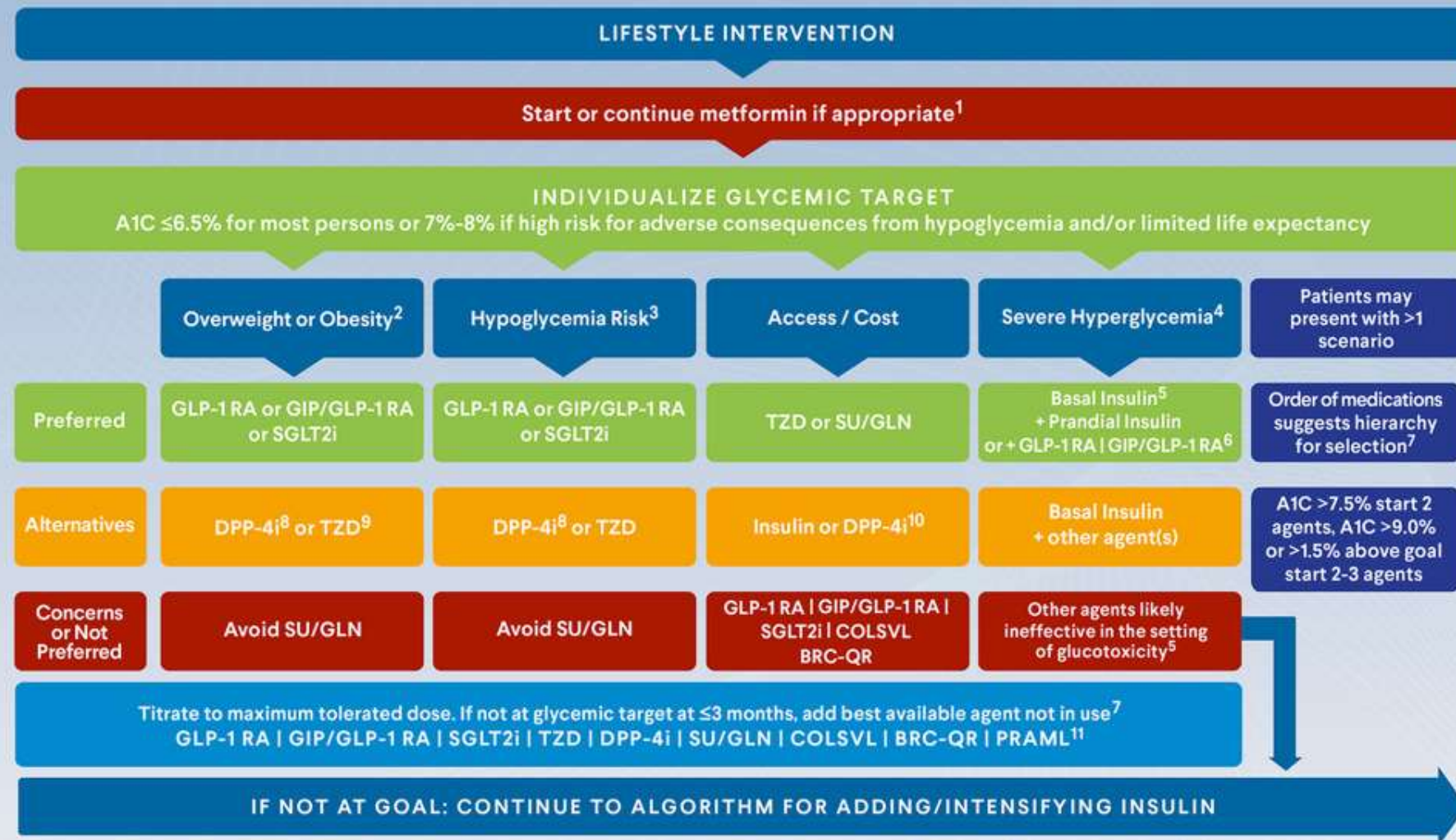
¹GLP-1 RA MACE benefits with liraglutide, semaglutide, dulaglutide. ²SGLT2i MACE benefits with empagliflozin, canagliflozin. Possible benefit for hemorrhagic stroke. ³GLP-1 RA, TZD, COLSVL can lower LDL. ⁴TZDs increase fluid retention and edema and are contraindicated in persons with NYHA Class III/IV CHF. There is increased risk of hospitalization for CHF with saxagliptin, and limited experience for persons with NYHA Class II/IV CHF with alogliptin. ⁵GLP-1 RA stroke benefits observed with semaglutide and dulaglutide. ⁶CKD3a no adjustment with monitoring, CKD3b decrease dose and do not initiate, CKD4 contraindicated. Hold for acute kidney injury, IV contrast. ⁷Dulaglutide, semaglutide decrease CKD progression. ⁸The eGFR thresholds for initiation and/or continuation of therapy in CKD vary among SGLT2i. Check medication-specific eGFR levels. ⁹Only linagliptin does not require adjustment. ¹⁰Slow titration, portion control, and consider reducing to prior tolerated dose. ¹¹Precipitants include significant current illness, surgery, inappropriate or rapid insulin dose reduction. ¹²Reported with canagliflozin, dapagliflozin. ¹³Cost varies widely with devices (e.g., pens), formulations (e.g., analogues), and combinations (e.g., 70/30). ¹⁴Single-agent risks of hypoglycemia may be low but increases when combined with other agents.

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Algorithm Figure 9-Antihyperglycemic Medications



GLUCOSE-CENTRIC ALGORITHM FOR GLYCEMIC CONTROL

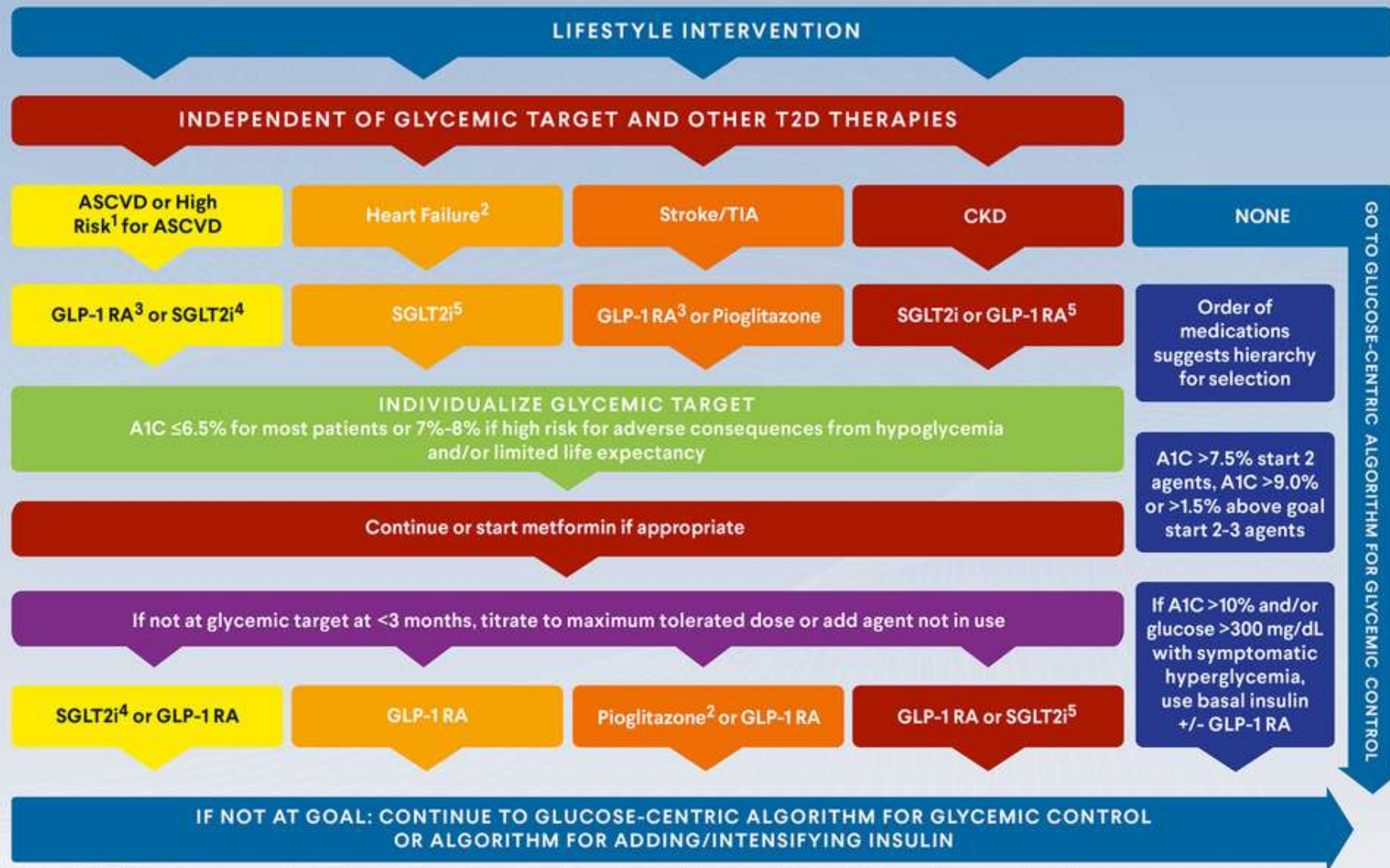


¹Take with food with dose titration for enhanced tolerance. ²See also COMPLICATIONS-CENTRIC MODEL FOR THE CARE OF PERSONS WITH OVERWEIGHT/OBESITY and PROFILES OF WEIGHT-LOSS MEDICATIONS table. ³Evaluate for issues leading to hypoglycemia or hypoglycemia unawareness and manage with patient-centered strategies. ⁴If A1C >10% and/or BG ≥300 with symptomatic hyperglycemia, reduce glucose/A1C as promptly and safely as possible. ⁵See also ALGORITHM FOR ADDING/INTENSIFYING INSULIN. ⁶GLP-1 RA requires titration phase which can delay glycemic control. After glucose toxicity is resolved, consider adding other agents. ⁷See also PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS table. ⁸GLP-1 RA and DPP-4i should not be combined. ⁹TZD can cause fluid retention but have benefit for NAFLD, CVD prevention, dyslipidemia. ¹⁰Access/Cost are dependent on location of the market. Insulin costs vary widely with devices (e.g., pens versus vials) and formulations (e.g., analogues versus combinations such as 70/30). ¹¹PRAML is used as an adjunct with prandial insulin.

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Algorithm Figure 7-Glucose-Centric Glycemic Control

COMPLICATIONS-CENTRIC ALGORITHM FOR GLYCEMIC CONTROL

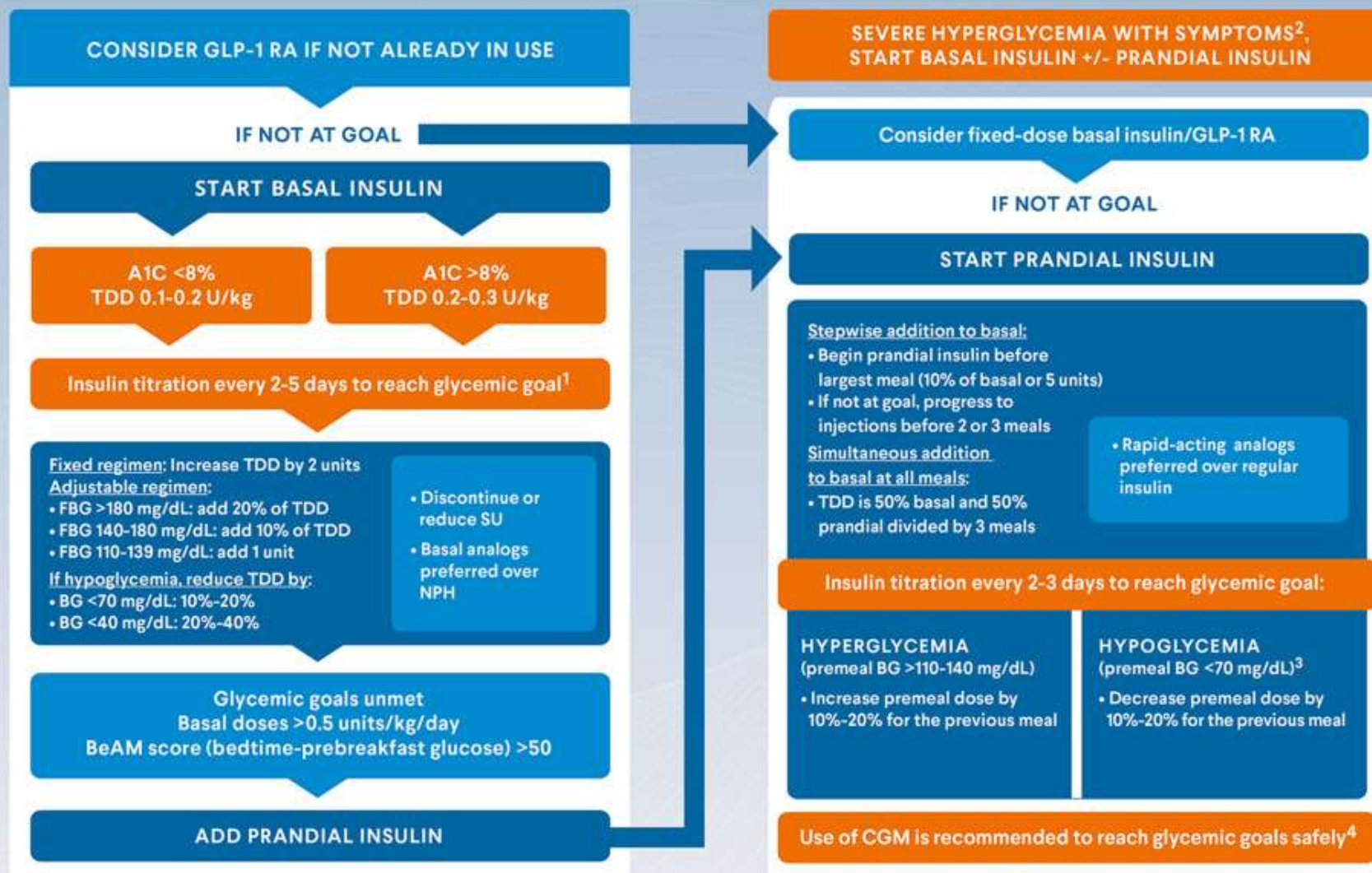


¹High risk for ASCVD: albuminuria or proteinuria, hypertension and left ventricular (LV) hypertrophy, LV systolic or diastolic dysfunction, ankle-brachial index <0.9.

²TZDs are contraindicated in NYHA Class III/IV HF. ³ASCVD: liraglutide/semaglutide/dulaglutide or Stroke: semaglutide/dulaglutide.

⁴canagliflozin/empagliflozin. ⁵Use SGLT2i or GLP-1 RA with proven benefit.

ALGORITHM FOR ADDING/INTENSIFYING INSULIN



¹Glycemic goals: A1C ≤6.5%-7% without hypoglycemia, fasting and premeal glucose <110 mg/dL, A1C should be individualized in people with comorbidities and at high adverse consequences of hypoglycemia and/or limited life expectancy. Longer-acting basal insulins (e.g., glargine U300, degludec U100 or U200) require slower titration ≥3 days because of a longer time to steady state. ²For symptomatic hyperglycemia with A1C >10% and/or BG ≥300 mg/dL, reduce glucose/A1C as promptly and safely as possible. Consider testing for autoimmune diabetes. GLP-1 RA requires titration phase which can delay glycemic control. ³Oral administration of rapidly absorbed source of glucose (tablet, fruit juice) if person can safely swallow. If unresponsive or unable to swallow, subcutaneous/intramuscular/intranasal glucagon or glucagon analogue can be given by a trained member of the household. ⁴See also American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons with Diabetes Mellitus.

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Algorithm Figure 8-Adding/Intensifying Insulin

Diabetes technologies

- CGM (continuous glucose monitoring):
 1. isCGM (flash glucose monitoring)
 2. rtCGM (continuous glucose monitoring)
- CSII (continuous subcutaneous insulin infusion)
 1. Tethered pumps vs patch pumps
 2. Open-loop vs closed-loop pumps



1920s



1960s

Intravenous glucose control:
Albisser et al, 1974;
Mirouze, Selam et al, 1977.
Pfeiffer et al, 1974

1970s

Understanding the Metabolic Network:
The Minimal Model of
Glucose Kinetics.
Bergman & Cobelli,
1979

1980s

The Incretin Effect:
GIP, GLP-1 and DPP-4
Nauck et al, 1986.

1990s

Subcutaneous Continuous
Glucose Monitoring
Minimed CGMS, 1999



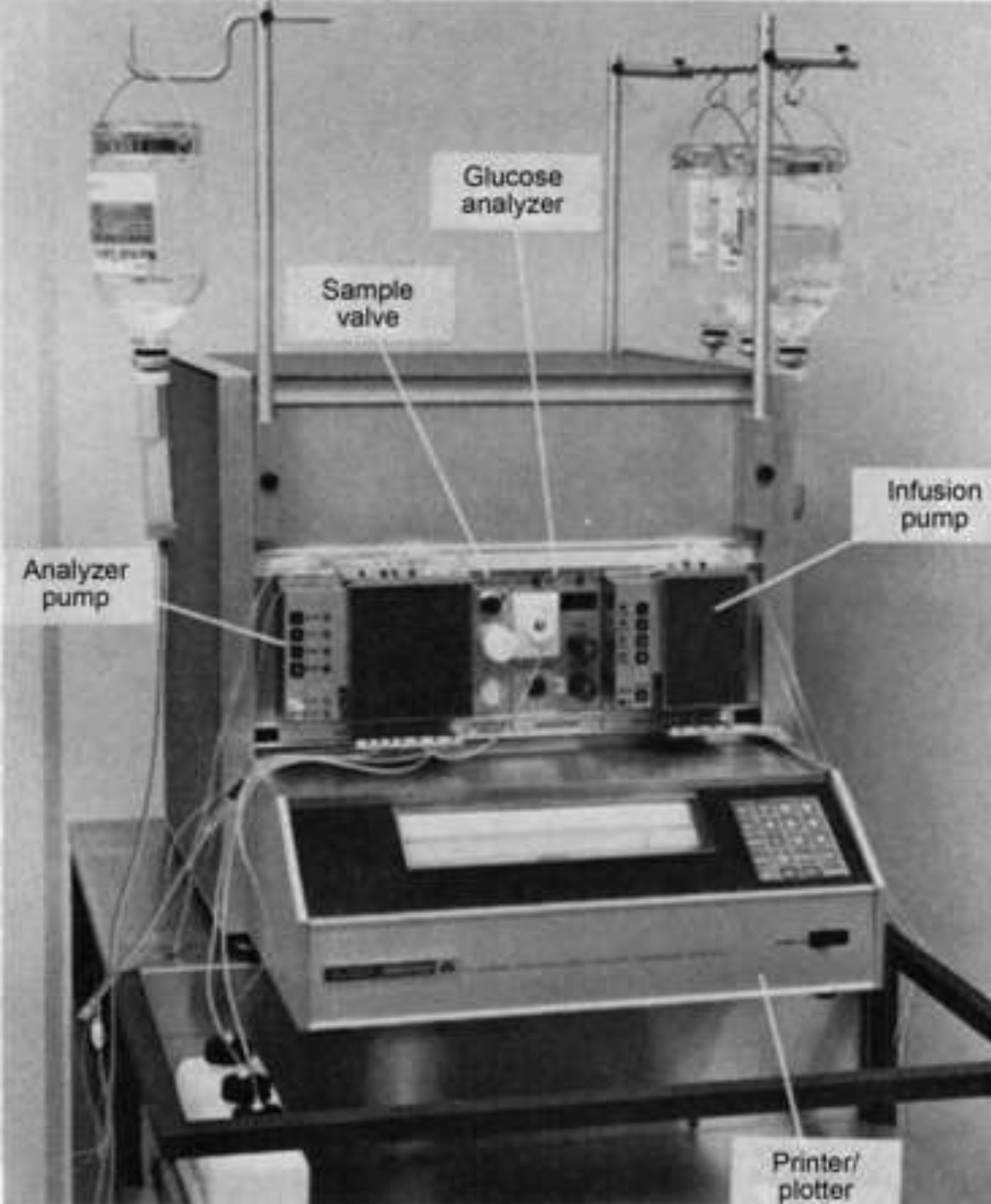
2000s



**First use of s.c.
insulin pump**
Tamborlane et al,
1979
Pickup et al. 1978.

**Quantifying
Diabetes:**
Glucose variability
and Risk Analysis.
Kovatchev et al.
1997





MILESTONES IN PUMP HISTORY



The prototype of the first pump that delivered glucagon as well as insulin, backpack style, was made in the early '60s.

In the late 70s and early 80's Dean Kamen's company, DEKA, developed a new system for outpatient care called AutoSyringe.

t:slim is the first insulin pump to use a touchscreen interface.







Sensor augmented pump (SAP)

- SAP
CGM integrated pump
- SAP with LGS
Suspend insulin delivery when sensor glucose reaches low threshold
- SAP with PLGS
Suspend insulin delivery once sensor glucose predicted to reach low threshold

Minimize and prevent hypoglycemia

Overnight closed loop (OCL)

Automatically determines the insulin infusion rate during nighttime

Improved overnight TIR

Hybrid closed loop (HCL)

Automatically determines basal insulin infusion rate all-day

with user-initiated meal-time bolus

Improved all-day TIR and TBR

Advanced hybrid closed loop (AHCL)

Automatically determines basal insulin infusion rate all-day

with user-initiated meal-time bolus

with automated correction bolus function

Improved TIR and time spent in auto-mode

Single hormone closed-loop system

Group	Algorithm	Commercialization (CE or US FDA approval)
CamDiab	MPC	Florence system ^a → CamAPS FX (2020)
DreaMed	MD-Logic (Fuzzy logic)	Glucositter (2015), AdvisorPro (2018) ^b
Medtronic	PID	Minimed 670G (2016), 780G (2020)
TypeZero	MPC	DiAs ^a → Tandem Control-IQ (2019)
Diabeloop	MPC	DBLG1 (2018), DBLHU ^a
Insulet	MPC	Horizon ^a → Omnipod 5 ^a

A

Dual hormone closed-loop system

Group	Algorithm	Commercialization (CE or US FDA approval)
Beta Bionics	MPC (insulin) PD (glucagon)	Bihormonal iLet ^a
Inreda	PID	Inreda Diabetic AP (2020)
IRCM	MPC (insulin) Heuristic logic (glucagon)	None
Oregon	FMPD ALPHA	None

B

Table 3**Advantages and disadvantages of insulin-pump therapy****Advantages**

Improves glycemic control
Offers precise dosage delivery
Can be programmed to increase or decrease to follow circadian rhythms
Allows for changes needed during growth or changes
Ideal for athletics/exercise to decrease insulin delivery either during event or afterward
Varied and prolonged bolusing for high-fat meals
Flexibility for varied work schedules, exercise regimens, flexible meal schedule
Helpful for multiple time-zone travel
Improves psychological well-being and quality of life
Assists with better pre-/postmeal blood sugar levels
Convenience of delivery of insulin
Avoids 3–4 injections/d
No math, owing to bolus calculators
Weight control by avoiding extra snacks

Disadvantages

Potential for rapid onset of hyperglycemia and diabetic ketoacidosis if insulin delivery is interrupted
Learning how to use the insulin pump
Learning how to count grams of carbohydrate
Learn how to troubleshoot insulin-pump problems
Site infection (not common)
Cost

VACCINE RECOMMENDATIONS FOR PERSONS WITH DIABETES MELLITUS

CDC IMMUNIZATION RECOMMENDATIONS FOR PERSONS WITH DIABETES MELLITUS¹

VACCINE	RECOMMENDATION
Age-appropriate vaccines	All persons should receive according to the CDC/ACIP immunization schedules.
COVID-19	Primary series and booster per current CDC recommendations and FDA approvals
Flu	Annually
HepB	All adults ≤59 years Based on risk and quality of immune response for adults ≥60 years
PCV	Adults with DM ages ≥19 years 1 dose PCV15 followed by PPSV23 at ≥1 year (or ≥8 weeks for adults who are immunocompromised) OR 1 dose PCV20 See also current CDC recommendations for details.
RZV	All adults ≥50 years
Tdap	Every 10 years following completion of the primary series

ACIP = Advisory Committee on Immunization Practices; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; DM = diabetes mellitus; FDA = Food and Drug Administration; HepB = hepatitis B; PCV = pneumococcal conjugate vaccine; PPSV23 = pneumococcal polysaccharide vaccine; RZV = recombinant zoster vaccine; TDAP = tetanus, diphtheria, acellular pertussis

¹<https://www.cdc.gov/vaccines/schedules/index.html>

For child/adolescent specific recommendations, see <https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html>

CDC STANDARDS FOR ADULT IMMUNIZATION PRACTICE

ASSESS

Assess immunization status of all individuals at every encounter.
 • Incorporate into workflow.
 • Stay up to date on the latest recommendations of the CDC Advisory Committee on Immunization Practices. Updated immunization schedules are released annually.

RECOMMEND

STRONGLY recommend vaccines based on age/risk factors.
 • Address questions and concerns.
 • Highlight positive experiences and benefits of vaccines.

ADMINISTER/REFER

Administer or refer patients for immunization.
 • Stock routine vaccines or know your local vaccine providers for referral.

DOCUMENT

Document receipt of vaccine in state immunization registry and electronic health record.

<https://www.cdc.gov/vaccines/hcp/adults/for-practice/standards/index.html>

- Davidson's
- WHO website
 - ADA
 - IDF
- EASD
- AACE



References