Pathophysiology of diabetes mellitus

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Definition

- Diabetes mellitus is a heterogeneous group of metabolic disorders whose common denominator is **chronic hyperglycemia**. It arises either from **insufficient insulin secretion**, **impaired insulin action**, or a combination of both mechanisms.
- Long-term hyperglycemia subsequently damages blood vessels, nerves, kidneys, eyes, and other organ systems; from the perspective of a dentist, it is particularly important that it worsens periodontal health, wound healing, and resistance to infections in the oral cavity.

Why diabetes is crucial for modern medicine

Epidemic, multi-organ consequences, economic impact

- According to the IDF, approximately **589 million adults** were living with diabetes in 2024, meaning about **1 in 9 adults worldwide**.
- More than **40% of cases remain undiagnosed**, so complications often develop even before the diagnosis is established.
- The pathophysiology of complications does not begin only after the “official diagnosis”; for many years, diabetes is a silent systemic disease and a core condition across internal medicine, nephrology, ophthalmology, neurology, surgery, and obstetrics.
- More than **90%** of cases are **T2DM**, but **T1DM**, gestational diabetes, and secondary forms have high individual morbidity.
- Diabetes substantially increases the risk of **CKD, retinopathy, neuropathy, atherosclerosis, heart failure, and infections**.
- From the perspective of the healthcare system, it is a paradigmatic example of a disease in which **prevention and early intervention are less costly than treating complications**.

Current global figures

589 million adults with diabetes

252 million undiagnosed

853 million projected by 2050

≥ 90% of cases are T2DM

Statistics are based on the IDF Diabetes Atlas, 11th edition (2025).

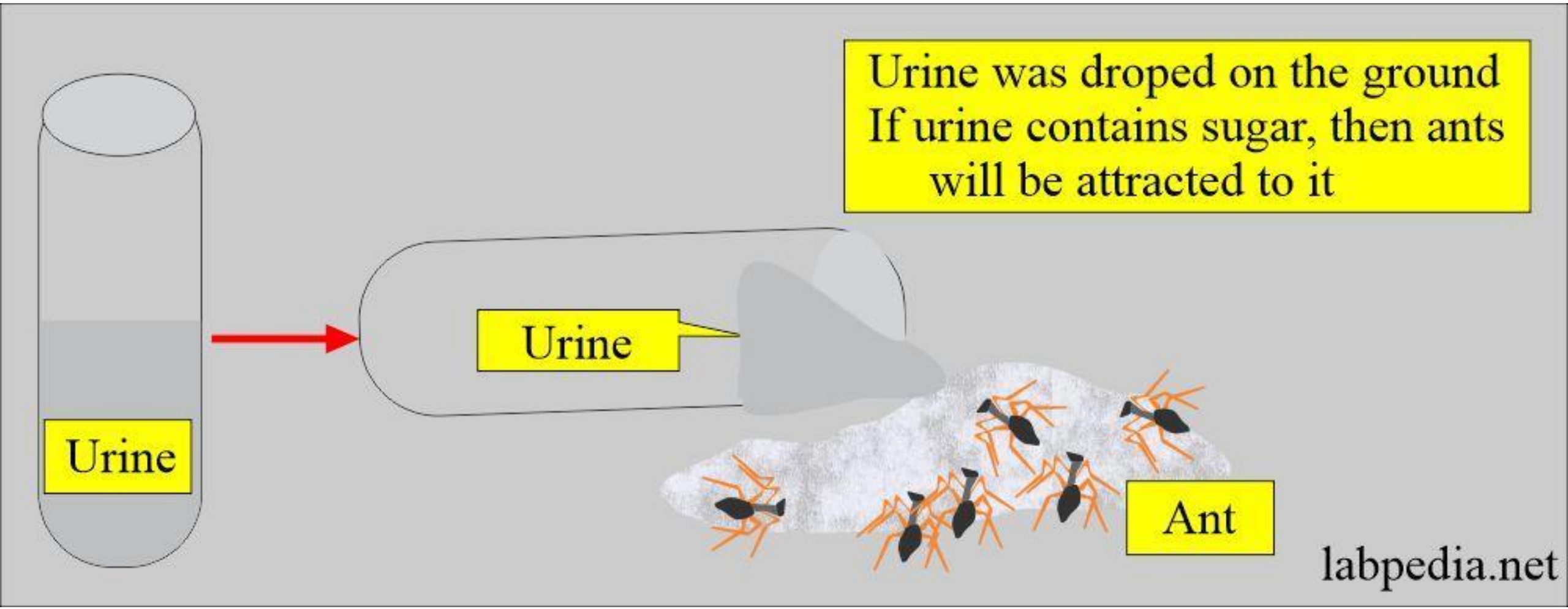
HISTORY OF DIABETES MELLITUS

Prehistoric period

- It is not known when diabetes as a disease first affected humans.
- In southern Moravia and the adjacent area of southwestern Slovakia more than 20,000 years ago, during the Paleolithic???
- The realistic figurine of the Venus of Věstonice – overall obesity, rarity, a symbol of prosperity and fertility (a symbol of a fertility cult from the Stone Age).

Ancient Times – the first observations (≈ 1500 BC) and the Middle Ages

- **Ancient Egypt** – in the Ebers Papyrus (≈ 1550 BC)
  - a disease characterized by excessive urination is described, the first description of diabetes as an illness in which the patient suffers from intense thirst and urinates constantly, while the "body wastes away and is excreted in the urine"
- **India (Ayurveda, Sanskrit literature)**
  - the term **"madhumeha"** = **"honey urine"**
  - physicians noticed that urine attracts ants
  - the disease was **clinically recognized**, but without understanding its mechanism, with a distinction between **two forms of diabetes**


Urine was droped on the ground
If urine contains sugar, then ants will be attracted to it
Urine
Urine
Ant
labpedia.net

Antiquity – naming of the disease

1st–2nd century AD

- **Aretaeus of Cappadocia**
  - first used the term **“diabetes”** (“passing through” / “siphon”) based on the Greek word **diabainein** (to pass through something)
  - description: **“the body dissolves into urine”**
  - in this period, the disease was **rare and fatal**, and treatment was practically nonexistent
- **Galen** – diet, physical exercise, hydrotherapy

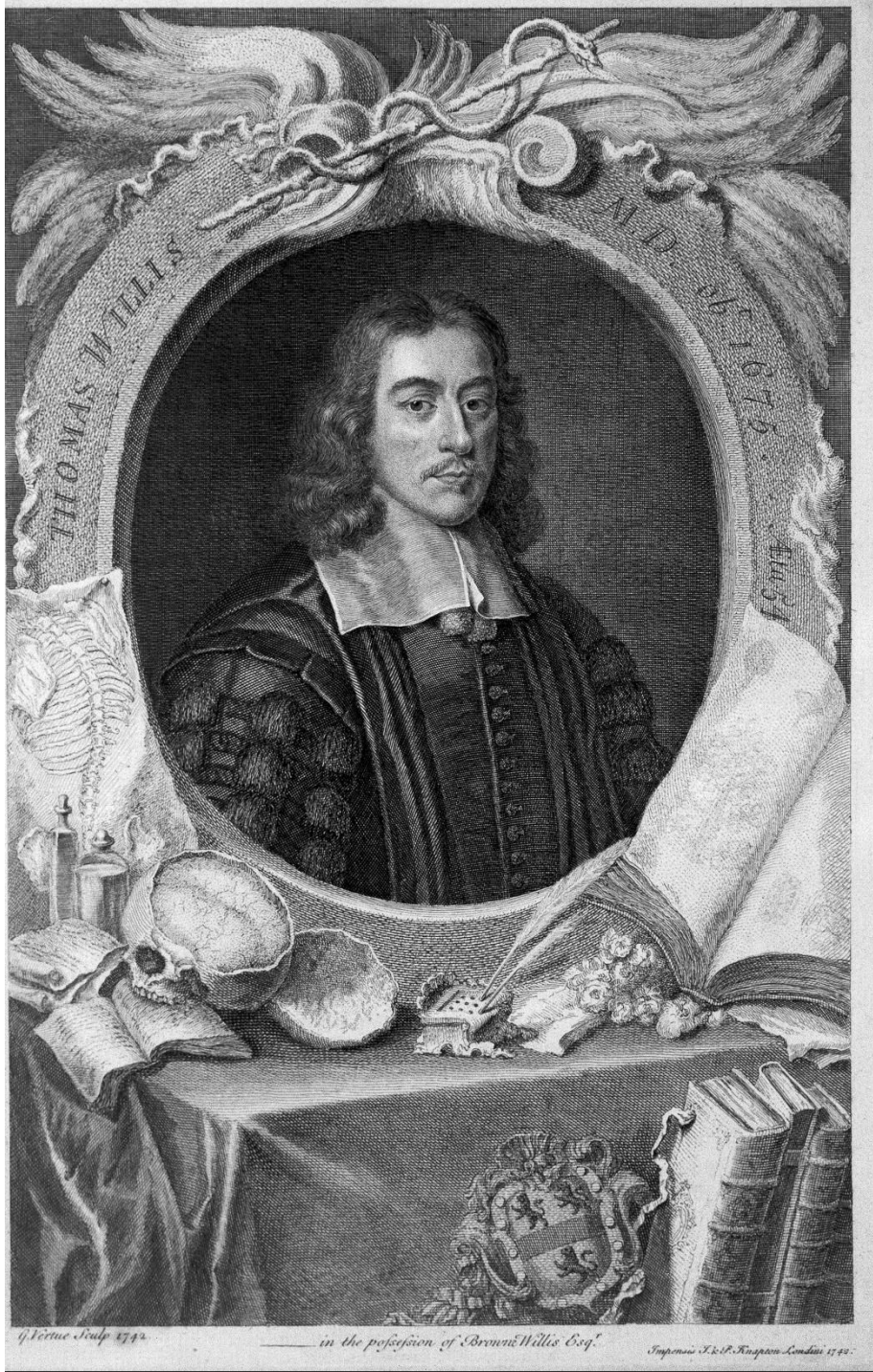
9th century AD – **Avicenna** – complications – **diabetic foot**

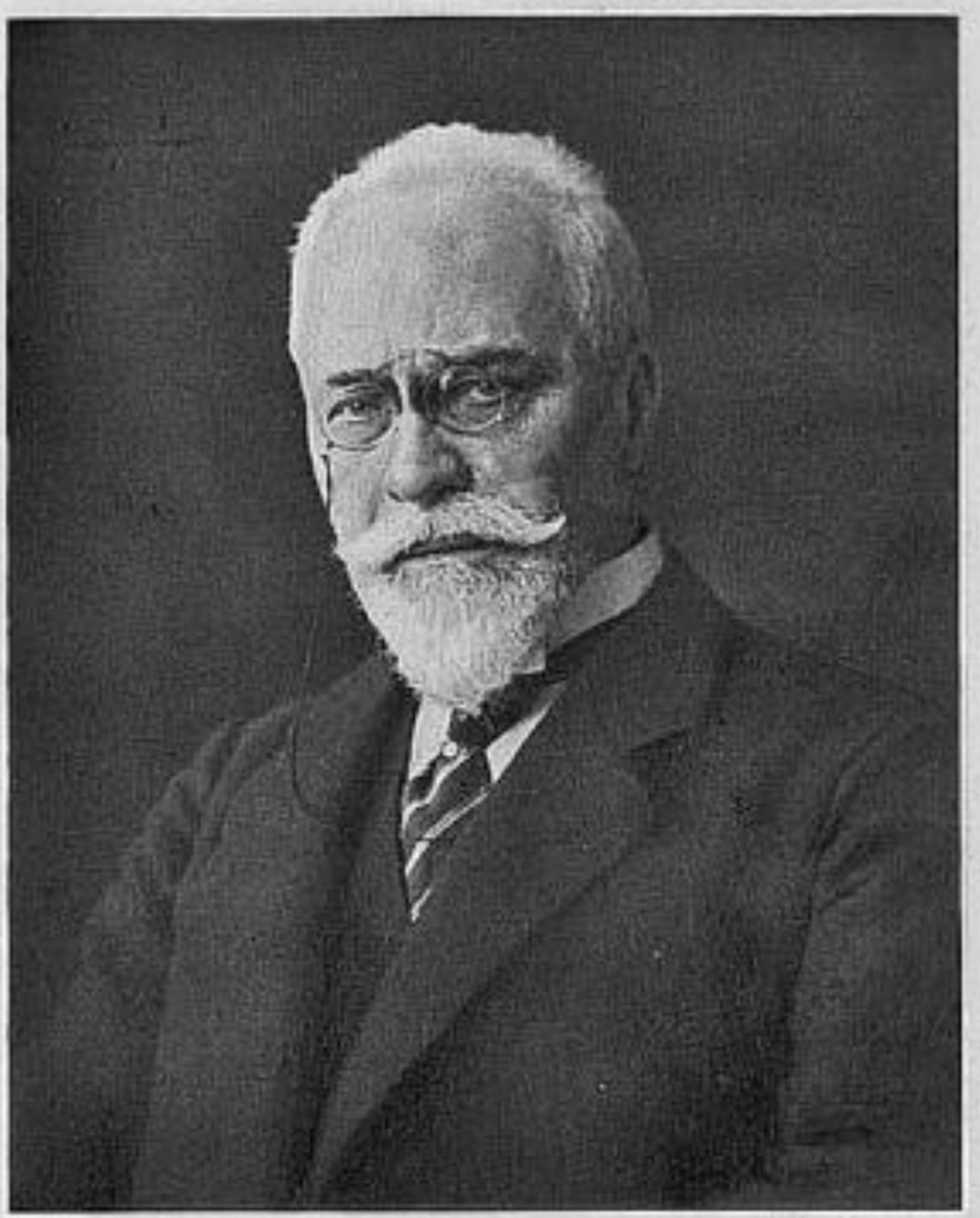
Aretaeus of Cappadocia, 150 AD

"Diabetes is a remarkable disorder, and not one very common to man. It consists of a moist and cold wasting of the flesh and limbs into urine... the secretion passes in the usual way, by the kidneys and the bladder. It is of improbable, also, that something pernicious, derived from other disease which attack the bladder and kidneys may sometimes prove the cause of this affliction. The patients never cease making water, but the discharge is as incessant as a sluice let off. This disease is chronic in character, and is slowly engendered, though the patient does not survive long when it is completely established for the marasmus produced is rapid and death is speedy."

Modern Era

- **Scientific research on diabetes**
- **1674 – Thomas Willis** – distinguished diabetes from other polyuric conditions; he tasted urine and found it to be sweet; he added the term **“mellitus”** (honeyed, sweet), distinguishing **diabetes mellitus** from **diabetes insipidus**; diagnosis was still based only on symptoms.
- **1869 – Paul Langerhans** – described the **islets of the pancreas**.
- **1889 – Oskar Minkowski and Joseph von Mering** → removal of the pancreas in a dog → development of diabetes, the first proof that the pancreas is connected with diabetes.
- **1909 – Jean de Meyer** – proposed a hypothetical hormone that lowers blood sugar levels and introduced the name **insulin**.





UNTERSUCHUNGEN

ÜBER DEN

DIABETES MELLITUS

NACH

EXSTIRPATION DES PANKREAS.

VON

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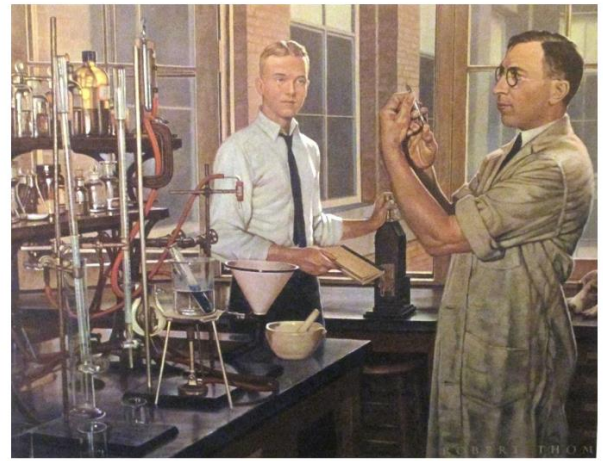
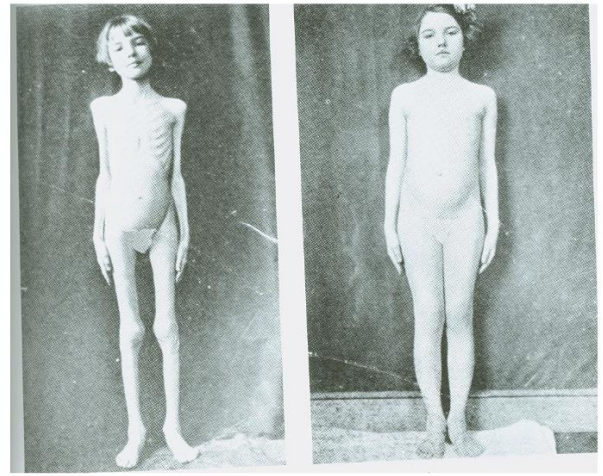
SONDERABDRUCK.

20th century – the revolution: insulin

- **Frederick Banting and Charles Best (1921)**
  - isolation of **insulin** from the pancreas of a dog; the hormone, originally called **isletin**, effectively reduced hyperglycemia in dogs with experimental diabetes
- **first patient:**
  - **Leonard Thompson**
- **1923 – Nobel Prize for the discovery of insulin**
- **diabetes changed from a fatal disease into a treatable one**

Insulin does not belong to me,
it belongs to the world.
~ Frederick Banting





Second half of the 20th century – understanding of pathophysiology

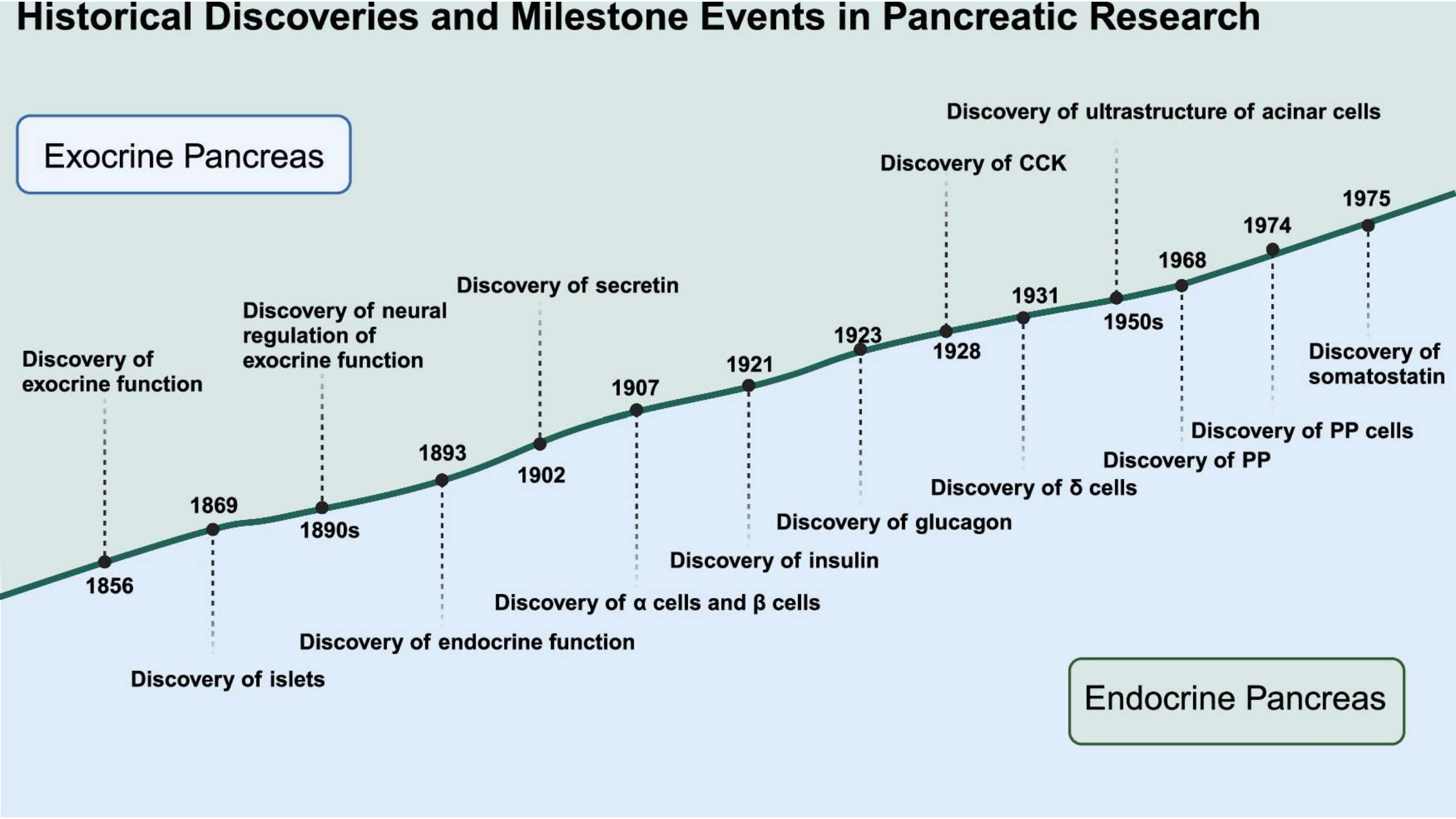
- **distinction:**
  - **Type 1 DM** – autoimmune destruction of β-cells
  - **Type 2 DM** – insulin resistance
- **discoveries:**
  - insulin receptor
  - signaling mechanisms

1955 – F. Sanger – precisely described the structure of the insulin molecule (Nobel Prize, 1958)

1966 – G. Katsoyannis – chemical synthesis of insulin

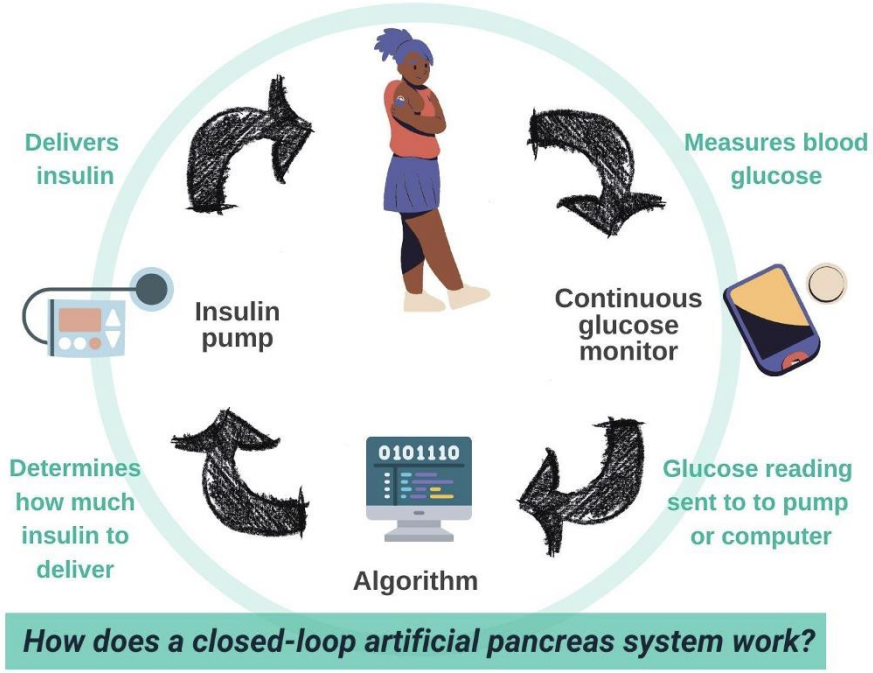
- **development of:**
  - glucose meters
  - oral antidiabetic drugs

Historical Discoveries and Milestone Events in Pancreatic Research

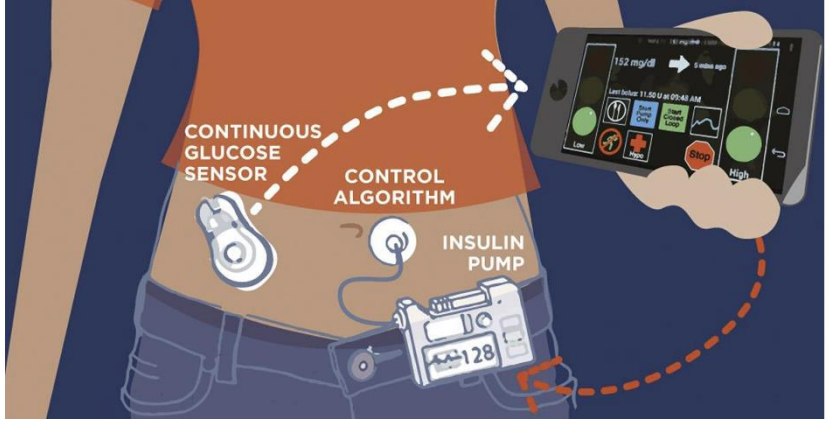


21st century – the modern era

- **technology:**
  - **CGM** (continuous glucose monitoring)
  - insulin pumps
  - “artificial pancreas”
- **treatment:**
  - GLP-1 agonists
  - SGLT2 inhibitors
- **research:**
  - gene therapy
  - islet transplantation



How does a closed-loop artificial pancreas system work?



Physiological basis

– normal glucose homeostasis

insulin and glucagon as the regulatory axis

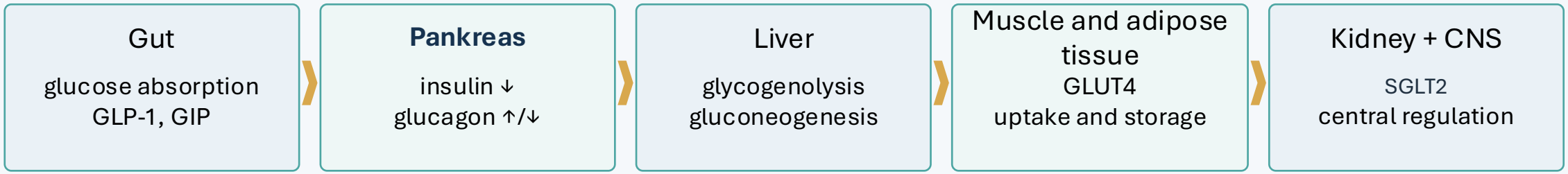
temporal difference between fasting and the postprandial state

organ communication: pancreas – liver – muscle – adipose tissue – gut – kidney – CNS

- most subsequent “pathological” processes are in fact an extreme or a failure of normal physiological regulatory mechanisms

Normal glucose homeostasis

Dynamic balance between glucose intake, production, and utilization



- **In the postprandial state**, insulin secretion increases, glucagon decreases, the liver switches from glucose production to glucose storage, and muscle and adipose tissue increase glucose uptake via GLUT4.
- **During fasting**, it is physiological for the liver to produce glucose.
- Diabetes does not arise only from **"insulin deficiency,"** but also from the inability to suppress hepatic glucose production or from the inability of peripheral tissues to utilize glucose.
- **The role of the kidney** – in hyperglycemia, it ceases to be only a passive filter and becomes an active player through the glucose threshold and SGLT2.
- **Glycemia is the result of the sum of organ fluxes, not an isolated function of the pancreas.**

Pancreatic β-cell: glucose sensor and timer of anabolism

What must function properly for insulin secretion to be normal

- Glucose enters the β-cell, increases the ATP/ADP ratio, closes KATP channels, depolarizes the membrane, and opens Ca2+ channels.
- Ca2+-dependent exocytosis releases insulin in a biphasic profile: a rapid first phase and a slower second phase.
- Insulin secretion is modulated by incretins, the autonomic nervous system, amino acids, and fatty acids.
- A functional β-cell does not only mean the ability to produce insulin, but also the ability to respond appropriately to the pace and amplitude of the metabolic stimulus.
- In T2DM, an early loss of the first phase of secretion is often present even before fully developed chronic hyperglycemia (postprandial hyperglycemia tends to appear earlier than persistent fasting hyperglycemia).

Key points of the β-cell

- glucose sensor
- KATP–Ca2+ exocytosis
- first vs. second phase of secretion
- incretin amplification

Loss of the first phase of secretion is an early sign of β-cell dysfunction in T2DM.

Pancreatic β-cell: glucose sensor and timer of anabolism

What must function properly for insulin secretion to be normal

- **KATP–Ca^{2+} exocytosis = the basic mechanism of insulin secretion from pancreatic β-cells:**
- **Blood glucose rises** → glucose enters the β-cell.
- **ATP production increases.**
- ATP **closes KATP channels** (ATP-sensitive potassium channels).
- This reduces **K^+ efflux** from the cell and causes **membrane depolarization**.
- Depolarization opens **voltage-gated Ca^{2+} channels**.
- **Ca^{2+} enters the cell.**
- The rise in intracellular **Ca^{2+}** triggers **exocytosis of insulin granules**.

Increase in ATP → closure of KATP channels → membrane depolarization → opening of Ca^{2+}channels → Ca^{2+}influx → insulin exocytosis

Key points of the β-cell

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Insulin signaling in target tissues

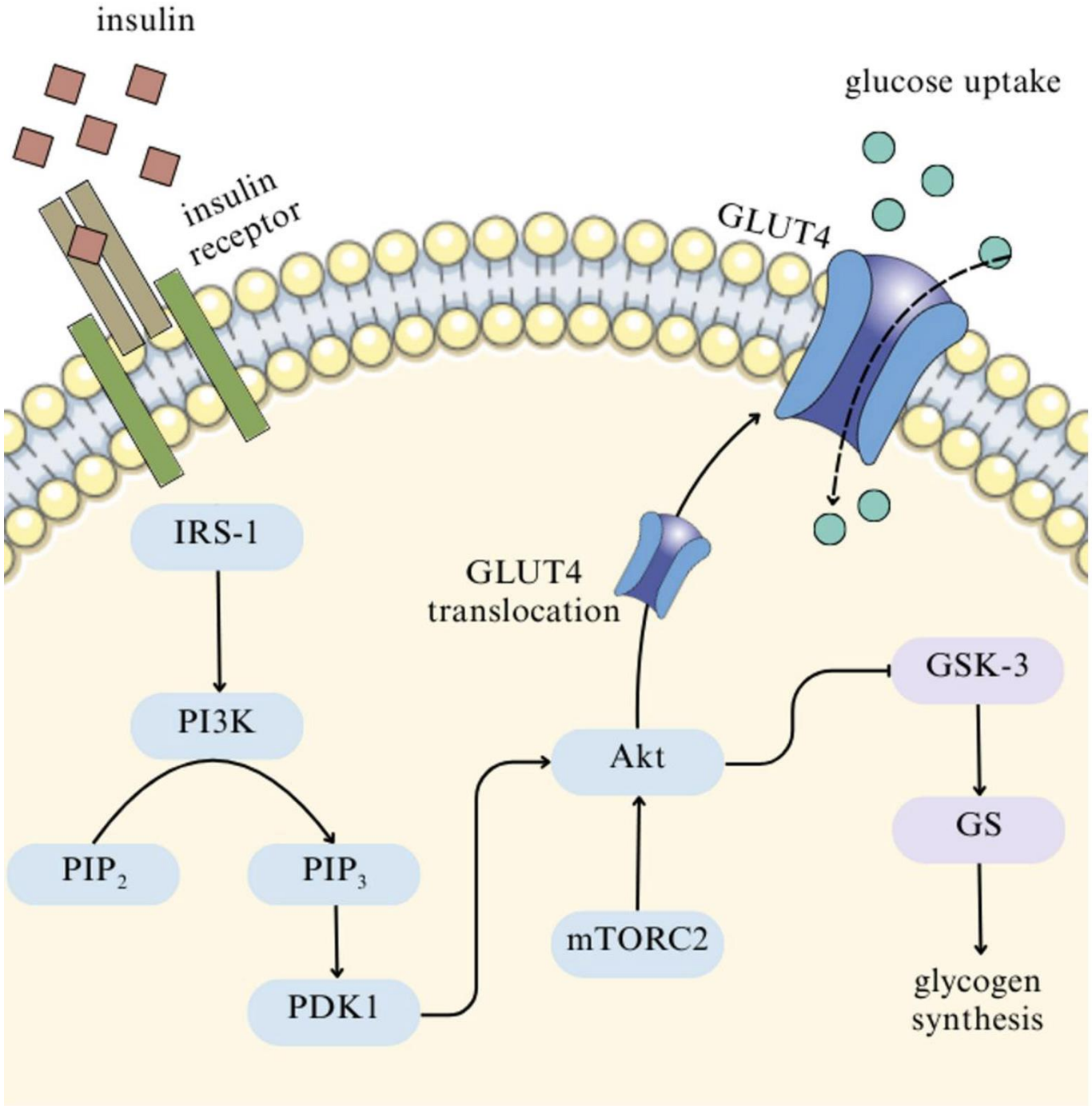
Where insulin resistance arises

- Binding of insulin to its receptor activates tyrosine kinase signaling and the IRS–PI3K–Akt and MAPK pathways.
- **IRS–PI3K–Akt and MAPK** denote the two main intracellular signaling branches that are activated after **insulin binds to the insulin receptor**.
- **IRS–PI3K–Akt** mediates the metabolic effects of insulin.
- **MAPK** mediates growth-promoting, proliferative, and gene-regulatory effects.

Tissue-specific insulin resistance helps explain the phenotypic heterogeneity of T2DM.

Schematic illustration of the insulin signaling pathway. Insulin binds to the insulin receptor, which leads to activation of IRS-1 and PI3K. PI3K catalyzes the conversion of PIP2 to PIP3, which activates PDK1. PDK1, together with mTORC2, phosphorylates and activates Akt. Activated Akt promotes the translocation of GLUT4 to the plasma membrane, thereby increasing glucose uptake, and inhibits GSK-3, which stimulates glycogen synthase activity and glycogen synthesis.

IRS-1, insulin receptor substrate 1;
PI3K, phosphatidylinositol 3-kinase;
PIP2, phosphatidylinositol 4,5-bisphosphate;
PIP3, phosphatidylinositol 3,4,5-trisphosphate;
PDK1, phosphoinositide-dependent kinase 1;
mTORC2, mechanistic target of rapamycin complex 2;
Akt, protein kinase B;
GLUT4, glucose transporter 4;
GSK-3, glycogen synthase kinase-3.



Insulin signaling in target tissues

Where insulin resistance arises

Significance in the pathophysiology of DM:

- In **insulin resistance**, the **IRS–PI3K–Akt branch** is usually more impaired, that is, the **metabolic effect of insulin**, whereas the **MAPK branch** may remain relatively preserved. This is important because:
- glucose utilization decreases,
- hepatic glucose production increases,
- endothelial dysfunction persists,
- at the same time, some proliferative and proatherogenic effects of insulin may remain preserved.

Tissue-specific insulin resistance helps explain the phenotypic heterogeneity of T2DM.

Insulin signaling in target tissues

Where insulin resistance arises

- Binding of insulin to its receptor activates tyrosine kinase signaling and the IRS–PI3K–Akt and MAPK pathways.
- Metabolic effects – GLUT4 translocation, inhibition of lipolysis, and suppression of hepatic gluconeogenesis – depend mainly on the PI3K–Akt axis.
- Chronic excess energy supply, inflammation, ectopic lipids, and serine phosphorylation of IRS disrupt the signal even before glucose transport itself.
- Insulin resistance is not a binary phenomenon; it may be selective and tissue-specific.
- Clinically, this explains why a patient may simultaneously have hyperglycemia, hyperinsulinemia, hepatic steatosis, and persistent lipogenesis.
- A defect in the signaling pathway leads to reduced glucose uptake in muscle, persistent glucose production in the liver, and insufficient suppression of lipolysis in adipose tissue.
- **“Selective” insulin resistance** = the liver is resistant to the suppression of gluconeogenesis, while at the same time remaining relatively sensitive to lipogenic signals.

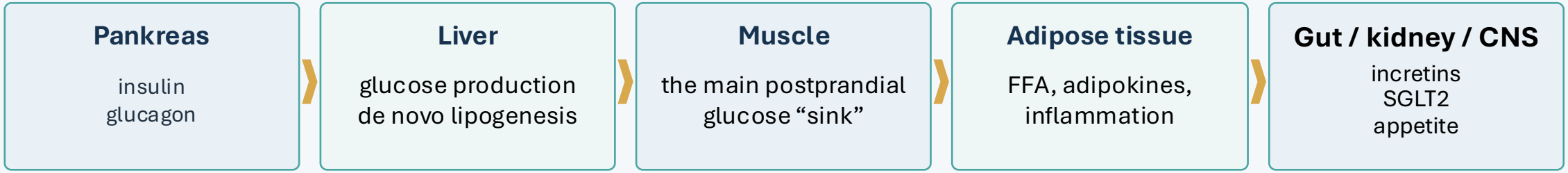
Sites of signal failure

- receptor / IRS
- PI3K–Akt pathway
- GLUT4 translocation
- selective hepatic resistance

Tissue-specific insulin resistance helps explain the phenotypic heterogeneity of T2DM.

Organ network in glycemic regulation

Diabetes is a disorder of inter-organ communication



The **multi-organ concept of T2DM** means that in diabetes we always ask which organ dominates the patient’s phenotype. The **liver** determines fasting glycemia, **muscle** is crucial after meals, **adipose tissue** supplies the body with free fatty acids and inflammatory mediators, the **gut** modifies the response through incretins, the **kidney** modulates glucose reabsorption, and the **CNS** influences both food intake and energy expenditure. Within this framework, diabetes appears as a failure of coordination, not as an isolated disorder of a single hormone.

Classification and Diagnosis

Hyperglycemia is a syndrome; a diagnosis of “diabetes” does not yet determine the underlying mechanism.

- four basic diagnostic categories
- criteria for diagnosis and prediabetes
- clinical warning signs of misclassification

The same laboratory criteria may lead to very different pathophysiological diagnoses. That is why it is important to consider age, BMI, speed of symptom onset, autoimmunity, family history, medications, pregnancy, and pancreatic diseases.

Classification

Note

- terminology is not yet fully standardized across all sources
- in its 2026 Standards, the ADA still relies on conventional clinical categories of diabetes
- in 2025, the IDF officially recognized **malnutrition-related diabetes mellitus** as **type 5 diabetes**, and is still in the process of developing formal diagnostic criteria and therapeutic recommendations for this entity

Current Classification of Diabetes Mellitus

- **Type 1 diabetes mellitus** – autoimmune diabetes characterized by destruction of pancreatic β-cells and an absolute or near-absolute insulin deficiency.
- **Type 2 diabetes mellitus** – diabetes based on a combination of insulin resistance and progressive β-cell failure; it is the most common type of diabetes and, according to the WHO, accounts for more than 95% of all diabetes cases worldwide.
- **Hyperglycemia first detected in pregnancy** – this includes both **gestational diabetes mellitus** and **diabetes in pregnancy** meeting the diagnostic criteria for overt diabetes. The WHO has long distinguished between these two situations and, in 2025, also issued the first separate global recommendations for the care of women with diabetes during pregnancy.
- **Other specific types of diabetes** – especially **monogenic forms** and diabetes due to **damage to or removal of the pancreas**, for example in pancreatitis, cystic fibrosis, or after pancreatectomy.
- **Type 5 diabetes** – a newly classified entity recognized by the IDF in 2025; it is diabetes associated with chronic undernutrition, previously referred to as malnutrition-related diabetes mellitus. Because the official diagnostic criteria are still under development, it is currently a **new, internationally recognized, but still evolving clinical entity**.

Basic Classification of Diabetes Mellitus

The clinical category must reflect the pathogenesis.

Category	Dominant mechanism	Typical clinical features
T1DM	Autoimmune or idiopathic loss of β-cells → absolute insulin deficiency	more rapid onset, ketosis/DKA, lower C-peptide, autoantibodies
T2DM	Insulin resistance + progressive β-cell dysfunction	obesity/visceral adiposity, long latent phase, comorbidities
Gestational diabetes	Pregnancy-induced insulin resistance with insufficient β-cell compensation	diagnosis during pregnancy, risk for both mother and fetus
Other specific types	Monogenic forms, exocrine pancreas disorders, endocrinopathies, medications, post-transplant diabetes	atypical age, family pattern, pancreatitis, steroids, etc.

The most common mistake is the automatic assumption: adult patient = T2DM.

The basic classification is simple, but its incorrect use leads to incorrect management. In adults in particular, T1DM, LADA, MODY, or pancreatogenic diabetes may be mistakenly classified as T2DM. “Is this patient insulin-resistant, insulin-deficient, or both?” This question is clinically more productive than the label itself.

Sources:

ADA. *Diagnosis and Classification of Diabetes*—2026.
ISPAD Clinical Practice Consensus Guidelines 2024: *Screening, Staging, and Strategies to Preserve Beta-Cell Function in T1D*.
WHO. *Diabetes fact sheet*, 2024.

Diagnostic Criteria for Diabetes and Prediabetes

Hyperglycemia is diagnosed in the laboratory; the mechanism is determined clinically.

Test	Diabetes mellitus	Prediabetes / intermediate dysglycemia
HbA1c	≥ 6.5% (48 mmol/mol)	5.7–6.4%
Fasting plasma glucose	≥ 7.0 mmol/L (126 mg/dL)	5.6–6.9 mmol/L
2-h OGTT	≥ 11.1 mmol/L (200 mg/dL)	7.8–11.0 mmol/L
Random glucose + symptoms	≥ 11.1 mmol/L	not used

If hyperglycemia is not unequivocally symptomatic, the diagnosis usually needs to be confirmed by repeat testing.

The diagnostic criteria themselves indicate the presence of dysglycemia, not the type of diabetes. For HbA1c, interpretation may be unreliable in situations such as anemia, hemoglobinopathies, pregnancy, rapid erythrocyte turnover, and certain renal and hepatic conditions. This is of practical importance especially in emergency medicine and in the differential diagnosis of newly detected hyperglycemia.

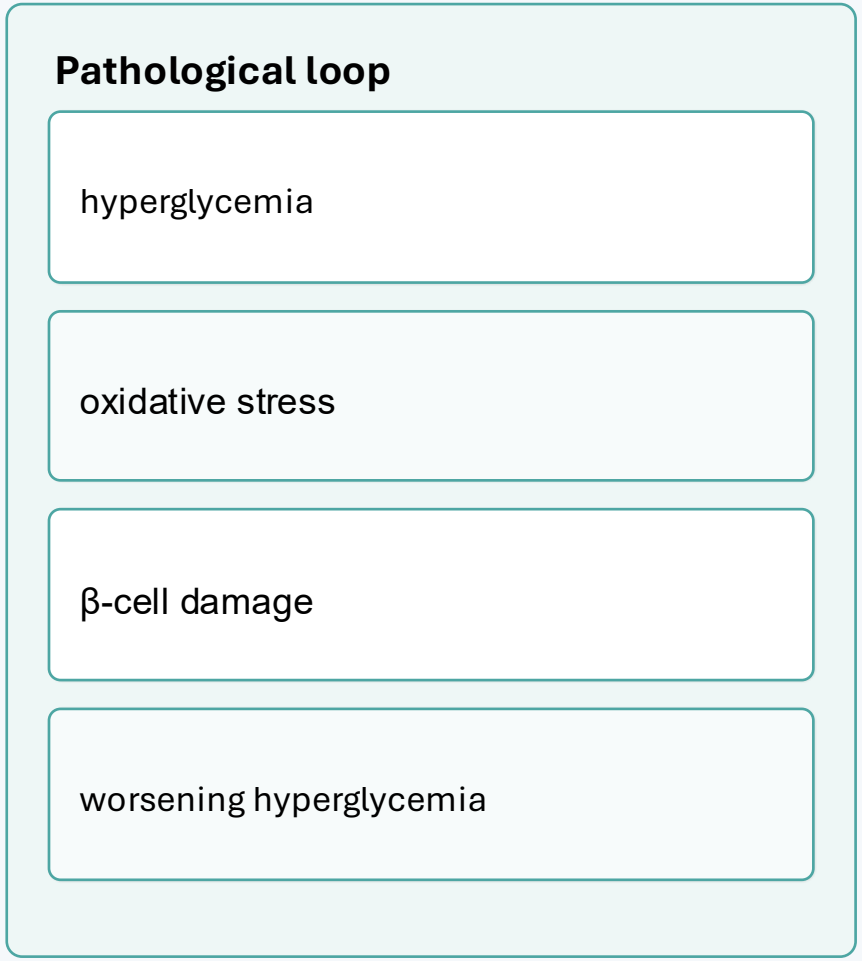
Sources:

ADA. *Diagnosis and Classification of Diabetes*—2026.
IDF Global Clinical Practice Recommendations for Type 2 Diabetes, 2025.
WHO. *Use of Glycated Haemoglobin in the Diagnosis of Diabetes Mellitus*.

Prediabetes, Glucotoxicity, and Lipotoxicity

The transition from risk to overt disease

- Prediabetes is a state in which metabolic dysregulation, endothelial damage, and partial β-cell dysfunction are already present.
- Prediabetes is not just “slightly elevated blood sugar,” but a biological state with real vascular and metabolic consequences.
- **Vicious cycle:** Chronically elevated glucose promotes oxidative stress, AGE formation, PKC activation, and mitochondrial damage.
- Excess free fatty acids and ectopic fat impair insulin signaling and insulin secretion.
- Glucotoxicity and lipotoxicity reinforce each other and create a self-amplifying metabolic loop.
- **Clinical significance:** The earlier the intervention, the greater the chance of slowing or reversing dysglycemia.



This is where the concept of “metabolic memory” arises: early glycemic control has long-term significance.

Type 1 diabetes mellitus

Model of absolute insulin deficiency and autoimmune β-cell damage.

genetic susceptibility and triggers

staging from autoimmunity to clinical diabetes

mechanism of DKA as a consequence of absolute insulin deficiency

Autoimmune T1DM:

- destruction of beta cells leading to absolute insulin deficiency
- highest incidence in Finland (29.5/100,000) and lowest in Japan (1.6/100,000)

Idiopathic T1DM:

- it is not possible to demonstrate the autoimmune nature of beta-cell destruction (more common in Asians and Africans)

Definition

- **Type 1 diabetes mellitus** is usually an autoimmune disease characterized by T-lymphocyte-mediated destruction of pancreatic β-cells. Its development involves genetic predisposition (HLA-DR3, DR4) and environmental factors. The result is an absolute insulin deficiency, which leads to hyperglycemia, increased lipolysis, and ketogenesis, with diabetic ketoacidosis being a typical complication.

Immunopathogenesis of T1DM

From genetic predisposition to β-cell destruction

- The HLA constellation and other genes affecting antigen presentation and immune tolerance play a key role.
- The autoimmune process leads to the development of islet autoantibodies (IAA, GAD, IA-2, ZnT8) and T-lymphocyte-mediated destruction of β-cells.
- Preclinical stages may last months to years; clinical manifestation occurs only after a critical decline in functional β-cell mass.
- Environmental and infectious triggers are probably important, but in an individual patient their contribution is often difficult to prove.
- The result is an absolute or near-absolute insulin deficiency with a high tendency toward ketogenesis.

Mechanistic sequence

genetic susceptibility

loss of tolerance

autoimmune insulitis

β-cell loss

Autoantibodies are markers of the process; the actual damage is mediated mainly by cellular immune mechanisms.

Basic Characteristics

- autoimmune disease
- selective destruction of pancreatic β-cells
- result → absolute insulin deficiency

Genetic Predisposition

- strong association with:
  - HLA class II:
    - **HLA-DR3**
    - **HLA-DR4**
- genetics ≠ a sufficient cause
  - an **environmental trigger** is also needed

Triggering Factors (Environmental)

- **viral infections:**
  - Coxsackie B
  - rubella
- **toxins / diet** (under discussion)
- **“hygiene hypothesis”**
- they trigger an **autoimmune response**

Hygiene Hypothesis (the “Old Friends” Hypothesis)

- In the context of the development of **type 1 diabetes mellitus (T1DM)**, it is used to explain the sharp increase in autoimmune diseases in developed countries.

➤ **Lack of immune stimulation:** The hypothesis assumes that an overly clean environment and reduced contact with microbes, parasites, and infections in early childhood (due to high hygiene standards, vaccination, and antibiotics) lead to the immune system becoming “bored.”

➤ **Autoimmune reaction:** Because the immune system does not have enough natural pathogens to react to, it becomes hyperactive and begins to “attack” the body’s own tissues—in the case of T1DM, the pancreatic beta cells that produce insulin.

➤ **Increase in cases:** This theory explains why the incidence of T1DM is rising especially in countries with a high standard of living and better hygiene, where contact with certain types of bacteria is limited.

Hygiene Hypothesis (the “Old Friends” Hypothesis)

Related facts:

- **Gut microbiota:** An imbalance in the gut microbiota plays an important role and may be influenced precisely by the modern lifestyle and the lack of natural microbial stimuli.
- **Protective factors:** Conversely, contact with nature, animals, or infections in childhood may “train” the immune system and act protectively against the development of autoimmunity.
- **Incidence:** Type 1 diabetes has been presenting more frequently in recent years, which supports the hygiene hypothesis as one of the possible causes of this increase.

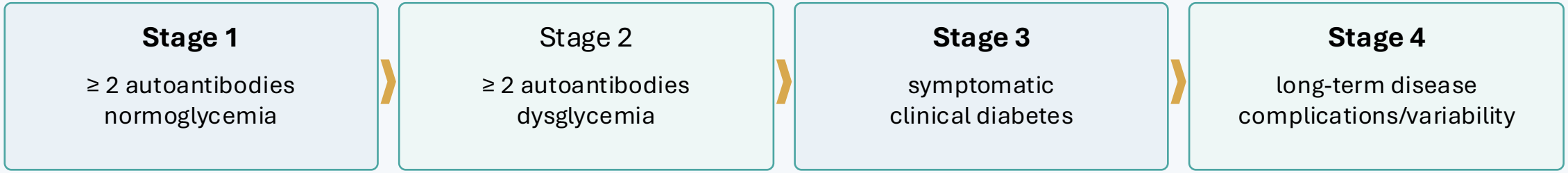
Autoimmune Reaction

Mechanism:

- presentation of β-cell antigens (APCs)
- activation of **T-lymphocytes** (**CD4+**, **CD8+**)
- infiltration of the pancreas → **insulitis**
- cytotoxic damage to β-cells

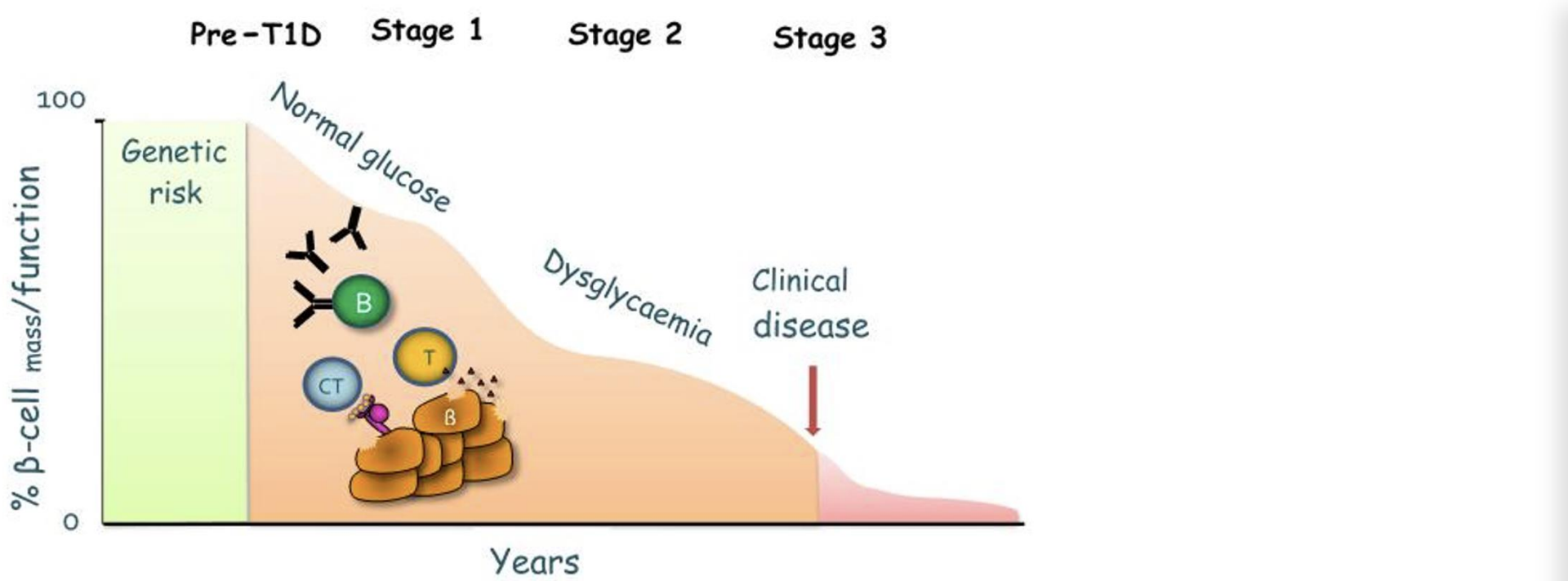
Staging of T1DM and the Importance of Screening

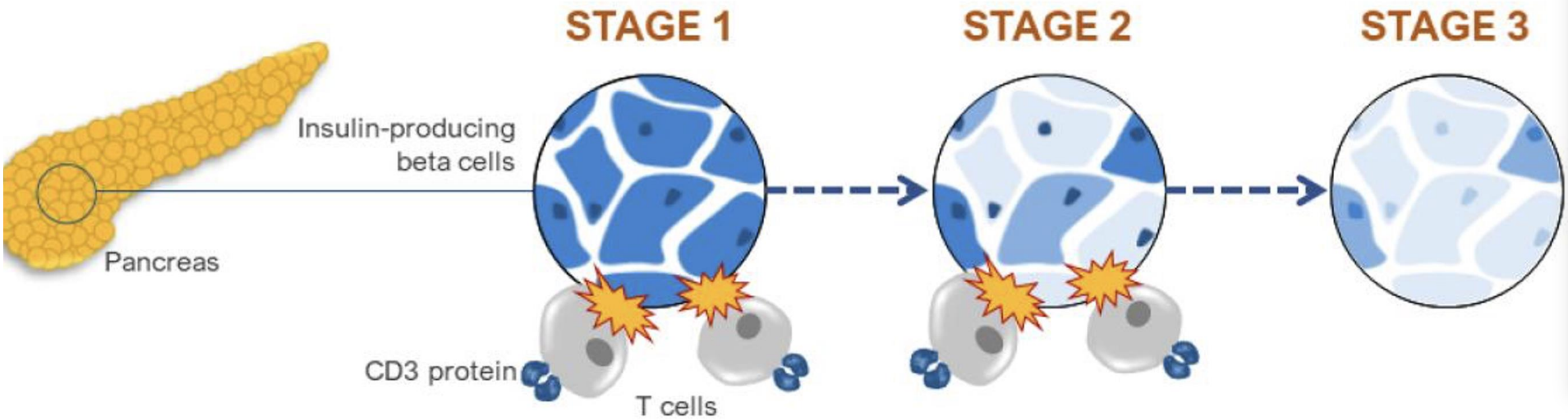
Modern concept: T1DM begins before hyperglycemia



Screening of at-risk individuals helps reduce DKA at presentation and creates an opportunity for early intervention. Multiple positive autoantibodies significantly increase the likelihood of progression to overt diabetes. The practical importance of screening lies in education, monitoring, and a lower risk of presentation with DKA.

- immunomodulatory approaches, teplizumab in the context of delaying progression in selected at-risk individuals


Pre-T1D
Stage 1
Stage 2
Stage 3
100
0
% β-cell mass/function
Genetic risk
Normal glucose
Dysglycaemia
Clinical disease
B
T
CT
β
Years

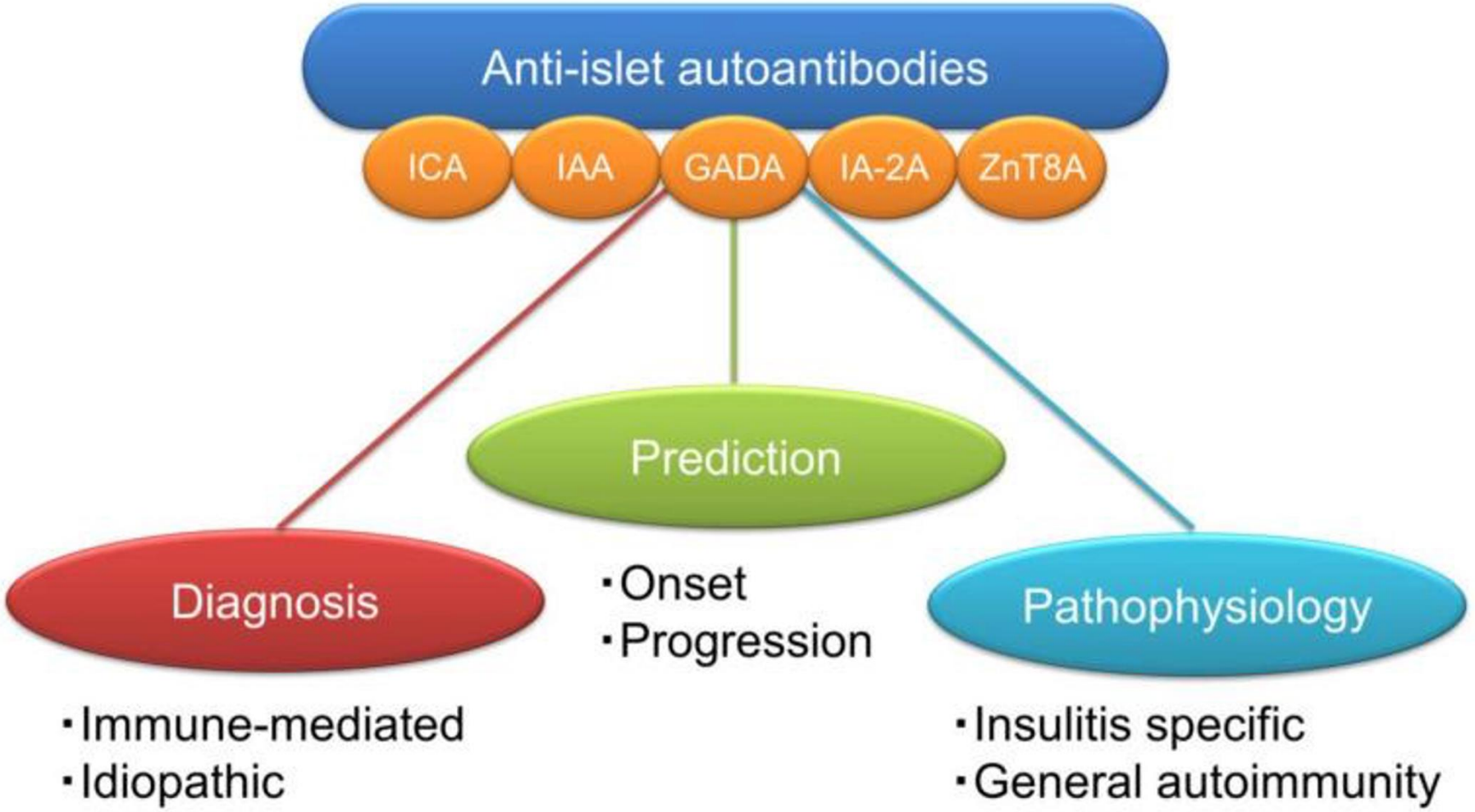

STAGE 1
STAGE 2
STAGE 3
Insulin-producing beta cells
Pancreas
CD3 protein
T cells

Autoantibodies

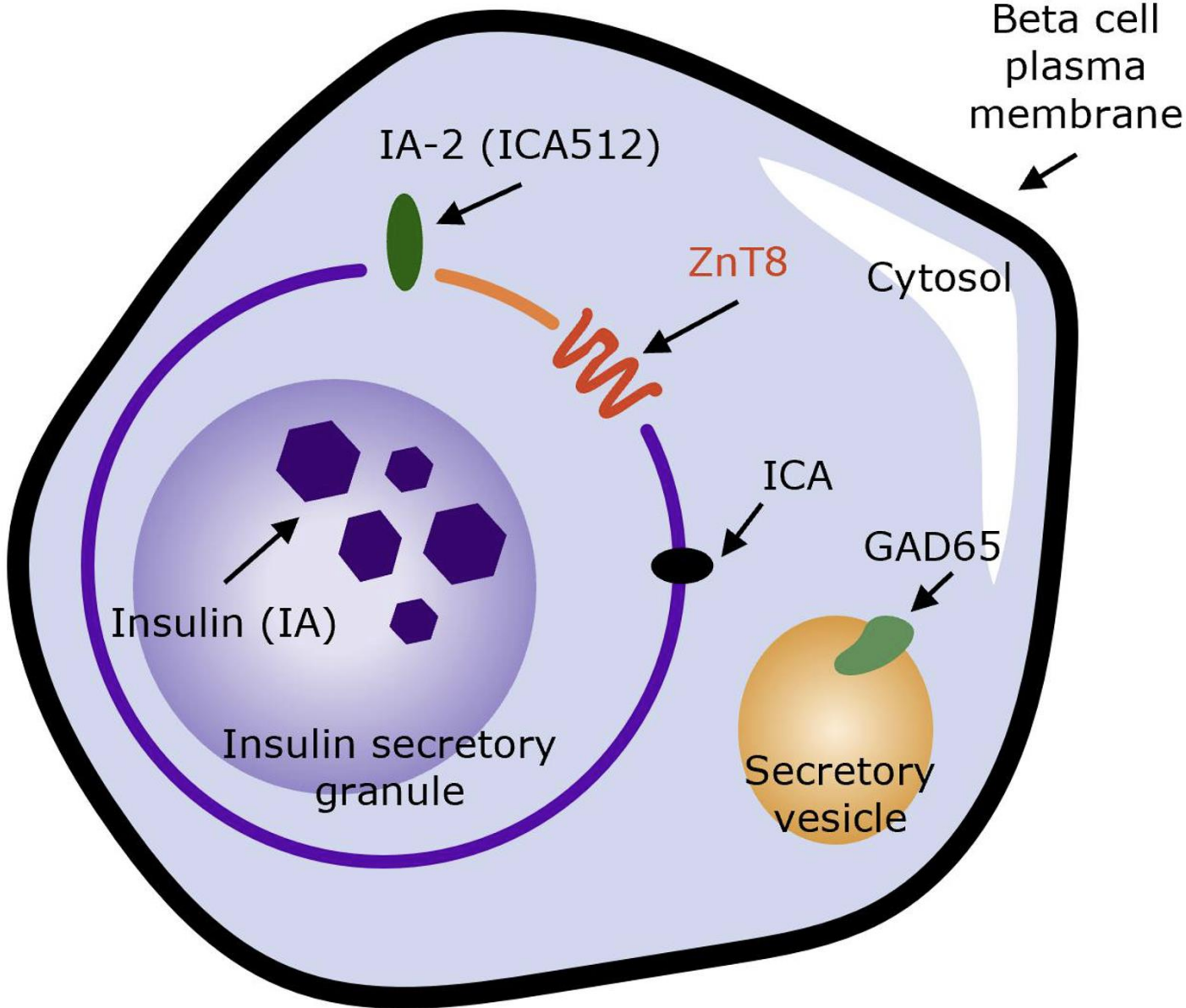
- group of antibodies against the pancreatic islets of Langerhans (**ICA**)
  - **anti-GAD65 (GADA)**, antibodies against glutamic acid decarboxylase
  - **anti-IA-2**, antibodies against tyrosine phosphatase
  - **IAA**, insulin autoantibodies
- **anti-ZnT8A**, antibodies against zinc transporter 8

➤ **markers of autoimmunity**

- The prevalence of **anti-GAD** in both pediatric and adult patients with type 1 diabetes is **70–80%**.
- Detection of **anti-GAD** in individuals has a **65–90% sensitivity** for the development of type 1 diabetes within **5–10 years**. With increasing age at the onset of type 1 diabetes, the value of **anti-GAD** increases.
- For prediction of risk for type 1 diabetes, a combination of at least **2 antibodies** is recommended: **GAD and IAA** or **GAD and IA-2A**. The risk of developing type 1 diabetes within **5 years** with the combined presence of **GAD and IAA** is **68%**, and with **GAD and IA-2A** it is **86%**.


Anti-islet autoantibodies
ICA
IAA
GADA
IA-2A
ZnT8A
Diagnosis
Prediction
Pathophysiology
・Immune-mediated
・Idiopathic
・Onset
・Progression
・Insulitis specific
・General autoimmunity

BETA CELL-SPECIFIC AUTOANTIGENS



β-Cell Destruction

- progressive loss of cells
- clinical signs appear only when:
    - approximately **80–90% of β-cells** have been destroyed
- development of:
    - hyperglycemia
    - ketogenesis

- At the beginning, insulitis is non-destructive (regulated by Th2 and Th3 lymphocytes).
- Later, under the influence of external factors (stress, infection), Th1 lymphocytes begin to predominate, insulitis becomes destructive, and diabetes develops.
- The factors that trigger the entire autoimmune process may differ from the factors that precipitate the development of destructive insulitis and subsequently diabetes.
- **destructive insulitis** – the cellular type of immune response predominates, mediated by cytotoxic T lymphocytes, NK cells, and macrophages; free oxygen radicals also play a role in the destruction
- **DM becomes clinically manifest after destruction of 80–90% of beta cells** (with destruction of 50–60%, **IFG** or **IGT** may appear)
  - manifestation during puberty (peak at 12 years of age)
  - seasonal pattern
  - long preclinical period

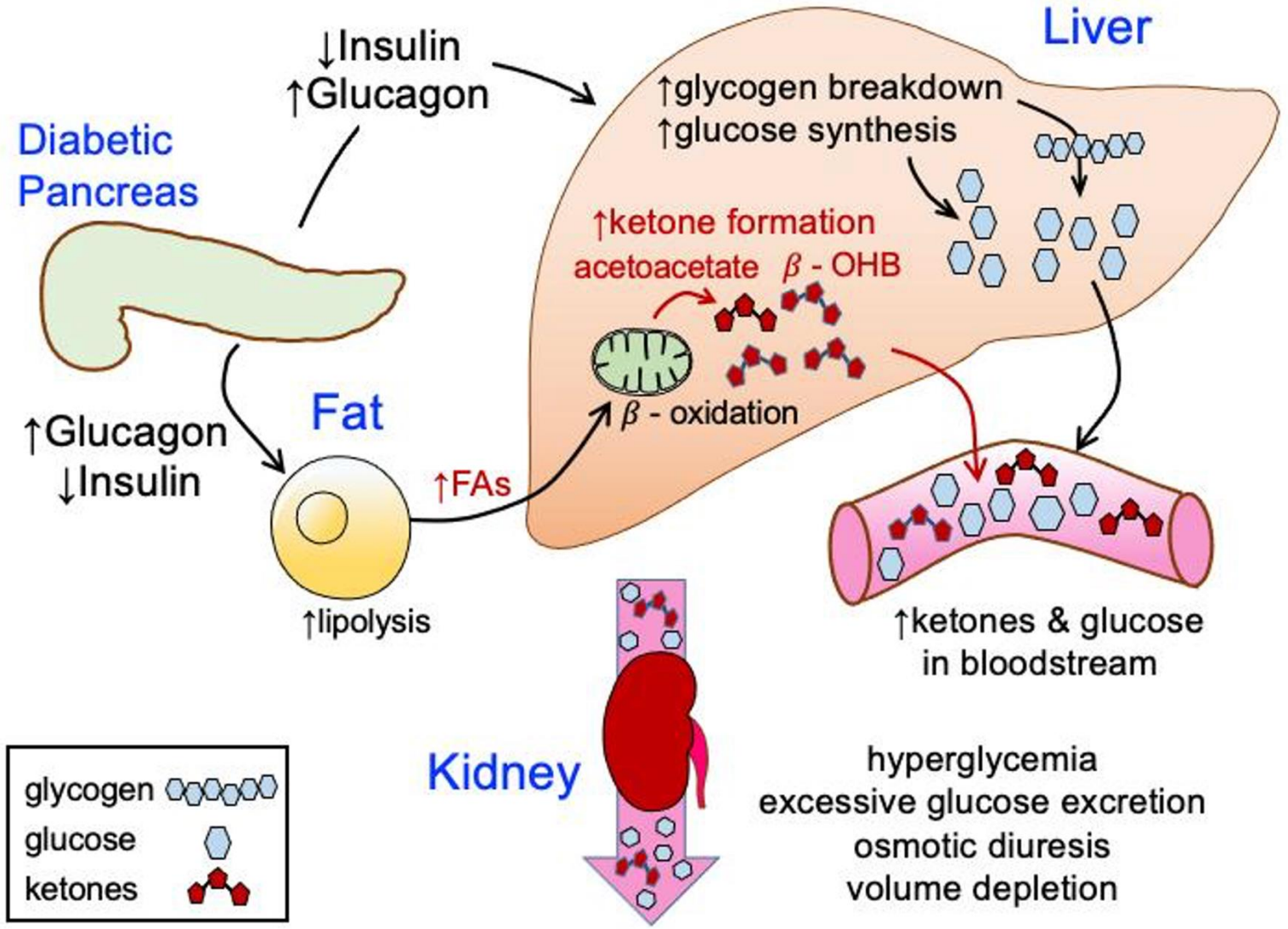
The character of insulitis and the rate of beta-cell destruction vary:

- **Rapidly progressive form of insulitis**
  - in children (but it may also occur in adulthood)
  - insulitis lasts on the order of weeks to months
  - progresses to destruction of most beta cells
  - onset of diabetes is dramatic, with classic symptoms
  - tendency to develop ketoacidosis
  - need for insulin therapy from the onset of the disease

- **Slowly progressive form of insulitis**
  - insulitis lasts for years to decades
  - manifestation of diabetes in adulthood
  - **LADA** (*latent autoimmune diabetes in adults*)
  - does not present with the typical symptoms of type 1 diabetes
  - no tendency toward ketoacidosis
  - frequently mistaken for type 2 diabetes – leading to inappropriate treatment with diet alone and **oral antidiabetic drugs (OADs)** – with apparently satisfactory control due to the persistence of some minimal insulin secretion (beta cells are destroyed more slowly)
  - also requires insulin treatment

Metabolic Consequences

- **1. ↓ insulin → ↓ glucose utilization**
- muscle, fat → “cellular starvation”
- **2. ↑ gluconeogenesis (liver)**
- further increases blood glucose
- **3. lipolysis**
- ↑ free fatty acids
- **4. ketogenesis**
- formation of ketone bodies → **ketoacidosis**


Liver
↓Insulin
↑Glucagon
Diabetic
Pancreas
↑glycogen breakdown
↑glucose synthesis
↑ketone formation
acetoacetate β - OHB
β - oxidation
↑Glucagon
↓Insulin
Fat
↑FAs
↑lipolysis
↑ketones & glucose
in bloodstream
glycogen
glucose
ketones
Kidney
hyperglycemia
excessive glucose excretion
osmotic diuresis
volume depletion

Diabetic Ketoacidosis (DKA)

- typical of **type 1 diabetes**
- **mechanism:**
  - ↓ insulin
  - ↑ glucagon
- **result:**
  - metabolic acidosis
  - dehydration
  - Kussmaul respiration

Why DKA Develops: Pathophysiological Logic

Absolute insulin deficiency + excess counterregulatory hormones

- insulin suppresses catabolism
- Insulin deficiency removes the inhibition of lipolysis, proteolysis, and hepatic gluconeogenesis; glucagon, catecholamines, cortisol, and GH further amplify the process.
- Free fatty acids are oxidized in the liver to ketone bodies; once buffering capacity is exceeded, metabolic acidosis develops.
- Hyperglycemia causes osmotic diuresis, dehydration, and loss of sodium, potassium, and other electrolytes.
- Total body potassium deficit may be substantial even when serum potassium is initially normal or elevated.
- Triggers may include infection, omission of insulin, first manifestation of T1DM, myocardial infarction, pregnancy, or SGLT2 inhibitor-associated euglycemic DKA.

Vicious cycle of DKA

↓ insulin

↑ lipolysis

↑ ketone bodies

acidosis + dehydration

The patient does not die from hyperglycemia itself, but from the combination of acidosis, dehydration, hyperosmolality, and electrolyte disturbances. Emphasis should be placed on the risk of an apparently normal serum potassium level.

In DKA, we treat three problems at once: volume depletion, insulin deficiency, and electrolyte losses.

Type 2 diabetes mellitus

Heterogeneous syndrome combining insulin resistance and progressive β-cell dysfunction.

- muscle, liver, adipose tissue, and the β-cell
- incretin system, kidneys, and CNS
- why T2DM is not just a consequence of obesity

Different patients may have different proportions of insulin resistance and β-cell failure. This explains the differing clinical phenotype as well as the differing response to treatment.

Definition

- **Type 2 diabetes mellitus** is a metabolic disease characterized by a combination of insulin resistance and relative insulin deficiency. Insulin resistance arises mainly in skeletal muscle, adipose tissue, and the liver, and is closely linked to obesity and chronic inflammation. Initially, compensatory hyperinsulinemia develops, but this is gradually followed by β-cell dysfunction as a result of gluco- and lipotoxicity, leading to the development of hyperglycemia.

T2DM as a Heterogeneous Multisystem Disease

Not a single disease, but a shared phenotype of several disorders

Pathophysiological mechanism: insulin resistance and beta-cell dysfunction

- the most common type of diabetes
- prevalence is higher in Black people, Japanese people, and Pacific populations than in White people
- prevalence in developed countries continues to rise – a diabetes epidemic
- unhealthy lifestyle (overeating, physical inactivity, obesity)
- poorer and less educated populations in developed countries
- highest prevalence – North American Pima Indians (80% of the population)

Risk factors:

- genetic predisposition (more significant than in type 1 diabetes)
- obesity – the most important risk factor (obese individuals have a 10× higher risk than non-obese individuals)
- lifestyle (inactivity, overeating)
- older age

Heredity:

- concordance in monozygotic twins is 80%; risk for a first-degree relative is 10–15%
- more frequent occurrence in women with previous gestational diabetes and in individuals with hypertension and dyslipidemia

T2DM should be understood as a process of adaptation and subsequent decompensation of the beta cell.

T2DM as a Heterogeneous Multisystem Disease

Not a single disease, but a shared phenotype of multiple disorders

- T2DM develops when the β-cell can no longer compensate for insulin resistance over the long term.
- Some patients have predominant visceral adiposity and insulin resistance, while others have relatively early β-cell failure.
- Ectopic fat deposition, low-grade inflammation, mitochondrial dysfunction, and disturbances of the gut–brain axis also play an important role.
- In clinical practice, T2DM therefore often coexists with MASLD, hypertension, dyslipidemia, CKD, and cardiovascular disease.
- The pathophysiology develops over years to decades before diabetes is actually detected in outpatient care (the β-cell must increase insulin secretion over the long term to overcome peripheral resistance. When this compensatory capacity fails, hyperglycemia appears; this is a time-dependent process: initially the organism compensates, later it decompensates.)

Dominant axes of T2DM

- insulin resistance
- β-cell insufficiency
- ectopic fat
- cardiorenal-metabolic associations

T2DM should be understood as a process of adaptation followed by β-cell decompensation.

Skeletal Muscle Insulin Resistance

Why postprandial glycemia rises

- Skeletal muscle is the largest target organ for postprandial glucose utilization.
- In insulin resistance, GLUT4 translocation decreases and the ability of muscle cells to store glucose as glycogen is reduced.
- Contributing factors include ectopic intramyocellular lipids, ceramides, inflammatory signals, physical inactivity, and mitochondrial dysfunction.
- The result is more pronounced postprandial hyperglycemia and, secondarily, a higher insulin requirement.
- Exercise improves glucose uptake partly through insulin-independent mechanisms, which is why it has exceptional pathophysiological significance.

Muscle in T2DM

- ↓ GLUT4
- ↓ glycogen synthesis
- ↑ lipid intermediates
- preserved response to exercise

why physical activity has an effect even in marked insulin resistance

Hepatic Insulin Resistance

Why fasting glycemia is elevated

- Under normal insulin action, the liver suppresses gluconeogenesis and glycogenolysis.
- In hepatic insulin resistance, the liver continues to produce glucose even in situations when it should be “switched off.”
- Important contributing factors are the supply of substrates from lipolysis and proteolysis, hyperglucagonemia, and steatotic overload of the liver.
- Selective hepatic insulin resistance helps explain parallel hyperglycemia together with persistent lipogenesis.
- Clinically, this leads to elevated fasting glycemia, MASLD, and impaired metabolic flexibility.

Liver in T2DM

↑ gluconeogenesis

↑ glycogenolysis

hyperglucagonemia

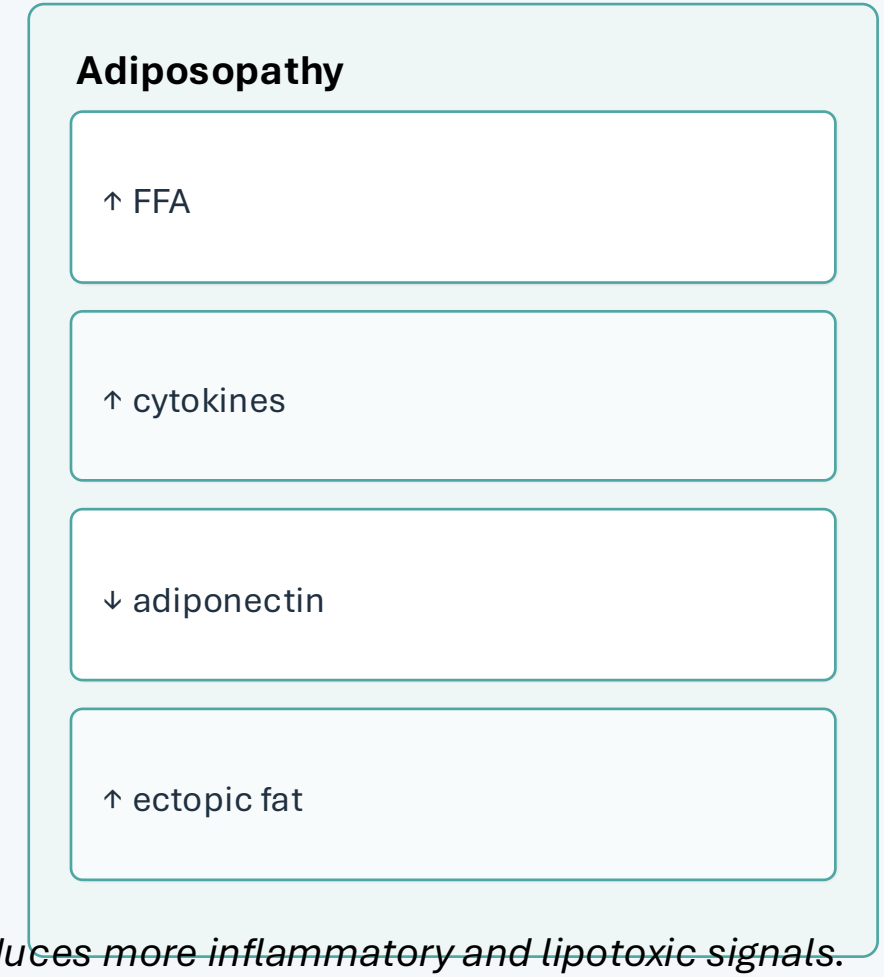
steatosis and de novo lipogenesis

Metformin primarily targets hepatic glucose production – its therapeutic relevance follows directly from the pathophysiology.

Dysfunction of Adipose Tissue and Adiposopathy

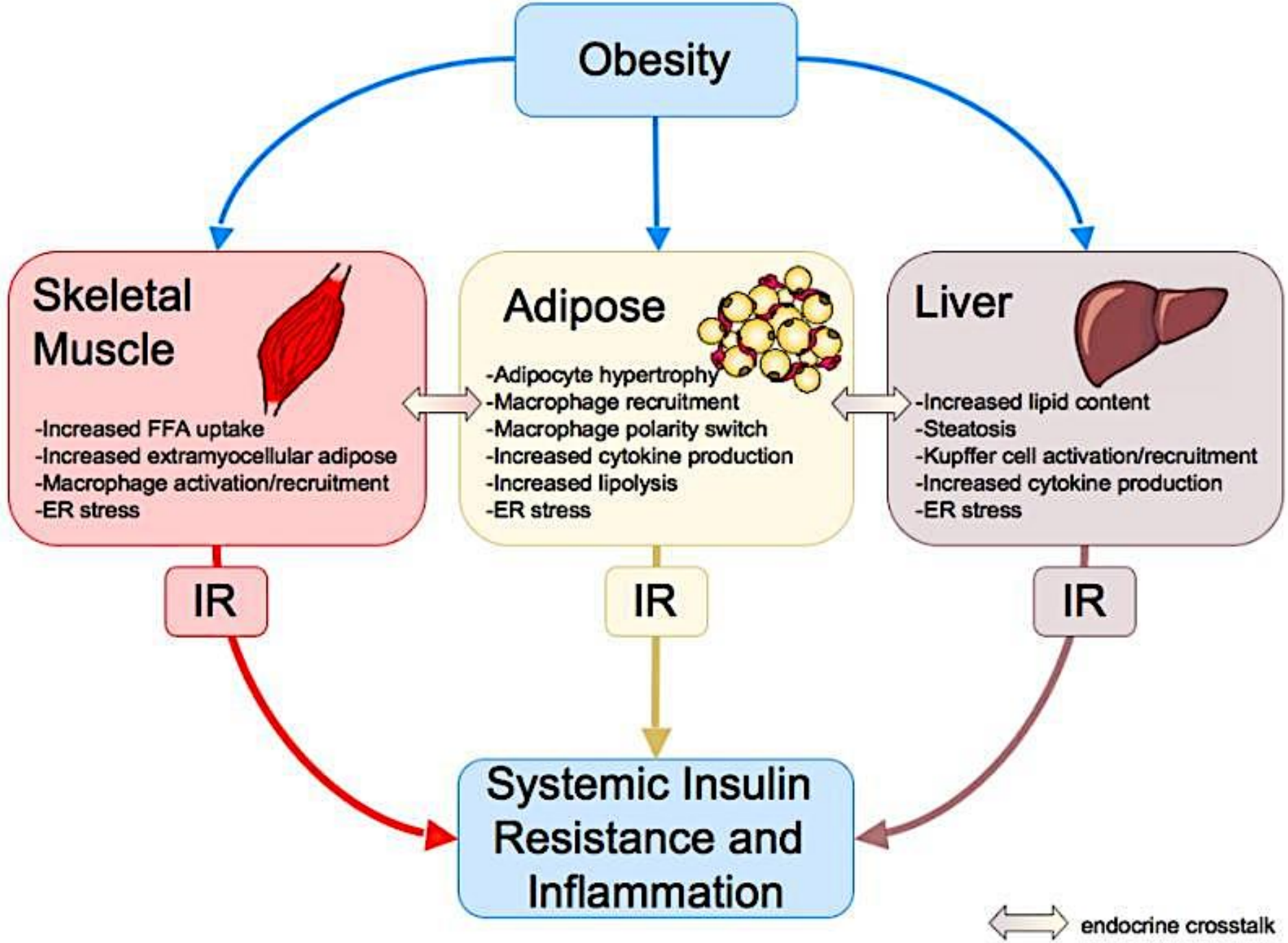
Fat as an endocrine and inflammatory organ

- Visceral adipose tissue is not an inert energy store; it is an active endocrine and immunologic organ.
- With adipocyte hypertrophy, lipolysis increases, along with the release of free fatty acids, TNF-α, IL-6, and other inflammatory mediators.
- The protective effect of adiponectin decreases, and the storage of fat in a “safe” depot worsens.
- Excess energy is then redistributed ectopically to the liver, muscles, pancreas, and heart.
- Adiposopathy explains why the quality and distribution of fat may be more important than BMI alone.



Visceral fat is metabolically more dangerous than subcutaneous fat because it produces more inflammatory and lipotoxic signals. Adiposopathy is the mechanistic bridge between obesity and diabetes and the reason why reducing visceral fat leads to improved insulin sensitivity.

Visceral adiposity correlates with metabolic risk better than total body weight alone.


Obesity
Skeletal Muscle
-Increased FFA uptake
-Increased extramyocellular adipose
-Macrophage activation/recruitment
-ER stress
Adipose
-Adipocyte hypertrophy
-Macrophage recruitment
-Macrophage polarity switch
-Increased cytokine production
-Increased lipolysis
-ER stress
Liver
-Increased lipid content
-Steatosis
-Kupffer cell activation/recruitment
-Increased cytokine production
-ER stress
IR
IR
IR
Systemic Insulin Resistance and Inflammation
endocrine crosstalk

β-Cell Failure and Incretin Dysfunction

Why compensation is no longer sufficient

- At first, the β-cell tries to compensate for insulin resistance with hyperinsulinemia, but later its functional reserve becomes exhausted.
- Glucotoxicity, lipotoxicity, amyloid deposition, oxidative stress, ER stress, and β-cell dedifferentiation all contribute.
- The incretin effect is weakened in T2DM; postprandial insulin secretion is inadequate and the glucagon response is insufficiently suppressed.
- Relative hyperglucagonemia further promotes hepatic glucose production.
- When β-cell compensation fails, the transition from insulin resistance to overt diabetes occurs.

Points of β-cell failure

- first-phase secretion disappears
- inkretínový efekt slabne
- glucagon is not suppressed
- progressive insulinopenia

GLP-1 receptor agonists and dual incretin drugs improve some of these mechanisms precisely because they target the incretin and satiety axis.

Long-standing T2DM often involves more marked insulinopenia than is clinically assumed.

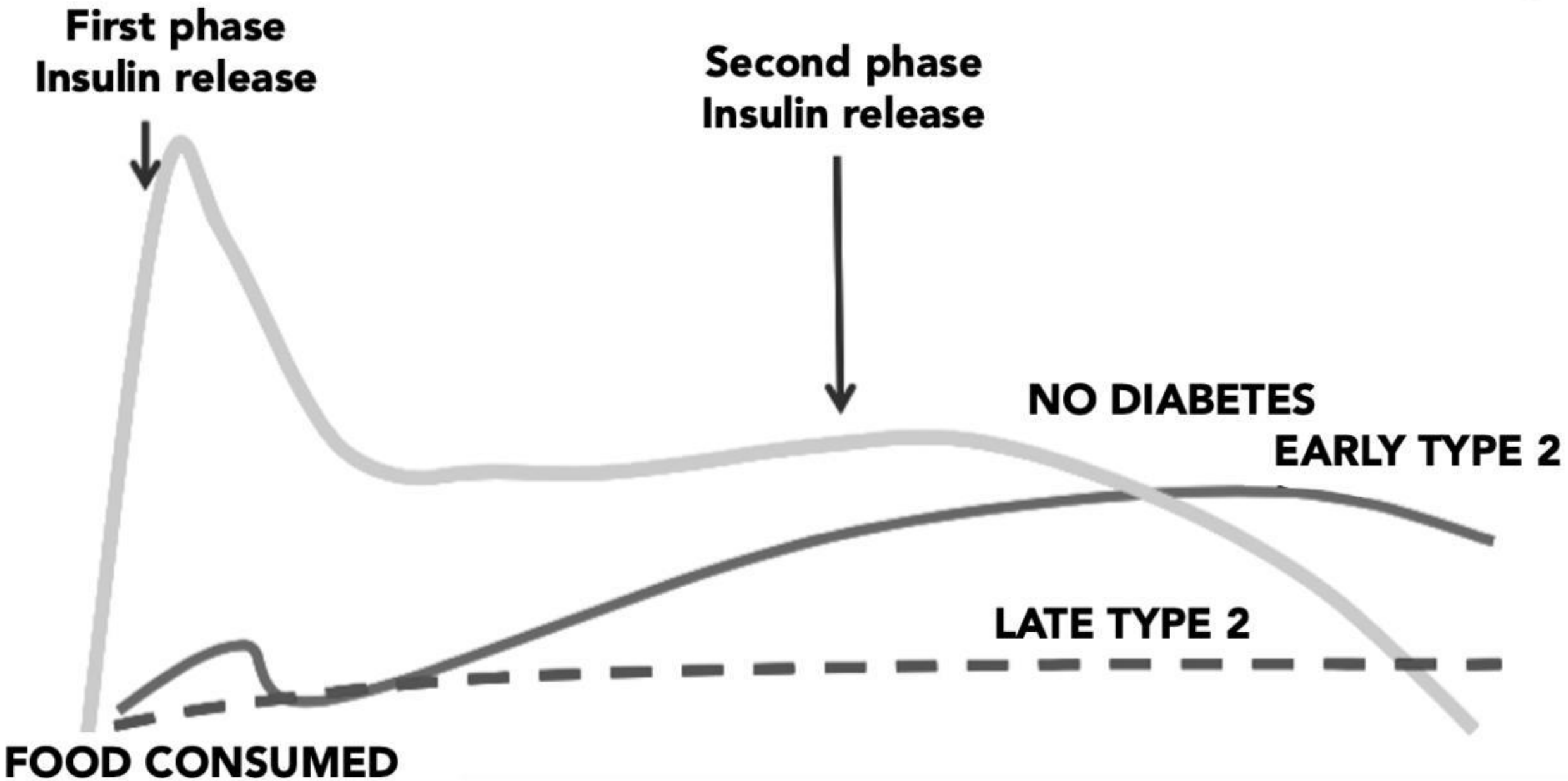
β-Cell Dysfunction

Mechanisms:

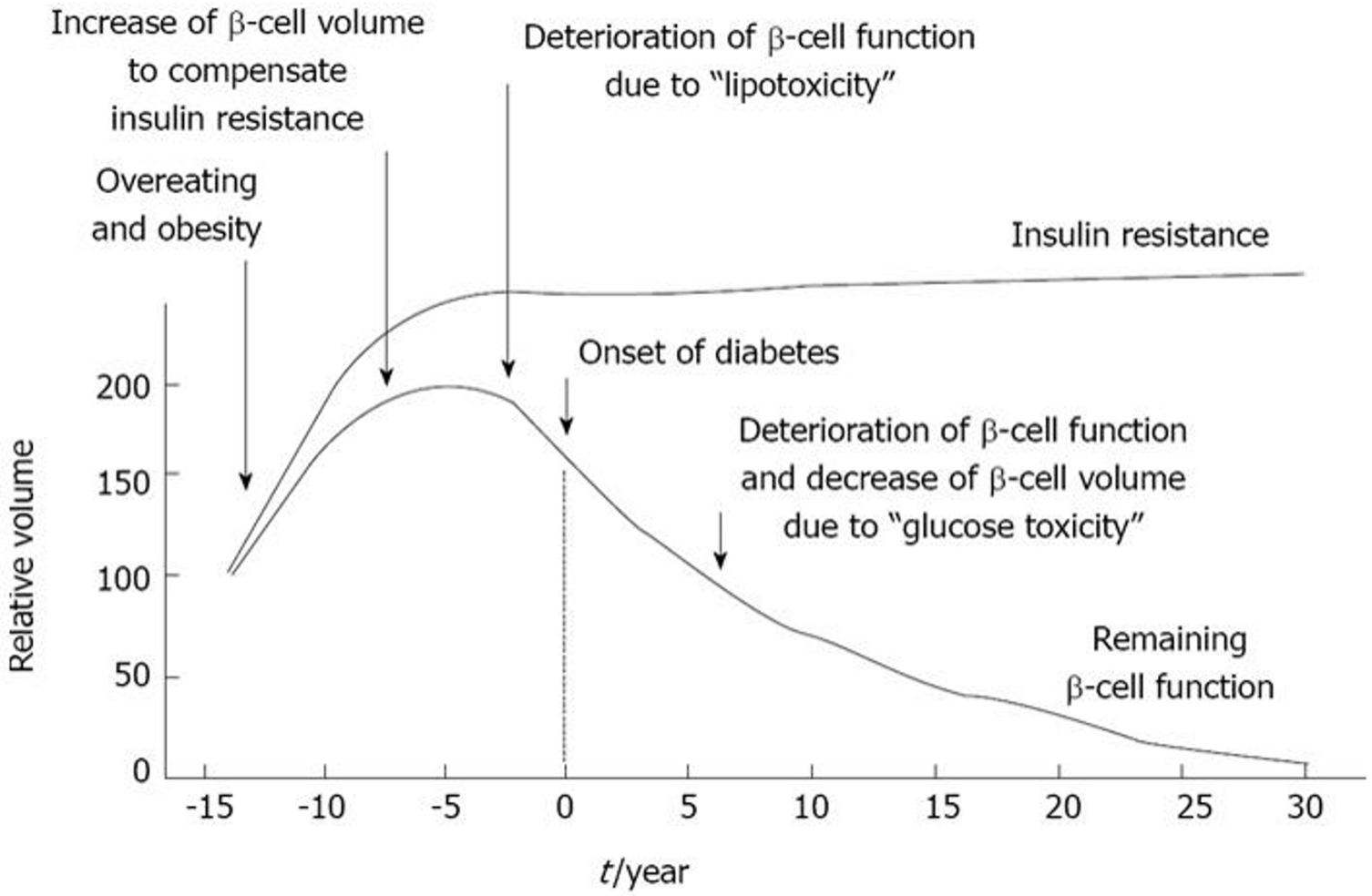
- glucotoxicity
- lipotoxicity
    - oxidative stress
    - amyloid (IAPP) deposition in the islets

Progressively:

- ↓ insulin secretion
- loss of first-phase secretion


First phase
Insulin release
Second phase
Insulin release
NO DIABETES
EARLY TYPE 2
LATE TYPE 2
FOOD CONSUMED

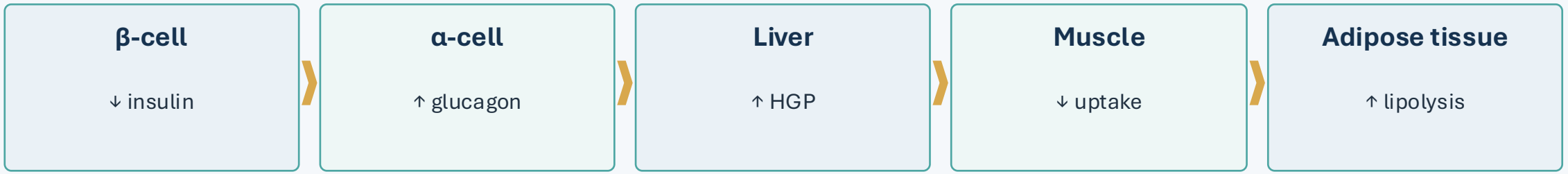
Typical course of type 2 diabetes.
The development of type 2 diabetes is associated with dysfunction of pancreatic β-cells and insulin resistance. Overeating and/or obesity lead to the development of insulin resistance, and normal β-cells secrete larger amounts of insulin to compensate for the increased insulin resistance. Subsequently, large adipocytes release greater amounts of free fatty acids and/or various inflammatory cytokines, which progressively worsen β-cell function and ultimately lead to the onset of diabetes. This process is known as **β-cell lipotoxicity**. Once hyperglycemia appears, β-cell function progressively deteriorates; insulin biosynthesis and secretion decline. This process is known as **β-cell glucotoxicity**, which is often observed in type 2 diabetes.



World J Diabetes 2013; 4(6): 263-269

“Ominous Octet” in Modern Interpretation

T2DM goes beyond the pair of insulin resistance + β-cell failure



Additional players are the **gut, kidneys, and CNS** – which is why modern therapy targets more than one organ at a time.
From Octet to "Egregious Eleven": also inflammation, immune system dysfunction, and imbalance of the gut microbiota.

T2DM is not a linear disorder, but a network dysregulation. That is why monotherapy often fails over time, and combination treatment makes biological sense.

Genetics, Environment, Youth-Onset T2DM, and Pregnancy

Same phenotype, different entry pathways

Genetics and environment

- Polygenic predisposition modulates both β-cell susceptibility and insulin sensitivity.
- Urbanization, sedentary lifestyle, energy-dense diet, sleep deprivation, and social determinants alter risk exposure.
- Epigenetic changes may explain the intergenerational transmission of risk.

Youth-onset T2DM and GDM

- T2DM in adolescents tends to be more aggressive, with a faster decline in β-cell function.
- In pregnancy, placental hormones increase insulin resistance; if the β-cell fails to compensate, gestational diabetes develops.
- GDM increases the risk of T2DM in the mother as well as metabolic risk in the offspring.

T2DM and GDM are biologically interconnected through insulin resistance, β-cell reserve, and fetal programming.

Gestational DM and Diabetes Detected During Pregnancy

- The **WHO distinguishes between gestational diabetes mellitus** and **diabetes in pregnancy**.
- **Gestational diabetes** means hyperglycemia above normal, but below the diagnostic threshold for overt diabetes.
- **“Diabetes in pregnancy”** refers to a situation in which the diagnostic criteria for diabetes mellitus as such are already met during pregnancy.
- This distinction is also important prognostically, because women after gestational diabetes have an increased risk of subsequent development of **type 2 diabetes**.

Other Specific Types of Diabetes

- **monogenic diabetes** – rarer forms caused by a change in a single gene. Clinically, the most important forms are **MODY** and **neonatal diabetes mellitus**. They are often mistakenly classified as type 1 or type 2 diabetes, although the correct genetic diagnosis can fundamentally change both treatment and prognosis.
- **diabetes due to damage to or removal of the pancreas**. It develops in pancreatitis, cystic fibrosis, after surgical removal of the pancreas, or in other pancreatic diseases. The pathomechanism is that the damaged pancreas produces less insulin, which leads to hyperglycemia. For a dentist, it is important to consider this group especially in polymorbid patients with a gastroenterological or surgical history.

Other Specific Types of Diabetes and Mechanisms of Acute Decompensation

Thinking mechanistically means not overlooking unusual diabetes

Other specific types

- **Monogenic forms (MODY)** – a β-cell disorder with a typical familial pattern.
- **Pancreatogenic diabetes** – after pancreatitis, resection, cystic fibrosis, or pancreatic tumor.
- **Endocrinopathies and drugs** – glucocorticoids, Cushing syndrome, acromegaly, transplantation.

Hypoglycemia and HHS

- **Hypoglycemia** is the result of a relative or absolute excess of insulin in relation to the current needs of the tissues (neuroglycopenia and the autonomic response are key pathophysiological phenomena).
- **HHS** develops in severe hyperglycemia and dehydration, when residual insulin still prevents massive ketogenesis.
- Neurological symptoms in **HHS** are caused mainly by hyperosmolality.

If the clinical picture does not "fit," the diabetes classification and precipitating factors should be reassessed.

Type 5 Diabetes – a New Entity

- the international recognition of **type 5 diabetes** – according to the IDF, this is diabetes associated with **chronic undernutrition**, especially in childhood and adolescence, followed by insufficient pancreatic development. Pathomechanistically, it is neither a typical autoimmune process as in type 1 diabetes nor predominantly insulin resistance as in type 2 diabetes; rather, the core problem is **insulin deficiency caused by underdeveloped pancreatic tissue**.
- this form is typically described in **lean adolescents and young adults** in low- and middle-income countries. IDF diagnostic criteria have not yet been standardized, and that is why, in 2025, a working group was established to develop formal recommendations. It is therefore a **new and relevant, but still methodologically unfinished classification category**.

Prediabetes

- **clinically significant**, an intermediate stage between normal glucose homeostasis and diabetes
- pathophysiologically, it most often represents an early manifestation of insulin resistance and an insufficient compensatory response of β-cells
- the **WHO** explicitly identifies **impaired fasting glycaemia** and **impaired glucose tolerance** as intermediate states associated with an increased risk of progression to **type 2 diabetes**

Diagnostic Criteria

- According to the **ADA 2026**, diabetes can be diagnosed on the basis of **HbA1c** or **plasma glucose**. The basic thresholds include **fasting glucose ≥ 126 mg/dL (7.0 mmol/L)**, **2-hour glucose during a 75 g OGTT ≥ 200 mg/dL (11.1 mmol/L)**, **HbA1c ≥ 6.5%**, or **random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)** in the presence of typical symptoms of hyperglycemia or a hyperglycemic crisis.
- For **prediabetes**, the ADA states a **fasting glucose of 100–125 mg/dL (5.6–6.9 mmol/L)**.

Relevance for Dentistry

- diabetes — also as a **disease with significant oral manifestations** — is associated with a higher risk of **periodontitis**, slower healing, **xerostomia**, and **candidiasis**. Elevated blood glucose and dry mouth additionally increase the risk of caries and infectious complications
- the relationship between diabetes and periodontal disease is bidirectional: poor periodontal health may make glycemic control more difficult
- in cases of recurrent periodontitis, impaired healing after extractions, frequent fungal infections, or marked xerostomia, the dentist should also consider a possible disorder of glucose metabolism
- in outpatient practice, the aim is not to establish the diagnosis of diabetes, but to correctly identify the at-risk patient and refer them early for internal medicine or diabetology assessment

Conclusion

- **Diabetes mellitus is not a single disease, but a group of pathophysiologically distinct conditions** that lead to the common phenotype of chronic hyperglycemia.
- The classical classification into **type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types** remains the foundation of clinical thinking in 2026. A new element is **type 5 diabetes**, which reflects the importance of undernutrition and global health inequalities in the pathogenesis of diabetes.
- For **dentistry**, it is essential to understand that diabetes significantly affects **periodontal status, healing, and infectious morbidity in the oral cavity**, and therefore belongs among the diagnoses that a dentist must always keep in mind.

Diabetes mellitus – pathophysiological summary

Key problem: chronic hyperglycemia
→ the result of **impaired insulin secretion, impaired insulin action, or both**

1. Pancreatic β-cell dysfunction

- ↓ insulin secretion (**absolute** in **T1DM**, **relative** in **T2DM**)
- glucotoxic and lipotoxic effects
- loss of insulin pulsatility

2. Insulin resistance (mainly T2DM)

- **muscle:** ↓ glucose utilization
- **liver:** ↑ gluconeogenesis
- **adipose tissue:** ↑ lipolysis → ↑ FFA

3. Dysregulation of other organs ("ominous octet")

- ↑ glucagon (**α-cells**)
- ↓ incretin effect (**GLP-1, GIP**)
- ↑ renal glucose reabsorption (**SGLT2**)
- **CNS:** impaired appetite regulation
- **adipose tissue:** adipokines, inflammation

Conclusion

4. Consequences of hyperglycemia

- non-enzymatic glycation (**AGEs**)
- polyol pathway (**sorbitol**)
- oxidative stress
- PKC activation

5. Clinical consequence

- **microangiopathy:** retinopathy, nephropathy, neuropathy
- **macroangiopathy:** accelerated atherosclerosis

Take-home message

👉 Diabetes mellitus = a **multiorgan metabolic disease**, not just “high blood sugar”

👉 Treatment must target **multiple pathophysiological mechanisms**

Chronic Complications

Shared mechanisms, distinct organ-specific phenotypes of damage.

- **endothelium, oxidative stress, and AGEs**
- **microvascular vs. macrovascular complications**
- **why complications begin earlier than we detect them clinically**

Pathophysiological mechanisms of chronic diabetic complications

Chronic diabetic complications arise as a consequence of **long-term hyperglycemia, glycemic variability**, and in type 2 diabetes also **insulin resistance, lipotoxicity, and chronic subclinical inflammation**. Their common denominator is the **overproduction of reactive oxygen species (ROS)** and the subsequent activation of multiple damaging metabolic pathways.

Main mechanisms:

- **Polyol pathway:** excess glucose is converted into sorbitol, NADPH is consumed, the cell's antioxidant capacity declines, and osmotic as well as oxidative stress increase.
- **Formation of AGEs and activation of RAGE receptors:** non-enzymatic glycation of proteins, lipids, and nucleic acids leads to impaired protein function, cross-linking of the extracellular matrix, inflammation, and endothelial damage.
- **PKC activation:** alters vascular permeability, vasomotor function, cytokine production, leukocyte adhesion, angiogenesis, and contributes to microvascular injury.
- **Hexosamine pathway:** changes gene expression and promotes pro-inflammatory and pro-fibrotic responses.
- **Oxidative stress, mitochondrial dysfunction, and inflammation:** these processes link the pathways above and lead to endothelial dysfunction, fibrosis, and progression of organ damage.
- The **key vascular consequence is endothelial dysfunction**: nitric oxide (NO) bioavailability decreases, vascular wall permeability increases, pro-inflammatory and prothrombotic mechanisms are activated, basement membranes thicken, and microcirculation worsens.
- At the same time, the phenomenon of **metabolic memory** also plays a role, meaning that damage may persist even after later improvement in glycemic control.

Shared Mechanisms of Diabetic Complications

One hyperglycemia, multiple damaging pathways

- Chronic hyperglycemia increases flux through the polyol pathway, AGE formation, PKC activation, and the hexosamine pathway.
- The result is oxidative stress, endothelial dysfunction, a pro-inflammatory milieu, and microcirculatory damage.
- The synergistic effect of hypertension, dyslipidemia, albuminuria, smoking, and a procoagulant state is also important.
- “Metabolic memory” explains why early good control provides long-term benefit even years later.
- Complications do not develop in isolation; patients often have both microvascular and macrovascular damage simultaneously.

Main damaging pathways

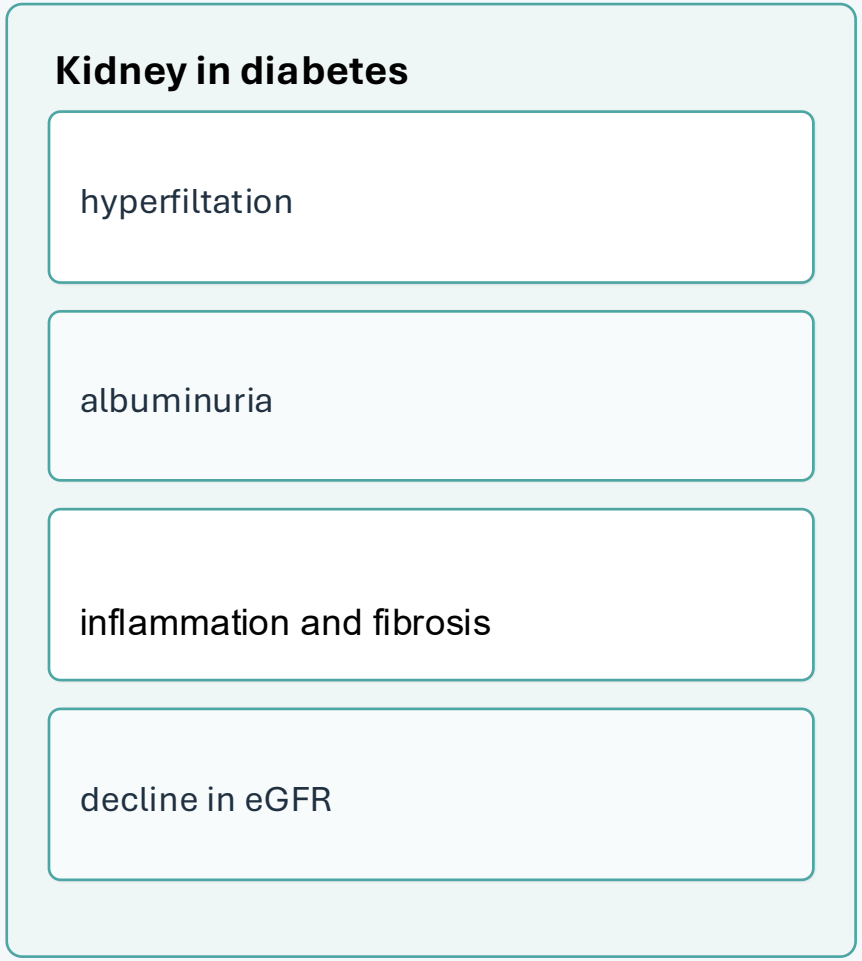
- AGE
- PKC
- oxidative stress
- endothelial dysfunction

Hyperglycemia is important, but by itself it is not enough — risk is determined by the overall cardiometabolic-renal profile.

Diabetic Kidney Disease (DKD)

Glomerular hyperfiltration, inflammation, fibrogenesis

- An early change may be **glomerular hyperfiltration** and **intraglomerular hypertension**.
- **Hyperglycemia, RAAS activation, tubuloglomerular dysregulation, and SGLT2-dependent reabsorption** promote progression of kidney damage.
- This is followed by **albuminuria, decline in eGFR, tubulointerstitial inflammation, and fibrogenesis**.
- DKD is not just a glomerulopathy; it is a **combined glomerular, tubular, vascular, and inflammatory injury**.
- Therefore, kidney protection is linked to **glycemic control, blood pressure control, RAAS blockade, and today also SGLT2 inhibitors and other nephroprotective strategies**.



The mechanism of action of SGLT2 inhibitors can be very well explained through tubuloglomerular feedback.

Diabetic Retinopathy

Microvascular and neurodegenerative damage of the retina

- Chronic hyperglycemia leads to **pericyte loss**, **damage to the capillary wall**, and **increased permeability of the blood-retinal barrier**.
- **Microaneurysms, ischemic areas, edema**, and in advanced stages **pathologic neovascularization driven by VEGF signaling** develop.
- Retinopathy is not only a vascular disease; **neurodegeneration and gliosis** are also present.
- Risk increases with **duration of diabetes, hyperglycemia, hypertension, pregnancy, and renal impairment**.
- **Rapid correction of glycemia** may transiently worsen the retinal findings, so patients should be monitored carefully.

Retina in diabetes

pericytes ↓ (capillary damage)

barrier damaged (increased permeability of the blood-retinal barrier)

ischemia + VEGF

edema / neovascularization

Clinical pearl: microvascular complications are often asymptomatic until they are advanced.

Diabetic Neuropathy and Diabetic Foot

Nerve, microcirculation, immunity, and mechanical load

- **Peripheral neuropathy** develops through the effects of **hyperglycemia, dyslipidemia, oxidative stress, mitochondrial dysfunction, and nerve ischemia**.
- **Loss of sensation** increases the risk of **unnoticed microtrauma, deformities, pressure injury, and ulceration**.
- **Autonomic neuropathy** impairs **sweating, vasomotor function, GI motility, sexual function, and cardiovascular response**.
- In **diabetic foot**, **neuropathy, ischemia, impaired healing, and increased susceptibility to infection** act together.
- Prevention is based on **control of risk factors, regular foot examinations, and early detection of ulceration**.

Path to ulceration

sensory loss

deformity / pressure

impaired healing

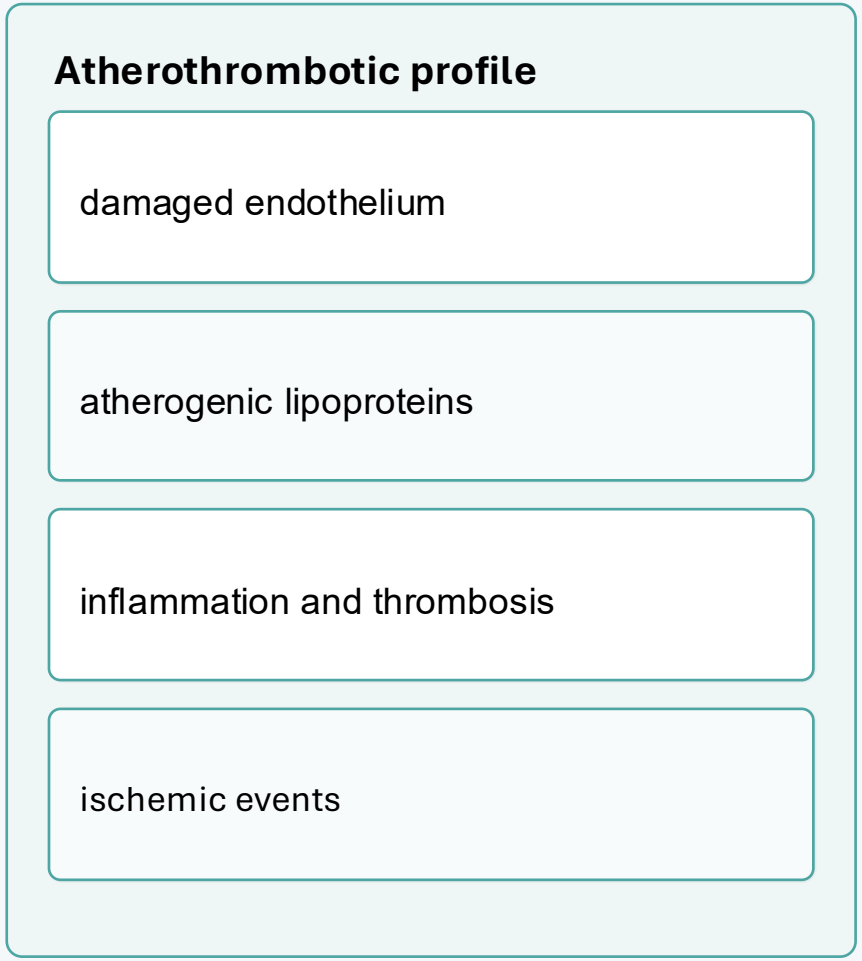
infection and amputation

Diabetic foot is a syndrome, not an isolated skin lesion.

Macrovascular Disease in Diabetes

Atherosclerosis, thrombosis, and endothelial dysfunction

- Diabetes accelerates atherogenesis through a combination of **hyperglycemia, dyslipidemia, inflammation, endothelial dysfunction, and a procoagulant state**.
- Typical is **atherogenic dyslipidemia**: **high triglycerides, low HDL, and a higher proportion of small dense LDL particles**.
- **Chronic hyperinsulinemia and insulin resistance** promote **hypertension, sympathetic activation, and vascular stiffness**.
- The result is a **higher risk of ischemic heart disease, stroke, peripheral arterial disease, and sudden death**.
- Therefore, modern diabetes management targets not only **HbA1c**, but also **blood pressure, lipids, body weight, and renal risk**.



People with diabetes most often do not die from hyperglycemia itself, but from its organ complications.

Heart Failure, MASLD, Infections, and Cognition

Diabetes is a disease of organ vulnerability

Cardio-hepatic consequences

- Diabetes increases the risk of **heart failure** even without proven **ischemic heart disease (IHD)**.
- **Diabetic cardiomyopathy**, impaired **myocardial energetics**, and **interstitial fibrosis** may contribute.
- **MASLD** represents the **hepatic phenotype of systemic insulin resistance**.

Immunity and the CNS

- Hyperglycemia impairs **neutrophil function**, **wound healing**, and **host defense against infection**.
- There is a higher risk of a more severe course of **skin infections, urinary tract infections, and systemic infections**.
- Long-term **dysglycemia** is also associated with **cognitive decline** and **cerebral vascular injury**.

In modern diabetes management, we must think beyond the "classic triad" of complications.

Pregnancy, Placenta, and Fetal Programming

Why diabetes in pregnancy matters for two generations

Pregnancy shows how the mother's metabolic environment shapes the child's future risk.

- **Maternal hyperglycemia** increases **fetal glucose exposure**; the fetus responds with **hyperinsulinemia** and a **growth stimulus**.
- The result may be **macrosomia, shoulder dystocia, neonatal hypoglycemia, and metabolic vulnerability**.
- In **pregestational diabetes**, the risk of **congenital malformations** increases if glycemic control during **organogenesis** is poor.
- The **placenta** is an active endocrine organ that increases **maternal insulin resistance** in the second half of pregnancy.
- **GDM** is a marker of future **diabetes** and **cardiometabolic risk** for both the mother and the offspring.

Mother – placenta – fetus

maternal insulin resistance

glucose crosses the placenta

fetal hyperinsulinemia

growth and postnatal consequences

Transgenerational effect – maternal insulin does **not** cross the placenta, but **glucose does**. The fetus therefore responds with its **own insulin**, which promotes **growth and fat deposition**. In **pregestational diabetes** with poor glycemic control during **organogenesis**, there is also an increased risk of **malformations**.

Treatment Linked to Pathophysiology

Therapy is most effective when it targets the dominant mechanism of disease.

- **body weight and energy balance**
- **drug selection according to organ involvement and risk**
- **technology and hospital care**

Organ- or process-based therapy: liver, kidney, incretin axis, insulin deficiency, body weight, cardiorenal risk.

Lifestyle and Weight Reduction as Pathophysiological Treatment

Energy balance is an upstream intervention

- Weight reduction decreases **visceral adiposity**, **ectopic fat in the liver and pancreas**, and improves **insulin sensitivity**.
- Physical activity improves **glucose utilization in muscle**, **cardiorespiratory fitness**, **blood pressure**, and **lipid profile**.
- Dietary interventions may differ, but the key factors are **long-term energy deficit** and **sustainability**.
- In some patients, intensive weight reduction may lead to **remission of T2DM**, especially when the disease duration is shorter.
- Pathophysiologically, this is an intervention at the very **source of metabolic overload**, not merely a symptomatic correction of glycemia.

What improves after weight loss

- visceral fat ↓
- liver fat ↓
- insulin sensitivity ↑
- β-cell burden ↓

Weight reduction does not act only through lower caloric intake, but biologically changes the **flux of substrates between organs**. The supply of **free fatty acids** falls, **hepatic steatosis** decreases, and the **β-cell** is less forced into **hypersecretory compensation**.

Remission of T2DM is not a "cure," but evidence that part of the pathophysiology is reversible.

Antidiabetic Drug Classes by Mechanism of Action

Do not memorize as a list — link each class to the organ and the pathophysiology

Class	Main mechanism	Pathophysiological rationale
Metformin	reduction of hepatic glucose production	targets the liver and fasting glycemia
GLP-1 RA / dual incretins	incretin effect, satiety, weight loss, ↓ glucagon	β-cell, CNS, body weight, cardiometabolic benefit
SGLT2 inhibitors	glycosuria, natriuresis, tubuloglomerular effect	kidney, heart failure, CKD
Sulfonylureas / meglitinides	stimulation of insulin secretion	useful in insulin deficiency, but with higher risk of hypoglycemia
Thiazolidinediones	improvement of insulin sensitivity via PPARγ	mainly targets peripheral resistance
Insulin	replacement of absolute or relative deficiency	essential in T1DM and in advanced insulin deficiency

Which organ does it act on, which defect does it correct, and what additional organ benefits does it bring? Modern algorithms are no longer strictly glucocentric. For example, **SGLT2 inhibitors** or **GLP-1 receptor agonists** are chosen also because of their benefits for the **heart, kidneys, and body weight**.

Today, drug selection is guided not only by HbA1c, but also by ASCVD, HF, CKD, body weight, risk of hypoglycemia, and patient preference.

Insulin as Physiological Replacement

Basal, prandial, and correction component

- In **T1DM**, insulin is a **life-saving hormonal replacement therapy**; in **T2DM**, it is added in **progressive insulin deficiency** or during **acute decompensation**.
- **Basal insulin** covers **hepatic glucose production** between meals and overnight.
- **Prandial insulin** is intended to mimic **rapid postprandial secretion** and suppress **post-meal glucose excursions**.
- **Incorrect timing** or an **inappropriate dose ratio** leads to **hyperglycemia, hypoglycemia, and increased glycemic variability**.
- **Educational key point:** insulin should be understood as a **dynamic system** linked to **food intake, physical activity, illness, and stress**.

Physiological model

- basal requirement
- meal boluses
- correction doses
- insulin sensitivity changes over time

The most common mistake is teaching insulin only as a "dose," rather than as a physiological model.

CGM, Insulin Pumps, and AID Systems

Technology changes not only monitoring, but also the pathophysiological control of the disease.

- **Continuous glucose monitoring (CGM)** makes it possible to capture **time in range, variability, and hidden hypoglycemia**.
- **Insulin pumps and hybrid closed-loop systems** improve insulin dosing according to the **real-time glucose trend**.
- In **T1DM**, technology today targets not only **HbA1c**, but above all the **reduction of variability and hypoglycemia**.
- Current recommendations are expanding the **early use of CGM and AID** to broader groups of insulin-treated patients.
- Pathophysiologically, this is an attempt to bring treatment closer to the **dynamics of a healthy β-cell**, which no static regimen can perfectly replace.

What technology brings

- trend, not just a single value
- time in range
- fewer hypoglycemic episodes
- adaptive dosing

It is no longer just about "prescribing insulin," but about managing a dynamic system.

Current ADA 2026 recommendations emphasize broader availability of CGM/AID earlier in the course of the disease.

Stress Hyperglycemia and Diabetes in the Hospital

Acute illness changes both insulin requirements and the risk profile

- **Acute stress, sepsis, myocardial infarction, surgery, and glucocorticoids** increase levels of **counterregulatory hormones** and **insulin resistance**.
- Even a patient **without known diabetes** may develop **significant hyperglycemia** in the hospital; this worsens treatment outcomes and prognosis.
- The goal of inpatient treatment is to avoid extremes — both **severe hyperglycemia** and **hypoglycemia**.
- In the **perioperative setting**, during **NPO status**, and in the **ICU**, one must account for changing **insulin and fluid requirements**.
- **DKA** and **HHS** are emergency conditions requiring a **protocolized approach** with emphasis on **volume resuscitation, electrolytes, and insulin**.

Inpatient dynamics

stress hormones ↑

insulin requirement ↑

NPO / steroids / infection

risk of hypoglycemia as the condition improves

Hospital diabetology is physiology in fast motion.

Case Study 1: Presentation of T1DM in a Young Patient

How to infer the mechanism from the symptoms

History and findings

- 19-year-old man
- 2 weeks of polyuria, polydipsia, 6 kg weight loss
- nausea, vomiting, acetone breath
- tachycardia, dry mucous membranes

Laboratory

- glucose 26 mmol/L
- pH 7.12; HCO_3^- 9 mmol/L
- ketones positive
- K+ 5.1 mmol/L, but total body deficit likely

Discussion questions

- Which hormone is absolutely deficient?
- Why is acidosis present?
- Why is serum K+ sometimes normal/high?
- What will be the first three treatment steps?

Absolute insulin deficiency triggered lipolysis and ketogenesis; acidosis together with hyperglycemia caused osmotic diuresis and dehydration; serum potassium is misleading because total body stores are depleted. Proposed approach: fluids, monitoring and correction of electrolytes, insulin.

Case Study 2: T2DM with Cardiorenal-Metabolic Risk

We are not determining only the "sugar," but the dominant axes of damage

History and findings

- 62-year-old woman, BMI 34 kg/m²
- hypertension, dyslipidemia, MASLD, NYHA II dyspnea
- albuminuria, eGFR 58 ml/min/1.73 m²
- HbA1c 8.4%

Pathophysiological axes

- visceral adiposity and insulin resistance
- hepatic glucose production
- renal and cardiac risk
- probable progressive β-cell insufficiency

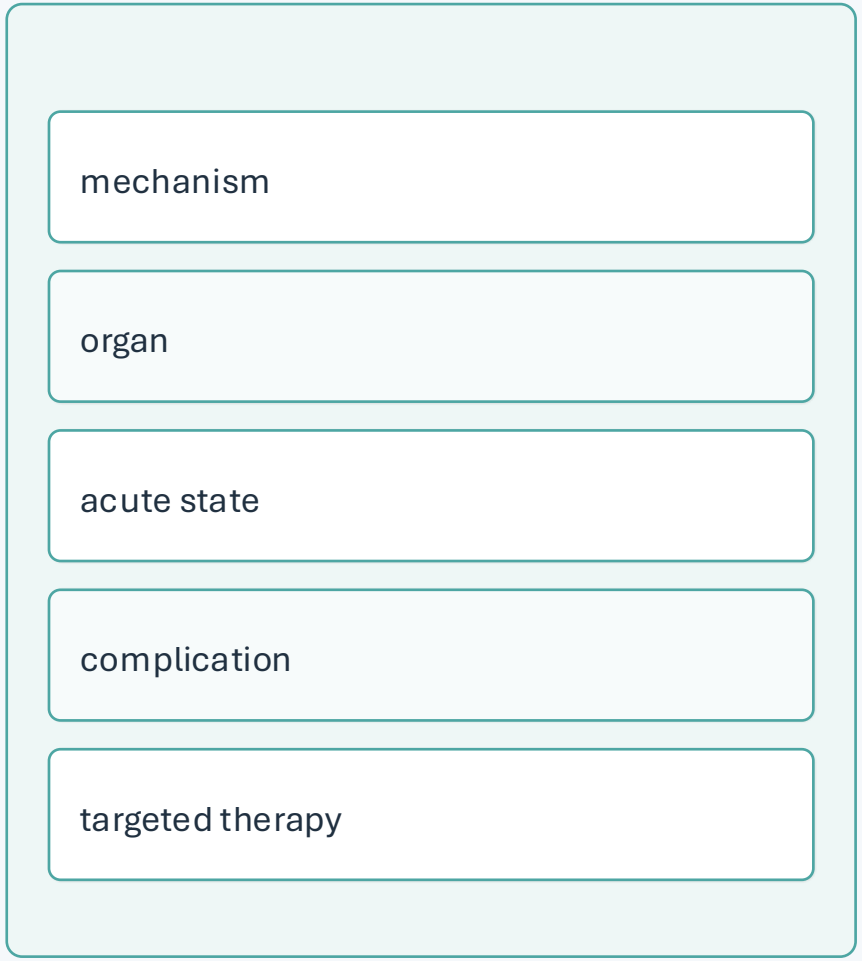
Discussion questions

- Which organs should be protected as a priority?
- Which drug classes have an organ-protective rationale?
- Why is it not enough to "just lower HbA1c"?
- How would you explain the role of weight reduction?

The priority is organ protection, weight reduction, and a drug with benefit for the heart/kidney.

Take-home Messages

- **T1DM** = autoimmune loss of **β-cells** and absolute **insulin deficiency**; **T2DM** = a combination of **insulin resistance** and progressive **β-cell failure**.
- **Fasting glycemia** is strongly linked to the **liver**; **postprandial glycemia** to the **β-cell, incretins, and muscle**.
- **DKA** results from absolute **insulin deficiency**; **HHS** from severe **hyperglycemia** and **dehydration** with preserved residual inhibition of **ketogenesis**.
- **Microvascular** and **macrovascular complications** share common mechanisms, but each organ has its own phenotype of injury.
- Modern treatment of diabetes is **cardiorenal-metabolic** and **pathophysiology-targeted**, not merely **glucocentric**.



Selected Recommended Sources

Primary texts for further study and lecture preparation

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Teplizumab and Diabetes Mellitus – Anti-CD3 (T Lymphocytes) – “Immune Reset”

- modern immunomodulatory treatment intended for **T1DM**
- this is **not** a classic antidiabetic treatment (like insulin), but an intervention targeting the **autoimmune process itself**
- **Teplizumab** is a monoclonal antibody against the **CD3 receptor on T lymphocytes**:
  - modulates T-cell activity → “exhaustion” of autoreactive **CD8+** cells + ↑ **Treg**
  - suppresses autoimmune destruction of pancreatic **β-cells**
  - promotes the development of **regulatory T lymphocytes**

👉 **Goal:** to slow or delay the onset of clinical diabetes
delay of T1DM manifestation (~2–3 years)
preservation of **C-peptide**

Stage: mainly **preclinical (stage 2)**
Status: ✓ approved (**FDA, also EU 2026**)
👉 so far the **only therapy with a real preventive effect**

Teplizumab and Diabetes Mellitus

🧪 Indication

Used in:

- individuals at **high risk of developing T1DM** (positive autoantibodies + impaired glucose tolerance)
- the so-called **preclinical stage of diabetes (stage 2)**

  👉 Approved, for example, in the **USA (FDA)** to **delay the onset of T1DM**

⏳ Effect

Clinical studies have shown:

- a delay in the onset of **T1DM** by an average of **~2–3 years**
- in some patients, even longer

Immunotherapies of type 1 diabetes mellitus

Therapy	Target	Effect on disease course	Duration of effect	Clinical significance
Teplizumab	**T lymphocytes (CD3)**	★★★★ delay of DM onset	years	✓ greatest
Abatacept	T-cell activation	★★	temporary	adjunctive
Rituximab	B lymphocytes	★★	short-term	combination use
Anti-thymocyte globulin	T lymphocytes (depletion)	★★★★	intermediate	effective, but more toxic
Cytokines	inflammation	★	weak	experimental
GAD vaccines	antigen	★	uncertain	research

What's New in the Treatment of Type 2 Diabetes

- **Awiqli®** (*insulin icodec-abae*) is an innovative drug from **Novo Nordisk** that was approved by the **U.S. FDA** in **March/April 2026** as the **first and only basal insulin administered once weekly**.
- **Tirzepatide** (brand name **Mounjaro**) is a dual **GIP and GLP-1 receptor agonist**, which reduces appetite and regulates metabolism. It is administered as a **once-weekly injection**. Studies suggest **greater efficacy for weight loss than semaglutide**.