

Diabetes Mellitus

Pathogenesis · diagnostic classification · metabolic physiology

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Learning outcomes

- Explain how defects of insulin secretion and action produce hyperglycemia.
- Describe pancreatic islet hormones and normal fasting–fed glucose regulation.
- Apply Robbins diagnostic thresholds to diabetes and prediabetes.
- Classify the major diabetes phenotypes and important secondary forms.

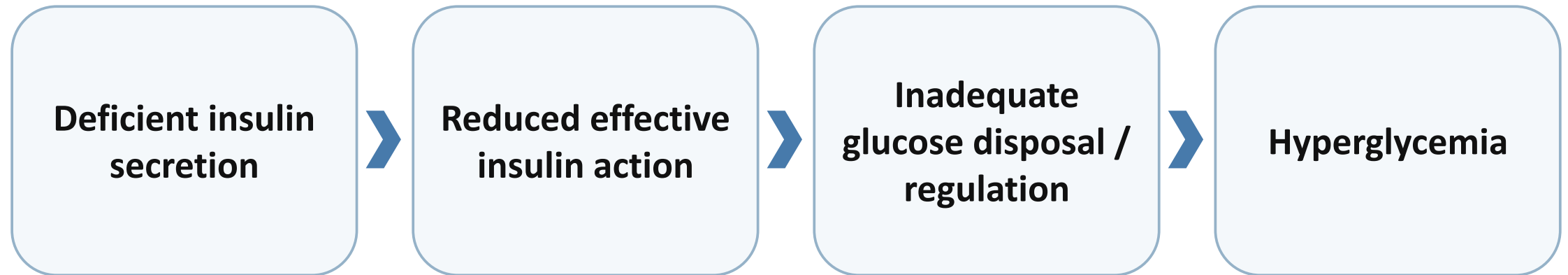
Integrated emphasis: Mechanism → laboratory recognition → disease classification.

Diabetes is a group of metabolic disorders

- Persistent hyperglycemia is the shared biochemical feature.
- The underlying defect involves insulin secretion, insulin action, or both.
- Distinct etiologies can therefore produce a similar elevated plasma glucose measurement.

Hyperglycemia defines the phenotype; Pathogenesis defines the subtype.

How insulin dysfunction produces hyperglycemia



Both impaired secretion and diminished tissue responsiveness can coexist.

Why chronic hyperglycemia matters

- Diabetes is not confined to the endocrine pancreas.
- Sustained hyperglycemia and metabolic dysregulation cause secondary organ injury.
- The kidney, retina, peripheral nerves, and blood vessels are particularly vulnerable.

Organ complications provide the central clinicopathologic significance.

The endocrine pancreas: Islets of Langerhans

- Approximately one million endocrine islet clusters are distributed through the pancreas.
- Each cluster contains several specialized hormone-secreting cell types.
- Local insulin–glucagon coordination contributes to systemic glucose homeostasis.

Islet-cell identity provides a basis for understanding diabetes.

Principal pancreatic islet-cell populations

Cell type	Major product	Glucose-related function
β cells	Insulin	Promotes glucose utilization; Lowers plasma glucose
α cells	Glucagon	Stimulates hepatic glucose production
δ cells	Somatostatin	Suppresses insulin and glucagon secretion
PP cells	Pancreatic polypeptide	Gastrointestinal regulatory effects

The endocrine response is coordinated rather than a single-hormone switch.

β cells regulate metabolic storage and utilization

- β cells synthesize insulin and release it in response to nutrient-associated stimuli.
- Insulin favors uptake and utilization of circulating glucose.
- Insulin deficiency is central to the hyperglycemia of type 1 diabetes.

The β cell is both a secretory organ and a metabolic glucose sensor.

α cells protect against falling blood glucose

- Pancreatic α cells synthesize glucagon.
- Glucagon increases hepatic glycogen breakdown and glucose release.
- Its physiological influence becomes prominent during fasting.

Fasting homeostasis requires an adequate counterregulatory response.

Somatostatin modulates intraislet signaling

- δ cells produce somatostatin.
- Somatostatin inhibits the release of both insulin and glucagon.
- This local endocrine brake shapes the balance of opposing glycemic signals.

Islet regulation depends on reciprocal control among cell populations.

Insulin and glucagon: Opposing metabolic instructions

INSULIN

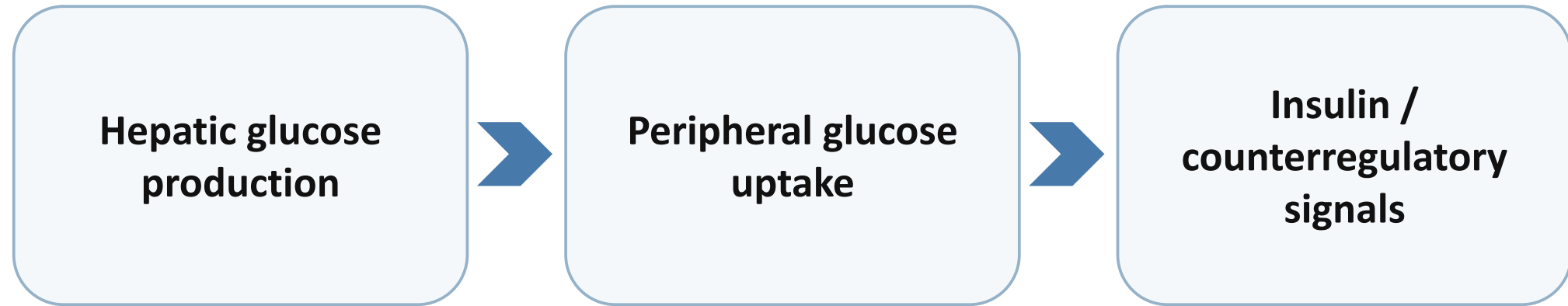
- Higher after meals
- Promotes glucose uptake and use
- Supports anabolic metabolism

GLUCAGON

- Relatively higher during fasting
- Supports hepatic glucose output
- Promotes glycogenolysis and gluconeogenesis

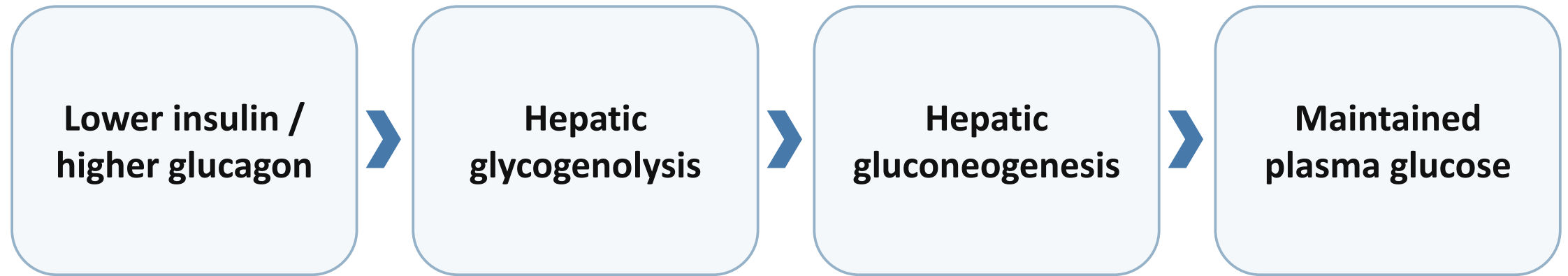
Their changing ratio links nutrient availability to circulating glucose.

Three determinants of circulating glucose



Alterations in production, uptake, or hormone balance can raise glucose.

Fasting physiology: Maintain glucose supply



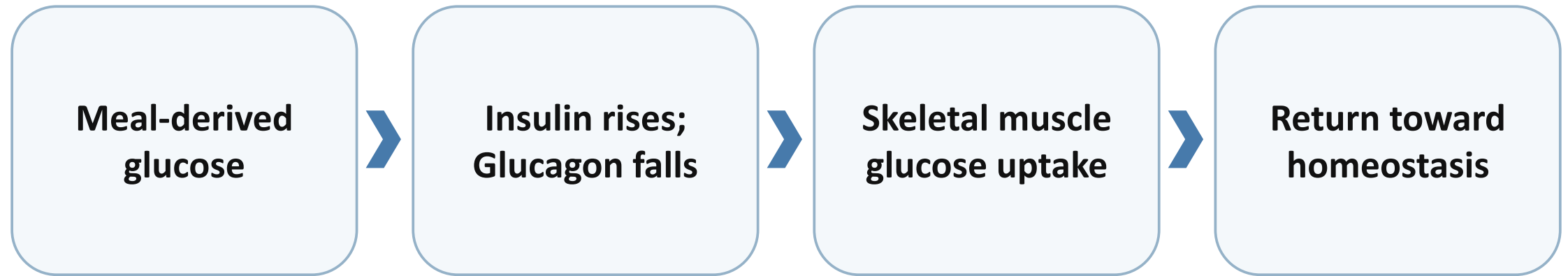
Fasting plasma glucose predominantly reflects liver glucose output.

The liver controls fasting plasma glucose

- During fasting, hepatic glycogen stores undergo breakdown.
- Gluconeogenesis generates glucose from noncarbohydrate precursors.
- Reduced glycogen synthesis and increased output protect against hypoglycemia.

Fasting hyperglycemia points toward failure to restrain hepatic glucose output.

Fed-state physiology: Dispose of the glucose load



Postprandial regulation depends heavily on insulin-responsive tissues.

Skeletal muscle is the major postprandial sink

- Skeletal muscle is an important insulin-responsive site for glucose utilization.
- Inadequate skeletal-muscle uptake promotes postprandial hyperglycemia.
- The metabolic defect may reflect insulin resistance despite available insulin.

Muscle insulin responsiveness is central to glucose tolerance.

Normal fasting and fed states

Feature	Fasting state	Fed state
Insulin	Relatively low	Rises
Glucagon	Relatively high	Falls
Hepatic output	Maintains blood glucose	Relatively suppressed
Muscle uptake	Less meal-driven	Major glucose disposal pathway

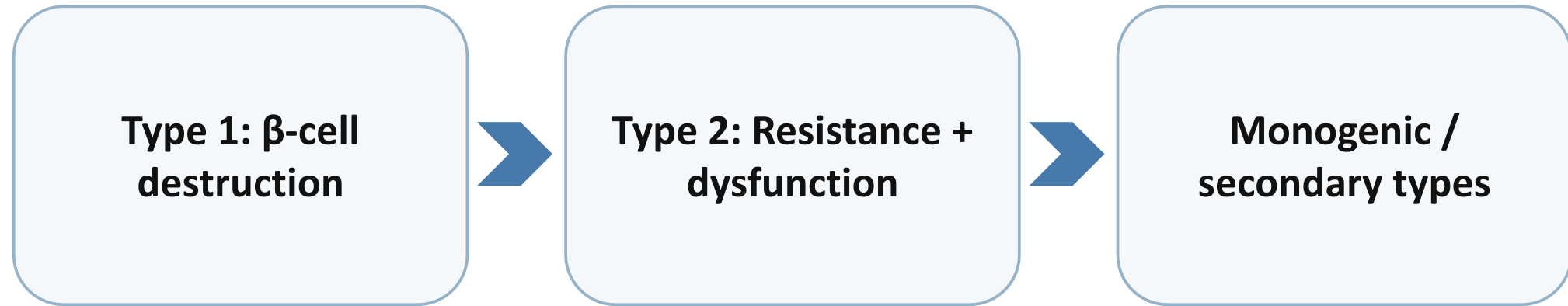
Diabetes may disturb one or more of these normal transitions.

Etiologic framework: Three points of failure

- Too little insulin is secreted for metabolic needs.
- Target tissues respond inadequately to available insulin.
- Combined resistance and inadequate β -cell compensation sustain hyperglycemia.

Measure the phenotype; Investigate the mechanism.

Pathogenesis-based classification



Mechanistic categories are more informative than age-based labels.

Type 1 diabetes: Absolute insulin deficiency

- The typical form is immune-mediated destruction of pancreatic β cells.
- Progressive β -cell loss leads to an absolute insulin deficit.
- Insulin deficiency predisposes to ketoacidosis when untreated.

T1D is defined by pathobiology, not simply childhood onset.

Type 2 diabetes: Failed β -cell compensation

- Peripheral tissues resist insulin action.
- β cells initially attempt to offset resistance through greater secretion.
- When the response is insufficient, persistent hyperglycemia develops.

T2D requires consideration of both insulin resistance and β -cell function.

Type 1 versus type 2: Clinical comparison

Characteristic	Type 1 diabetes	Type 2 diabetes
Typical onset	Often childhood/adolescence	Often adulthood; Increasingly youth
Weight phenotype	Normal weight or weight loss common	Overweight/obesity common
Insulin status	Progressive severe deficiency	Initially high, later declines
Acute crisis tendency	Ketoacidosis prominent	Hyperosmolar state more typical

Typical patterns are not absolute diagnostic rules.

Type 1 versus type 2: Biological comparison

Characteristic	Type 1 diabetes	Type 2 diabetes
Immune markers	Islet autoantibodies often present	Generally absent
Major genetic pattern	MHC class II association	Polygenic / obesity-linked
Islet pathology	Insulitis, β -cell depletion	Islet amyloid, mild β -cell loss
Primary lesion	Autoimmune β -cell destruction	Insulin resistance + secretory failure

A pathology-led classification guards against misleading demographic shortcuts.

Age of presentation does not establish diabetes type

- Type 1 diabetes is common in the young but is not confined to children.
- Type 2 diabetes increasingly affects children and adolescents.
- Clinical phenotype, immune markers, insulin secretion, and context must be integrated.

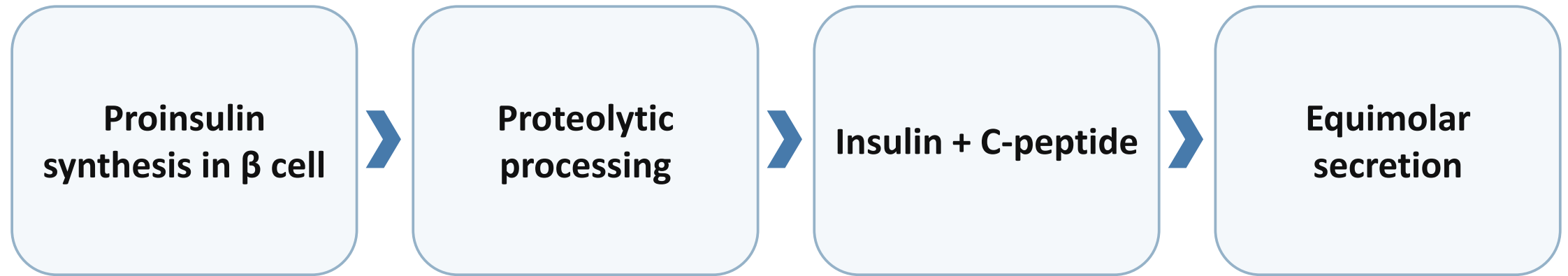
Avoid equating type 1 with “juvenile” and type 2 with “adult-onset.”

Body mass is a clue, not a classification test

- Many individuals with T2D have excess adiposity.
- Weight loss may accompany untreated marked insulin deficiency.
- The body-habitus distinction overlaps and cannot replace mechanistic diagnosis.

Weight contributes context but does not establish subtype.

Insulin maturation yields insulin and C-peptide



C-peptide reports endogenous insulin-secretory activity.

C-peptide is a window into β -cell function

- Insulin and C-peptide arise from the same proinsulin precursor.
- Both products are released together after secretory stimulation.
- A low C-peptide can accompany severe loss of endogenous β -cell function.

C-peptide helps separate insulin secretory failure from resistance.

C-peptide patterns follow pathophysiology

MARKED β -CELL LOSS

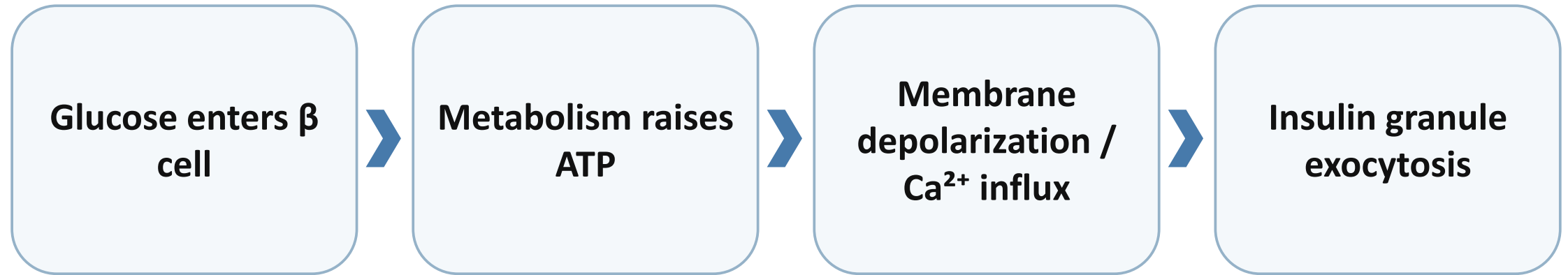
- Endogenous insulin production diminishes
- C-peptide tends to decrease
- Characteristic of advanced absolute insulin deficiency

INSULIN RESISTANCE

- Insulin demand increases
- Compensatory hypersecretion may occur
- C-peptide may initially be elevated

Interpret with prevailing glucose concentration and disease stage.

Glucose-stimulated insulin release



The coupling of nutrient metabolism to Ca^{2+} entry triggers secretion.

Metabolic sensing initiates secretion

- Rising blood glucose is the principal physiological stimulus for insulin release.
- Glucose entry and metabolism increase intracellular ATP.
- Changes in ATP-sensitive ion-channel activity initiate membrane depolarization.

Glucose detection is translated into an electrical signal.

Calcium converts the signal into exocytosis

- ATP-linked membrane changes lead to opening of voltage-dependent calcium channels.
- Intracellular Ca^{2+} rises.
- Ca^{2+} stimulates release of insulin from secretory granules.

Calcium influx is the immediate trigger for granule release.

Biphasic β -cell insulin secretion

EARLY PHASE

- Rapid response to rising glucose
- Release of stored insulin granules
- Initial immediate secretory burst

LATER PHASE

- Develops with persistent stimulation
- More sustained hormone output
- Includes ongoing insulin synthesis

The temporal pattern matters as much as the total amount secreted.

Oral nutrients produce an incretin effect

- Intestinal hormones amplify glucose-stimulated insulin secretion.
- The effect explains why oral glucose provokes more insulin release than an equivalent intravenous load.
- The major incretins are GIP and GLP-1.

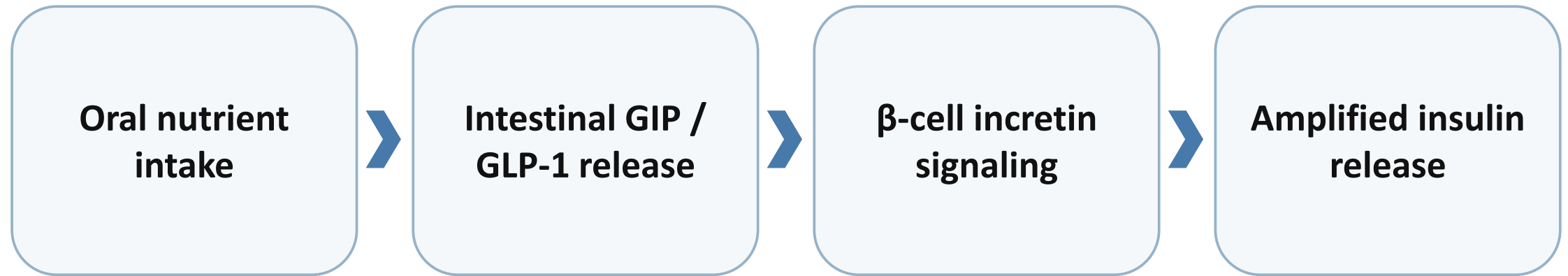
The intestine participates in endocrine regulation of blood glucose.

Two major incretins

Hormone	Physiologic source	Key metabolic effect
GIP	Intestinal enteroendocrine cells	Augments meal-related insulin secretion
GLP-1	Intestinal enteroendocrine cells	Augments insulin secretion; Promotes satiety

Both exert effects through β -cell G-protein–coupled receptors.

The enteroinsular axis



An intravenous glucose load bypasses much of this gut hormonal contribution.

Incretins coordinate multiple post-meal effects

- Incretins stimulate glucose-dependent insulin secretion.
- They attenuate glucagon secretion after nutrient intake.
- Delayed gastric emptying and satiety-related effects modify nutrient appearance and appetite.

The response involves pancreas, gut, and central appetite regulation.

DPP-4 terminates endogenous incretin signals

- GIP and GLP-1 are degraded in the circulation.
- Dipeptidyl peptidase-4 is a key enzyme mediating this breakdown.
- Rapid hormone degradation limits the duration of the endogenous incretin response.

Incretin lifetime is a pharmacologically modifiable process.

Incretin-related therapeutic principles

GLP-1 RECEPTOR AGONISTS

- Activate GLP-1 receptor signaling
- Enhance insulin secretion in a glucose-dependent manner
- Promote satiety / weight reduction

DPP-4 INHIBITORS

- Reduce breakdown of endogenous incretins
- Extend native incretin signaling
- Improve glycemic regulation

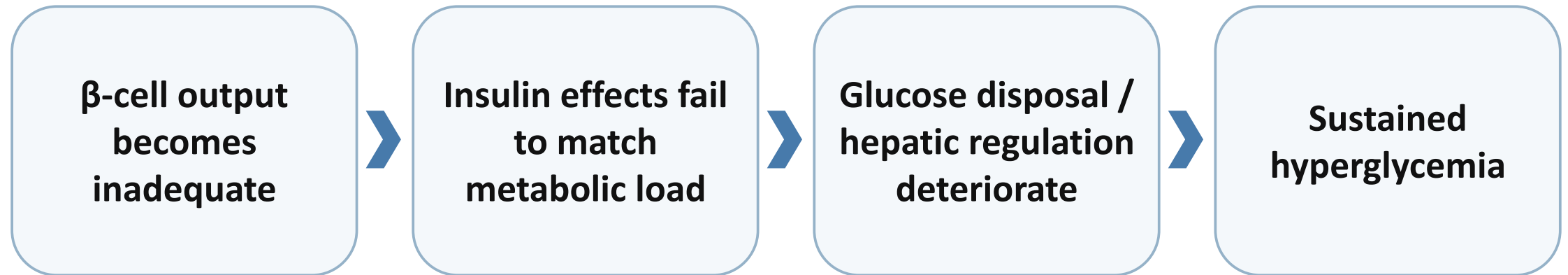
Mechanistic illustration only; Clinical prescribing guidance is outside this lecture.

Dual incretin-receptor agonism

- Tirzepatide as a dual GIP/GLP-1 receptor agonist.
- Its endocrine action engages both incretin-receptor pathways.
- This drug class demonstrates the translational significance of gut–islet physiology.

Drug mechanisms are included to illuminate pathology, not to prescribe treatment.

From normal physiology to diabetic hyperglycemia



This common endpoint arises through different initiating lesions.

Four Robbins diagnostic pathways

Test	Diabetes threshold
Fasting plasma glucose	≥126 mg/dL
Random plasma glucose + classic symptoms	≥200 mg/dL
2-hour plasma glucose (75-g OGTT)	≥200 mg/dL
HbA1c	≥6.5%

These are textbook criteria; Verify current local laboratory standards for clinical decisions.

Fasting plasma glucose

≥ 126 mg/dL

Diabetes diagnostic threshold

- Measure plasma glucose in the fasting state.
- A threshold-level result generally requires confirmation if hyperglycemia is not unequivocal.
- The fasting value is strongly influenced by hepatic glucose output.

Random plasma glucose

≥ 200 mg/dL

**With classic hyperglycemic
manifestations**

- A random glucose threshold is diagnostic in the specified symptomatic context.
- The textbook makes this the exception to its separate-day confirmatory rule.
- Without that clinical context, do not interpret a single random result in isolation.

Oral glucose tolerance test

≥ 200 mg/dL

**2-hour value after a 75-g glucose
load**

- The test directly challenges systemic glucose handling.
- The diagnostic comparison uses the 2-hour plasma glucose measurement.
- Impaired insulin secretion or disposal may become apparent after glucose loading.

Glycated hemoglobin

$\geq 6.5\%$

HbA1c diagnostic threshold

- HbA1c provides an integrated marker of antecedent glycemic exposure.
- It is an alternative laboratory pathway to diabetes diagnosis.
- Interpret assay results in clinical context and confirm when indicated.

Confirming hyperglycemia before labeling diabetes

- The Robbins text recommends repeat confirmation on a separate day for most diagnostic pathways.
- An unequivocal symptomatic random plasma glucose ≥ 200 mg/dL is its stated exception.
- Clinical context and test concordance determine interpretive confidence.

Distinguish persistent dysglycemia from a single abnormal measurement.

Discordant diagnostic assays

- Fasting glucose, oral glucose tolerance, and HbA1c measure related but distinct manifestations of dysglycemia.
- Discordance can occur between glucose-based and HbA1c-based tests.
- The more abnormal assay as the diagnostic readout; Confirmation and clinical assessment remain important.

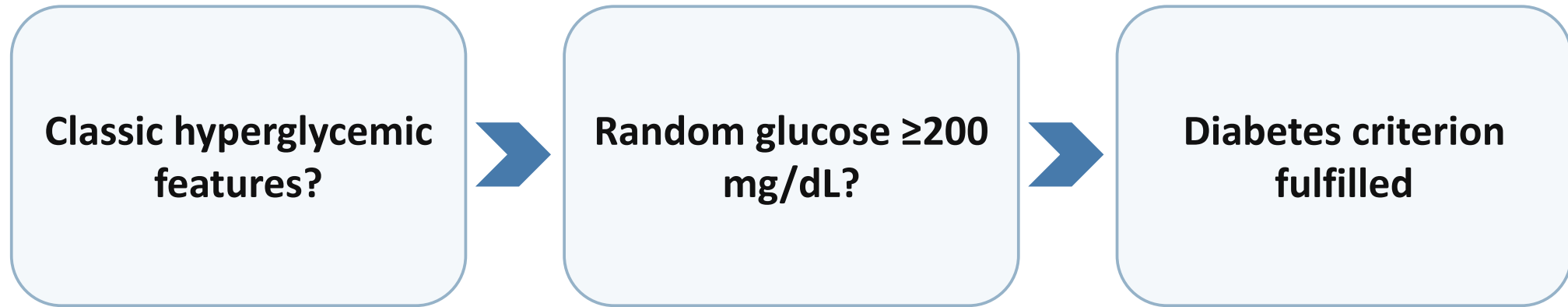
Laboratory disagreement should prompt interpretation—not arbitrary averaging.

Acute stress may cause transient hyperglycemia

- Severe infection, burns, or trauma may provoke transient glucose elevation.
- Catecholamines and cortisol oppose insulin action during stress.
- Evaluate whether hyperglycemia persists after the acute illness resolves.

Stress hyperglycemia is not automatically chronic diabetes.

Diagnostic logic in a symptomatic patient



If symptomatic criteria are absent, use fasting glucose, OGTT, or HbA1c with appropriate confirmation.

Prediabetes: Robbins laboratory intervals

Test	Prediabetes interval
Fasting plasma glucose	100–125 mg/dL
2-hour plasma glucose (75-g OGTT)	140–199 mg/dL
HbA1c	5.7–6.4%

Any qualifying interval indicates elevated future diabetes risk.

Impaired fasting glucose

100–125 mg/dL

Fasting plasma glucose range

- The value is elevated but does not meet the diabetes threshold.
- It indicates abnormal basal glucose regulation.
- Coexisting obesity and family history influence progression risk.

Impaired glucose tolerance

140–199 mg/dL

**2-hour plasma glucose after 75-g
OGTT**

- A glucose challenge reveals reduced tolerance to a carbohydrate load.
- The value lies below the diabetes threshold of 200 mg/dL.
- The state identifies increased risk of later type 2 diabetes.

Prediabetes by HbA1c

5.7–6.4%

Glycated hemoglobin interval

- This range signifies dysglycemia below the diabetes criterion.
- HbA1c may identify people with elevated future diabetes risk.
- Interpret alongside other risk factors and glucose-based tests.

Prediabetes is clinically consequential

- Prediabetes can precede overt type 2 diabetes.
- The progression rate is influenced by factors such as obesity and family history.
- The textbook also links prediabetes with cardiovascular risk.

Risk begins before the threshold for established diabetes is crossed.

Interpreting the three glycemic categories

Measurement	Prediabetes	Diabetes
Fasting glucose	100–125 mg/dL	≥126 mg/dL
2-hour OGTT	140–199 mg/dL	≥200 mg/dL
HbA1c	5.7–6.4%	≥6.5%

Values below prediabetes intervals are not automatically normal in every clinical context.

No single number establishes the etiologic subtype

- Glucose and HbA1c tests establish the hyperglycemic phenotype.
- They do not identify autoimmune β -cell destruction versus insulin resistance.
- Classification uses history, phenotypic findings, and where relevant tests of islet immunity and endogenous secretion.

Diagnosis of diabetes and classification of diabetes are separate tasks.

Islet autoantibodies support type 1 diabetes

- GAD65, IA-2, and ZnT8 as characteristic islet-autoantibody targets.
- Their presence supports autoimmune β -cell destruction in an appropriate setting.
- Autoantibody-negative or atypical presentations require careful classification.

An immune biomarker is not interchangeable with a glucose diagnostic criterion.

Genetic architecture distinguishes common types

- Type 1 susceptibility is strongly linked to MHC class II loci.
- Robbins also notes CTLA4, PTPN22, and insulin-gene regulatory polymorphisms.
- Type 2 risk involves multiple metabolic and obesity-associated loci rather than HLA linkage.

Susceptibility alleles do not serve as standalone clinical diagnostic tests.

Two characteristic islet pathology patterns

TYPE 1 DIABETES

- Immune-cell insulitis may be present
- Progressive β -cell depletion
- Atrophy of affected islets

TYPE 2 DIABETES

- Islet amyloid deposition may occur
- Variable mild β -cell loss
- No characteristic insulitis

Morphologic descriptions are textbook findings; No synthetic photomicrograph is shown.

Early T2D can show compensatory hyperinsulinemia

- Insulin resistance raises the amount of insulin needed for normal glucose handling.
- β cells can initially compensate by increasing insulin secretion.
- The eventual mismatch between secretion and demand promotes hyperglycemia.

High insulin levels do not exclude diabetes.

Type 1 and type 2 share a metabolic endpoint

- Type 1 starts predominantly with profound insulin secretory loss.
- Type 2 combines peripheral resistance with relative β -cell secretory inadequacy.
- Both result in sustained hyperglycemia and risk of multisystem injury.

Similar glucose values may conceal fundamentally different mechanisms.

Beyond type 1 and type 2: Other diabetes groups

- Single-gene defects of β -cell function or insulin action can cause diabetes.
- Pancreatic exocrine disease, endocrine disorders, and medications may lead to secondary hyperglycemia.
- Gestational diabetes is a distinct context classification.

Atypical clinical features should stimulate etiologic reconsideration.

Selected MODY-associated genes

MODY designation	Gene	Encoded function / designation
MODY1	HNF4A	Hepatocyte nuclear factor 4 α
MODY2	GCK	Glucokinase
MODY3	HNF1A	Hepatocyte nuclear factor 1 α
MODY4	PDX1	Pancreatic / duodenal homeobox 1
MODY5	HNF1B	Hepatocyte nuclear factor 1 β

These are examples from the textbook classification, not a comprehensive gene panel.

Neonatal and mitochondrial monogenic diabetes

- Activating changes in KCNJ11 or ABCC8 are associated with certain neonatal diabetes forms.
- The genes encode components of the ATP-sensitive potassium-channel system.
- Robbins also lists maternally inherited diabetes and deafness due to mitochondrial DNA variation.

Molecular mechanisms can pinpoint rare etiologic subgroups.

Pancreatogenic diabetes: Injury to pancreatic tissue

- Chronic pancreatitis or pancreatic resection may compromise endocrine function.
- Pancreatic malignancy and cystic fibrosis are additional listed causes.
- Hemochromatosis and fibrocalculous pancreatopathy are also recognized.

Exocrine pancreatic pathology can secondarily impair islet-cell function.

Endocrine and drug-related secondary diabetes

- Acromegaly, Cushing syndrome, and hyperthyroidism are listed endocrine associations.
- Glucocorticoids, certain antiretrovirals, thiazides, and other drugs may contribute.
- A medication and endocrine history is part of etiologic classification.

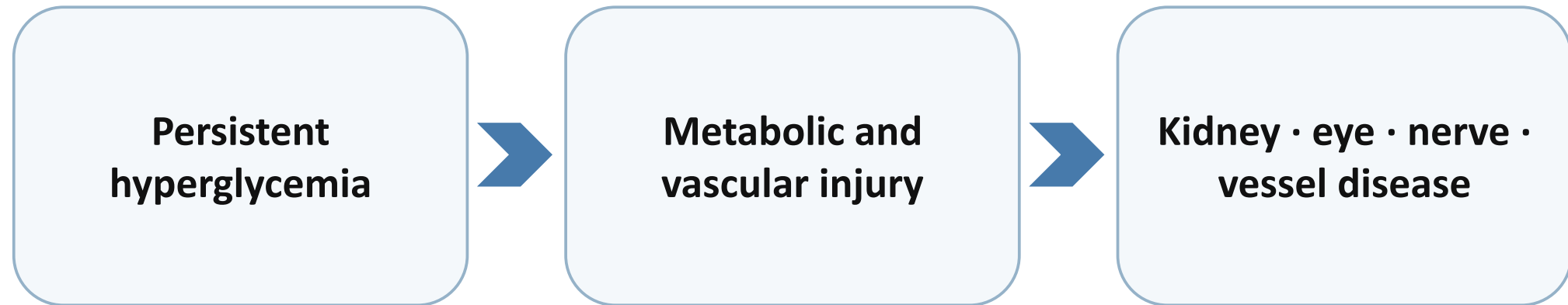
Hormones antagonizing insulin can produce a diabetes phenotype.

Diabetes and pregnancy in the classification

- Gestational diabetes is a separately recognized category.
- The physiological context of pregnancy matters when interpreting hyperglycemia.
- Detailed pregnancy-specific diagnostic approaches belong to the dedicated topic.

Do not automatically classify hyperglycemia in pregnancy as ordinary T2D.

Organ injury from sustained diabetes



These complications motivate early detection and etiologic management.

Clinical impact: Kidneys, eyes, nerves, vessels

- Renal failure and ocular, neural, and vascular consequences.
- Chronic injury produces functional disease beyond elevated laboratory glucose.
- Specific lesion morphology and chronic complications are developed in separate Robbins topics.

A diabetes lecture must link laboratory diagnosis to end-organ pathology.

Case application: Symptomatic hyperglycemia

CLINICAL VIGNETTE

An adult has polyuria, polydipsia, and a random plasma glucose of 236 mg/dL.

Does the reported test meet the Robbins diabetes diagnostic criterion?

INTERPRETATION

Yes. Random plasma glucose ≥ 200 mg/dL with classic hyperglycemic manifestations meets the stated diagnostic pathway.

Case application: Prediabetes classification

CLINICAL VIGNETTE

A fasting plasma glucose is 116 mg/dL and HbA1c is 6.1%.

How should these measurements be classified?

INTERPRETATION

Both values fall within the Robbins prediabetes intervals; They do not reach diagnostic thresholds for established diabetes.

Case application: Mechanism versus phenotype

CLINICAL VIGNETTE

A person has hyperglycemia, high endogenous insulin, and a phenotype suggesting reduced peripheral response to insulin.

Which pathogenic process is most consistent with the early presentation?

INTERPRETATION

Compensatory hyperinsulinemia associated with insulin resistance, often an early feature of type 2 diabetes.

Integrated summary: Four diagnostic decisions

- Establish a persistent hyperglycemic phenotype using appropriate criteria.
- Separate diabetes from prediabetes using the correct assay interval.
- Classify the underlying mechanism, not merely age or weight.
- Connect the biochemical disorder to long-term organ pathology.

Correct classification informs clinical interpretation and future evaluation.

Principal source and scope

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026) · Chapter 24: The Endocrine System

Primary sections: Endocrine Pancreas; Diabetes Mellitus; Diagnosis; Classification; Glucose Homeostasis; Regulation of Insulin Release.

Primary classification and comparison tables: 24.6 and 24.7.