

Metabolic Defects in Type 2 Diabetes

Insulin resistance • β -cell dysfunction • metabolic feedback

A mechanism-focused pathology lecture

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Learning outcomes: Connect mechanisms with glycemia

- Distinguish insulin resistance from inadequate β -cell compensation.
- Explain the glucose and lipid consequences in liver, muscle and fat.
- Trace obesity-associated lipotoxic and inflammatory pathways.
- Explain why hyperglycemia eventually emerges despite early hyperinsulinemia.

Two indispensable abnormalities

Insulin resistance

Target tissues respond inadequately to insulin

Dominant sites: Liver, muscle, adipose tissue

Usually appears before overt hyperglycemia

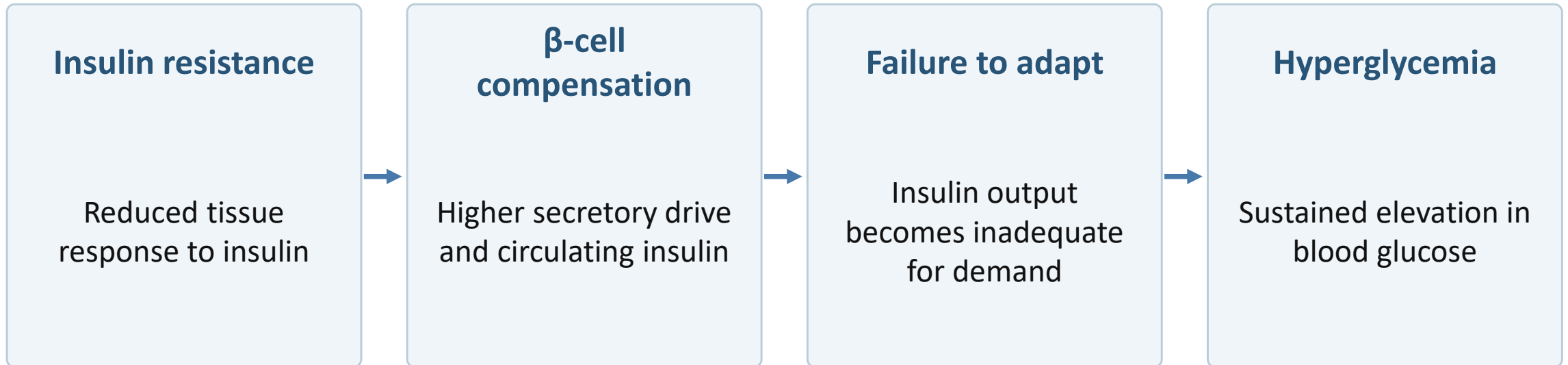
β -cell dysfunction

Insulin secretion becomes insufficient for demand

Initially may be compensatory hyperfunction

Required for progression to overt T2D

Disease evolution: Resistance precedes hyperglycemia



This is a conceptual sequence, not a quantitative time course.

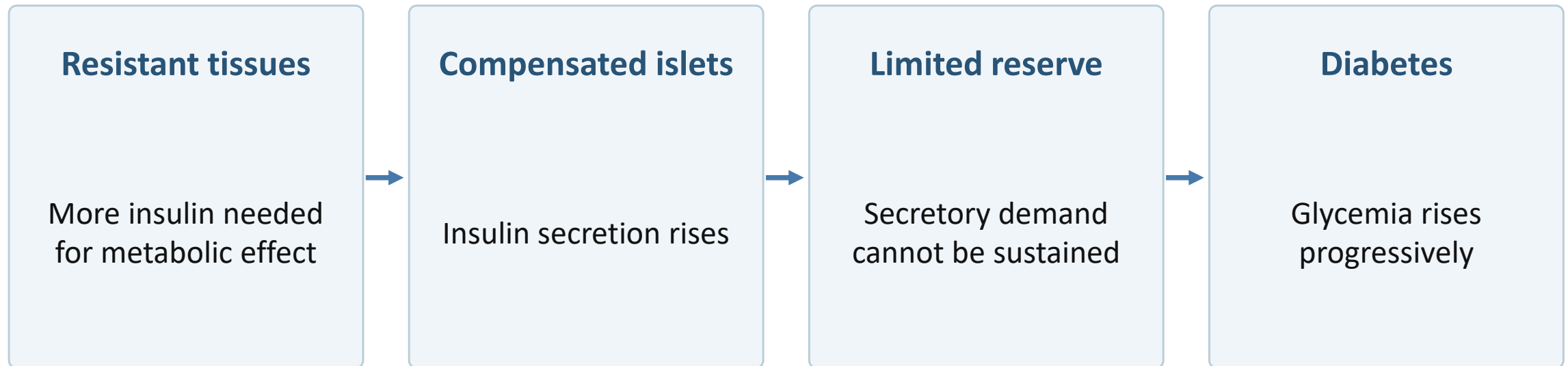
Early compensation can preserve normal glucose

- Tissues become less responsive while β cells initially increase insulin release.
- Compensatory hyperinsulinemia partly offsets the tissue defect.
- Glucose tolerance may remain normal or become impaired before overt diabetes.

Overt T2D reflects failure of adaptation

- The insulin requirement rises as resistance persists.
- β -cell secretory capacity eventually fails to match the requirement.
- Relative insulin deficiency permits chronic hyperglycemia.

The compensatory transition is mechanistically important



A high insulin concentration need not imply adequate insulin action.

Insulin resistance is distributed across three tissues

INSULIN RESISTANCE

Diminished normal response to insulin

Liver

Endogenous glucose output
inadequately suppressed

Skeletal muscle

Meal-related glucose uptake
and glycogen synthesis
impaired

Adipose tissue

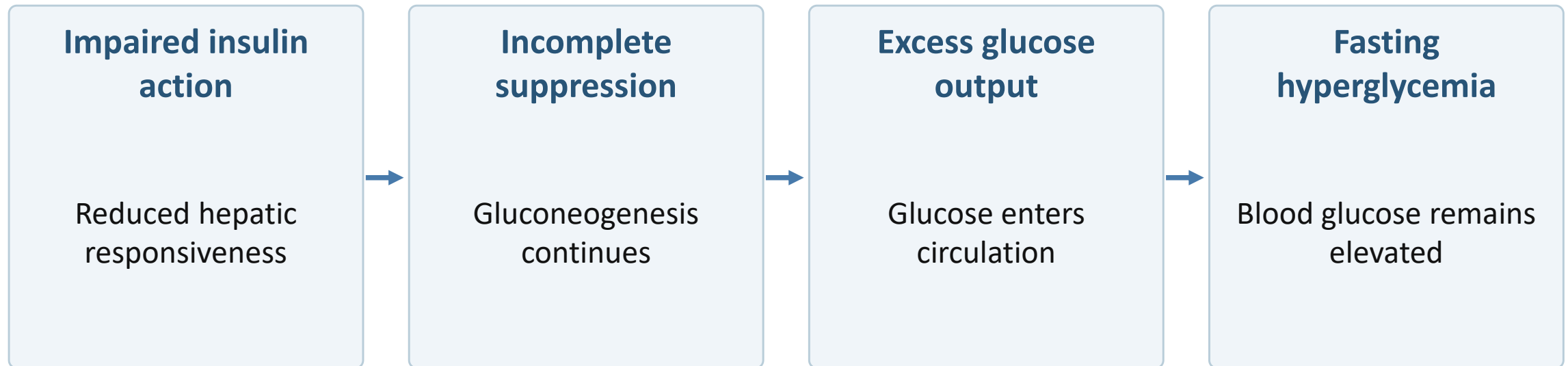
Triglyceride breakdown
inadequately suppressed

Different tissue defects converge on disordered glucose homeostasis.

The liver: Insulin normally restrains glucose output

- The liver generates endogenous glucose, including through gluconeogenesis.
- Insulin normally suppresses this glucose-producing activity.
- Fasting glucose depends partly on whether this suppression is effective.

Hepatic resistance explains elevated fasting glucose

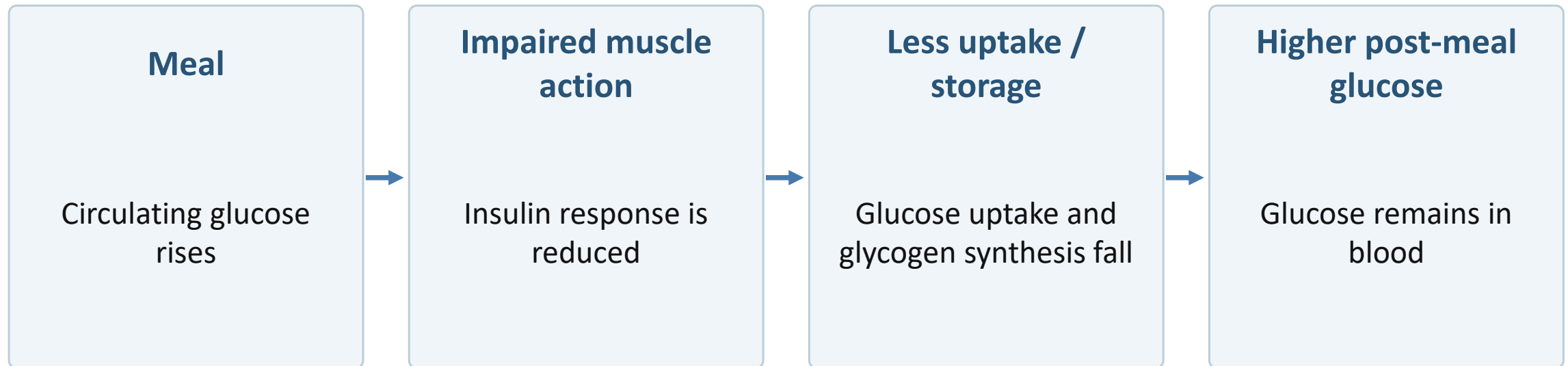


This mechanistic pathway is explicit in the source.

The muscle: Insulin facilitates glucose disposal

- Skeletal muscle normally takes up circulating glucose after meals.
- Insulin promotes glucose uptake and conversion to glycogen.
- This tissue response reduces the postprandial glucose load.

Muscle resistance explains postprandial dysglycemia

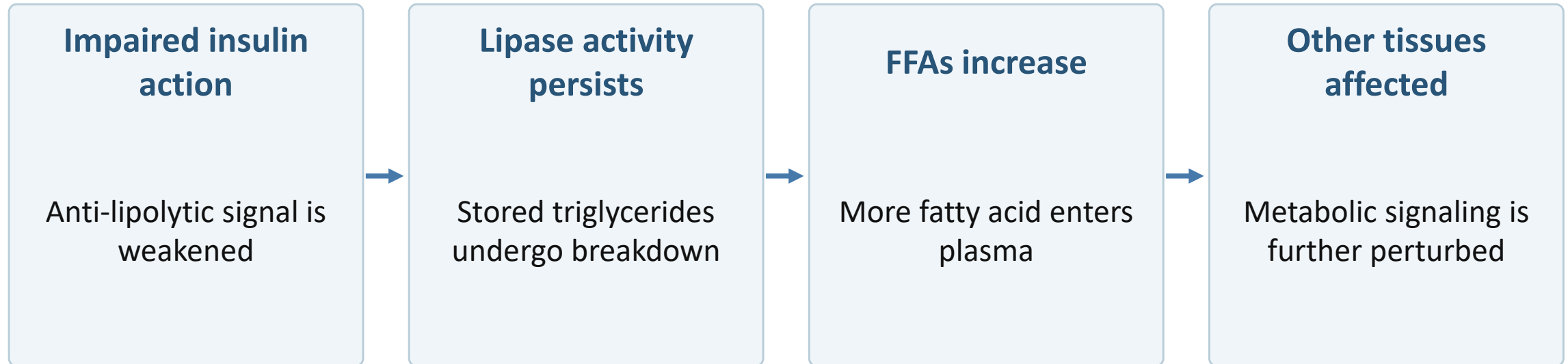


The source explicitly links muscle defects to postprandial hyperglycemia.

Adipose tissue: Insulin suppresses triglyceride breakdown

- Insulin normally restrains hormone-sensitive lipase activity.
- This reduces triglyceride breakdown within adipocytes.
- When adipose insulin action is weak, more free fatty acids enter blood.

Adipose resistance increases circulating free fatty acids



FFAs = free fatty acids; Source describes lipolysis as mediator of peripheral and islet dysfunction.

A tissue-by-tissue account of the metabolic defects

Tissue	Action normally promoted by insulin	Result of resistance
Liver	Suppression of gluconeogenesis	Persistent endogenous glucose production
Skeletal muscle	Glucose uptake and glycogen formation	Postprandial glucose remains elevated
Adipose tissue	Inhibition of hormone-sensitive lipolysis	Free fatty acids increase in circulation

Fasting and post-meal hyperglycemia

Fasting state

Failure to suppress hepatic glucose production

Endogenous glucose output persists

Hepatic insulin resistance is central

Post-meal state

Skeletal muscle removes less circulating glucose

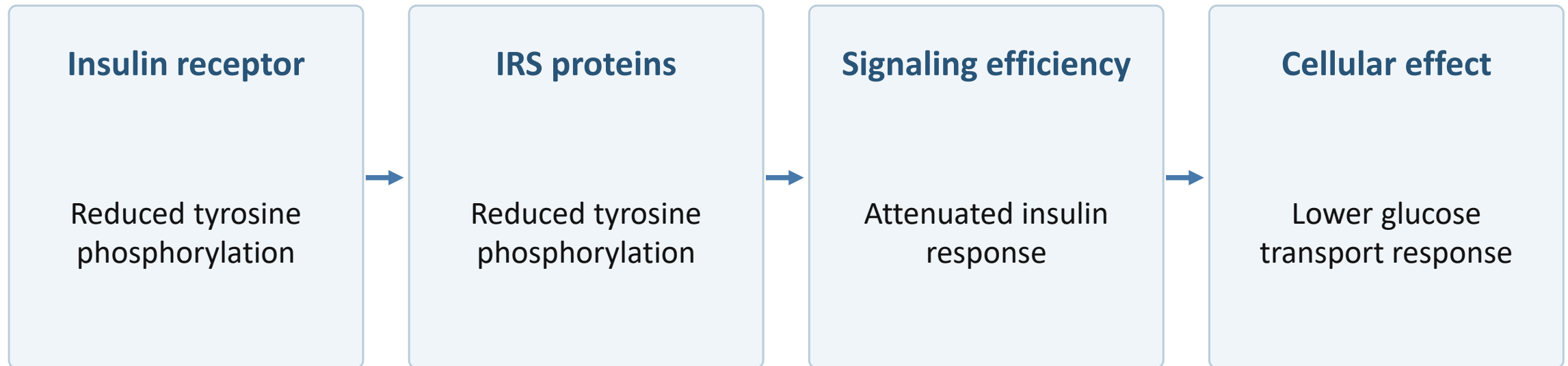
Glycogen synthesis is reduced

Muscle insulin resistance is central

Insulin signaling begins with receptor phosphorylation

- Insulin receptor signaling normally depends on regulated phosphorylation.
- Reduced tyrosine phosphorylation of insulin receptors is reported in resistant tissues.
- The weakened signal impairs downstream metabolic responses.

IRS defects compromise the downstream insulin signal

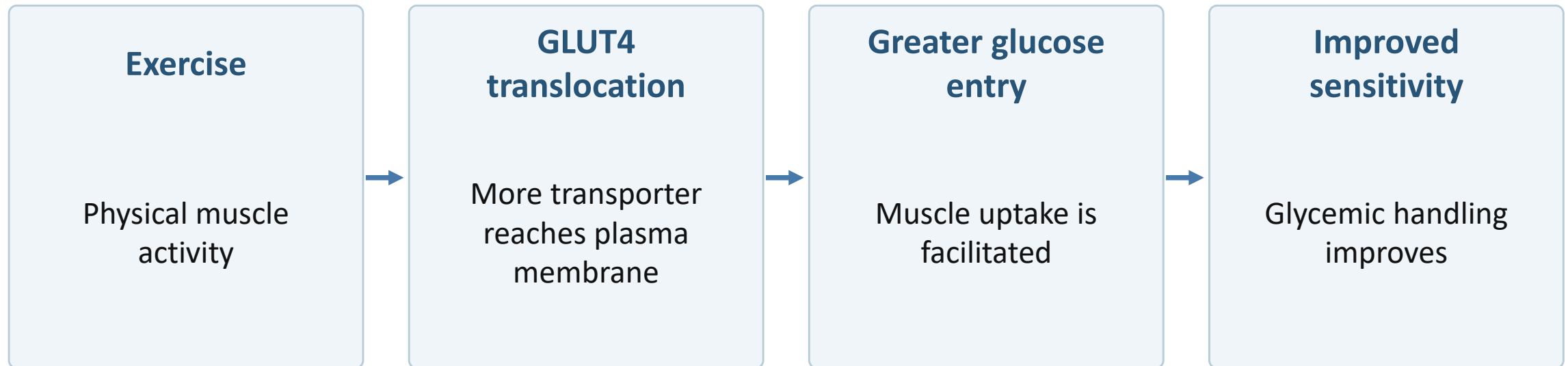


IRS = insulin receptor substrate proteins.

GLUT4 translocation is a key skeletal-muscle endpoint

- The amount of GLUT4 at the cell surface helps determine glucose uptake.
- Impaired insulin signaling reduces surface GLUT4 availability.
- Consequently, skeletal muscle responds less effectively to circulating insulin.

Exercise can improve a defined insulin-response step



Text attributes part of the exercise effect to GLUT4 translocation; Exact quantitative benefit not provided.

Receptor signal versus tissue-level phenotype

Molecular abnormality

Reduced receptor / IRS tyrosine phosphorylation

Less effective GLUT4 recruitment at the surface

Impaired downstream signaling

Metabolic expression

Muscle glucose uptake decreases

Hepatic glucose suppression fails

Adipose lipolysis is less inhibited

Obesity is a major determinant of insulin resistance

- Among acquired influences, obesity is emphasized as particularly important.
- Diabetes risk rises with increasing adiposity.
- Body-fat distribution modifies risk beyond total body size.

Why body mass index is an imperfect proxy

- BMI estimates overall body size rather than the location of fat.
- Two people with comparable BMI may have different fat distributions.
- The metabolic consequences of abdominal and peripheral adiposity differ.

Visceral and subcutaneous adiposity

Central / visceral pattern

Stronger association with insulin resistance

Greater lipolytic activity described

Free-fatty-acid burden tends to be greater

Peripheral / subcutaneous pattern

Comparatively weaker association with resistance

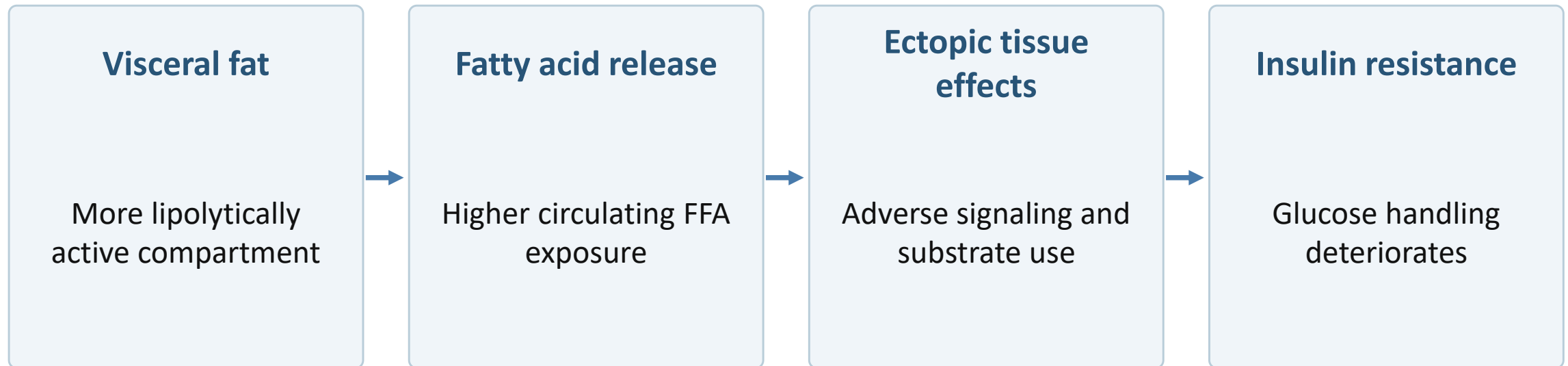
May confer relative metabolic protection

Protection is not absolute

Visceral adiposity matters without overt obesity

- An apparently nonobese phenotype does not exclude excess visceral fat.
- The source highlights this pattern in some Asian and Middle Eastern populations.
- Body composition can therefore be more informative than BMI alone.

Central adiposity changes lipid flux



Qualitative pathway; The source discusses inverse FFA/insulin sensitivity association.

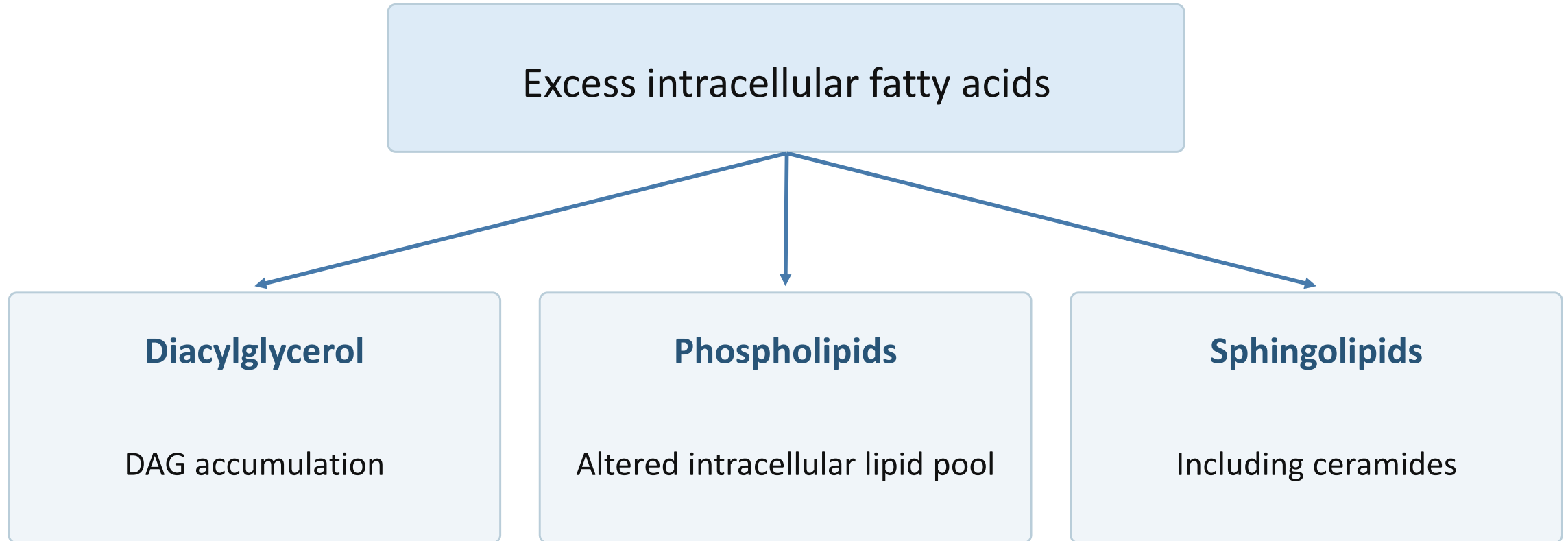
FFA exposure correlates inversely with insulin sensitivity

- Fasting plasma FFAs are inversely associated with insulin sensitivity.
- Cross-sectional association does not, on its own, prove causation.
- The mechanistic evidence provides biological plausibility.

Excess fatty acids can exceed oxidation capacity

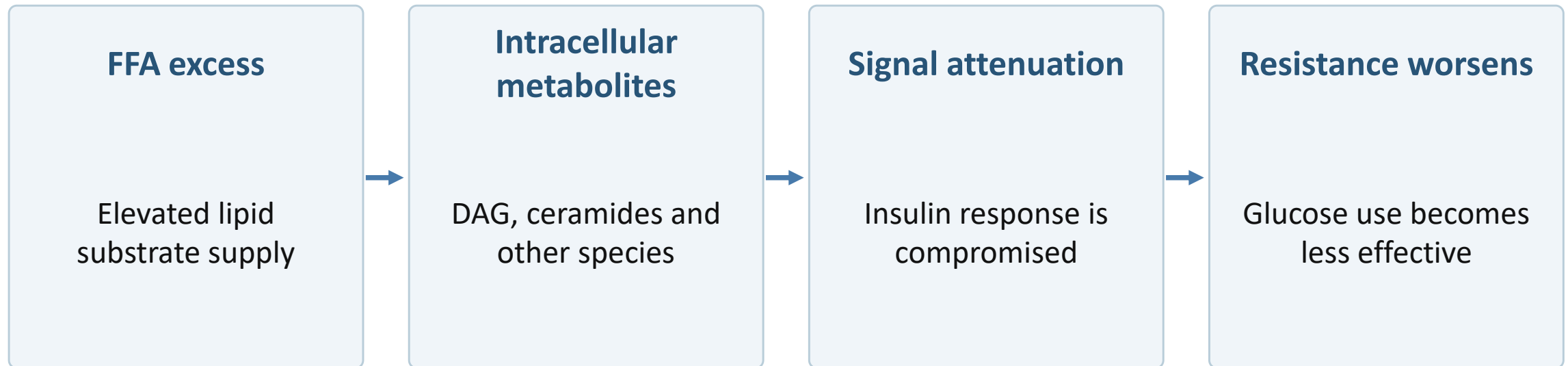
- A high fatty-acid supply increases the burden of intracellular lipid handling.
- When oxidative pathways are overwhelmed, lipid intermediates accumulate.
- The accumulated intermediates can interfere with metabolic signaling.

Lipid intermediates link FFAs to cellular dysfunction



The listed intermediates are source examples; Relative concentrations are not asserted.

Lipotoxic metabolites suppress effective signaling

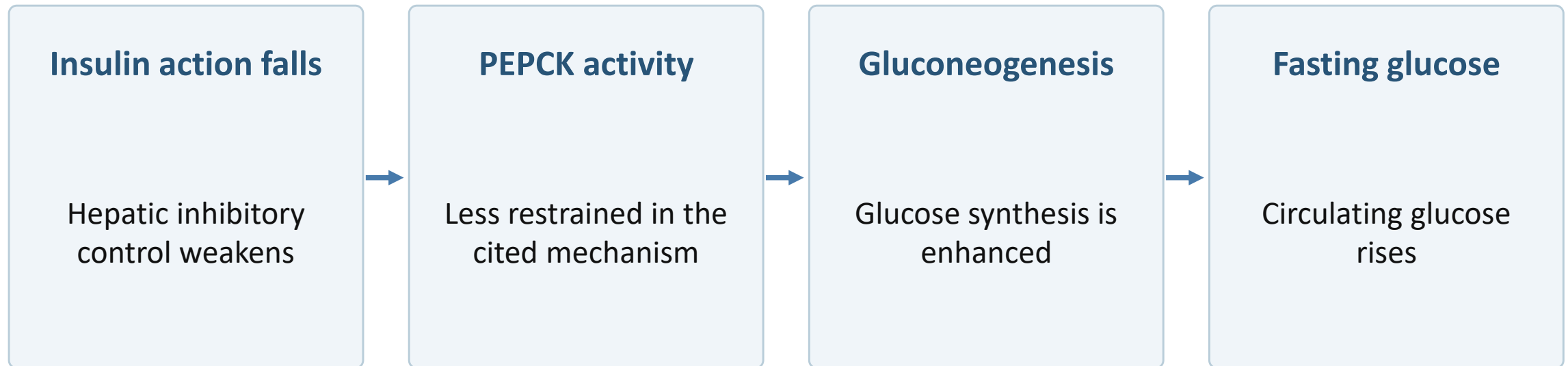


Specific molecular intermediates are those named excerpt.

Fatty acids and glucose compete as oxidative substrates

- A higher fatty-acid supply favors the use of fatty acids as fuel.
- Competition with glucose for oxidation.
- This competition can exacerbate reduced glucose utilization.

Hepatic PEPCK links signaling to glucose production



Phosphoenolpyruvate carboxykinase (PEPCK) as a key regulated step; No claim it is the first enzymatic step.

Adipose tissue is an endocrine organ

- Adipocytes store energy and secrete circulating signaling proteins.
- These secreted molecules are termed adipokines or adipose cytokines.
- Some adipokines favor hyperglycemia; Others enhance insulin sensitivity.

Adipokine effects are not uniformly harmful

Insulin-sensitizing signals

Adiponectin is the principal named example

Supports peripheral insulin sensitivity

Can contribute to lower blood glucose

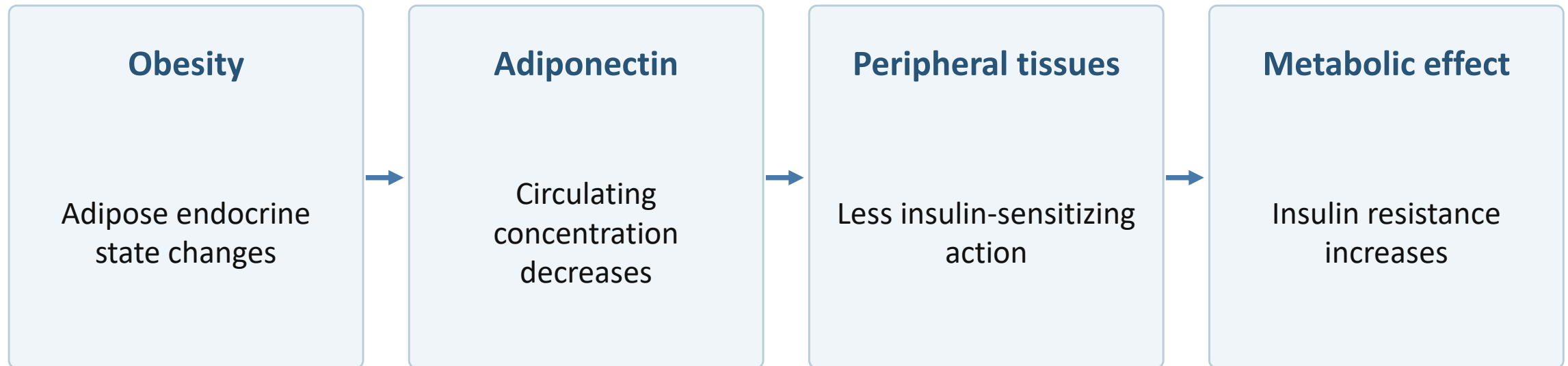
Hyperglycemia-promoting signals

Other adipokines can promote dysglycemia

Net adipose output depends on metabolic state

The excerpt does not enumerate individual harmful adipokines

Reduced adiponectin contributes to insulin resistance

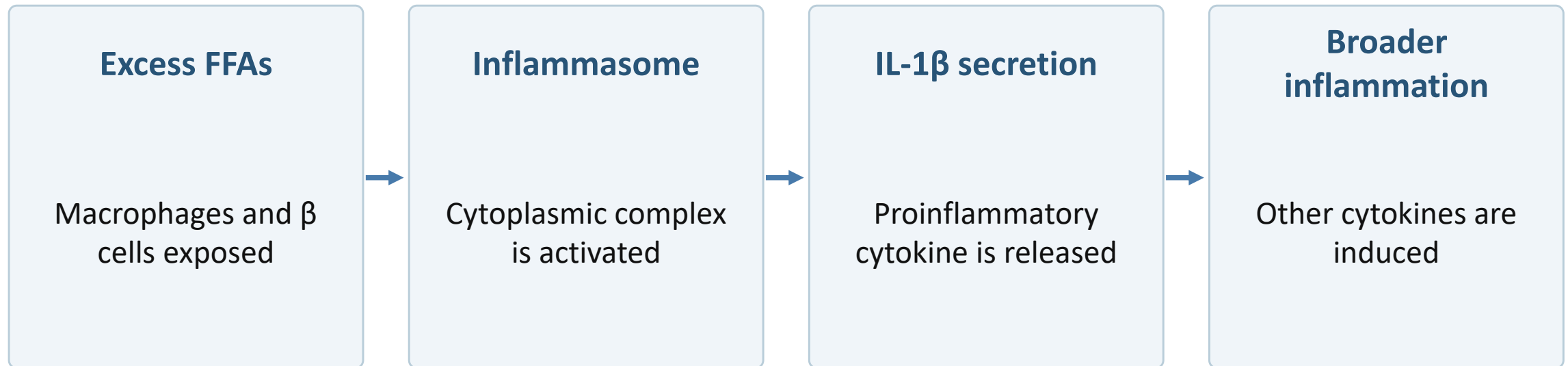


Some adiponectin effect to improved peripheral insulin sensitivity.

Nutrient overload can promote sterile inflammation

- FFAs and glucose are metabolic triggers for proinflammatory responses.
- The ensuing cytokine milieu impairs insulin action.
- Islet dysfunction can occur alongside peripheral resistance.

The inflammasome provides a mechanistic bridge



Robbins specifies inflammasome activation and IL-1 β release; Pathway presented conceptually.

IL-1 β amplifies the cytokine environment

- Inflammasome activation is linked to secretion of IL-1 β .
- IL-1 β promotes additional cytokine secretion in several cellular compartments.
- The combined inflammatory environment can worsen tissue insulin resistance.

FFA-driven resistance has direct and indirect routes

Elevated free fatty acids

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graph TD; A[Elevated free fatty acids] --> B[Direct tissue effect]; A --> C[Inflammatory route]; B --> D[Lipid intermediates impair insulin signaling]; C --> E[Cytokine production further attenuates insulin action];
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Direct tissue effect

Lipid intermediates impair insulin signaling

Inflammatory route

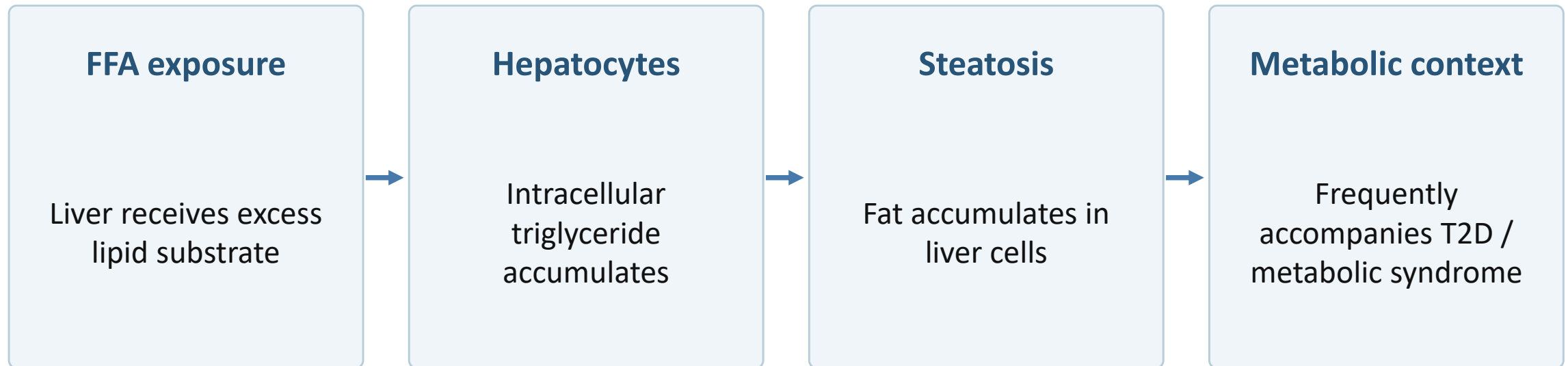
Cytokine production further attenuates insulin action

Two converging mechanisms are explicit.

Inflammation also affects the pancreatic islet

- Islet β cells can respond to excess FFAs with inflammatory activation.
- The inflammatory milieu contributes to secretory dysfunction.
- Peripheral resistance and reduced insulin output therefore reinforce each other.

High circulating FFAs can cause hepatic steatosis



Liver steatosis, not any particular histologic specimen, is described; Schematic only.

Steatotic liver disease spans different injury states

Steatosis without injury

Excess intrahepatocellular fat

No liver-injury evidence described

Metabolic dysfunction context may be present

Steatohepatitis

Steatosis with hepatocyte injury

Inflammatory reaction accompanies injury

Fibrosis may or may not be present

MASLD is a metabolic correlate, not a glucose mechanism alone

- Hepatic fat accumulation is common in T2D and metabolic syndrome.
- The spectrum includes steatosis and steatohepatitis.
- Hepatic insulin resistance and hepatic steatosis are related but not identical findings.

β -cell dysfunction is essential for overt T2D

- Resistance alone can produce impaired glucose tolerance.
- Overt diabetes emerges when insulin secretion cannot meet tissue demand.
- This requirement distinguishes β -cell failure from resistance as an isolated lesion.

The β -cell response changes with disease stage

Earlier stage

Insulin secretory function rises

Compensatory hyperinsulinemia develops

Euglycemia may be preserved

Later stage

Adaptation becomes insufficient

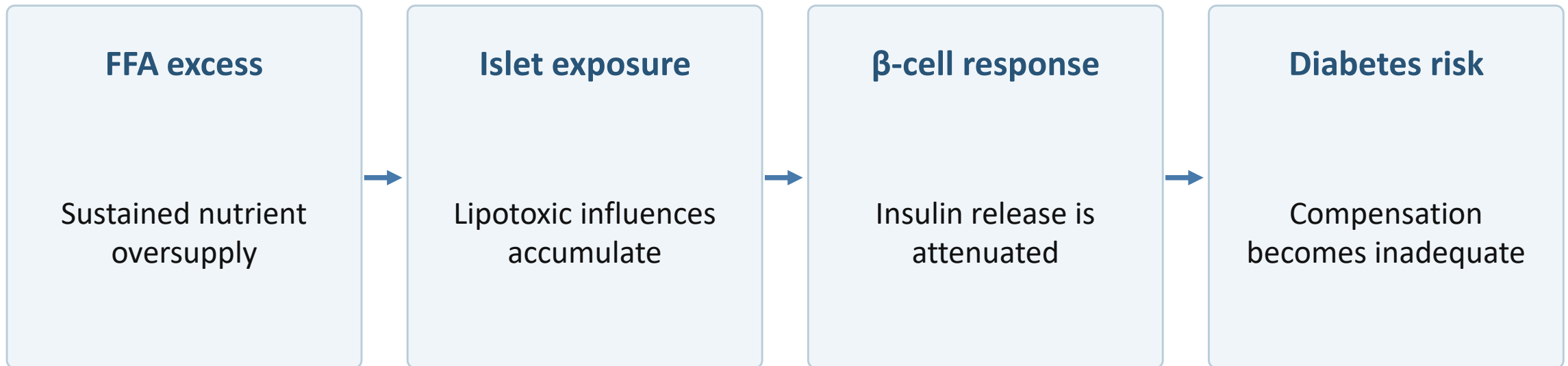
Relative insulin deficiency develops

Chronic hyperglycemia follows

Relative insulin deficiency is contextual

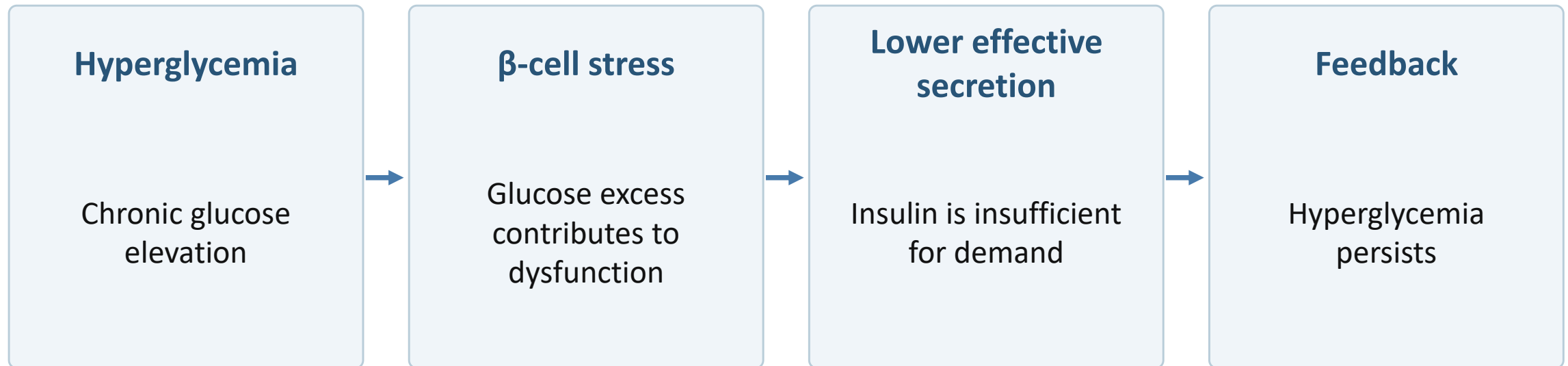
- Absolute insulin may still be detectable or substantial.
- For the prevailing resistance and glycemia, however, output is inadequate.
- Clinical dysfunction depends on supply relative to metabolic requirement.

β -cell lipotoxicity links excess FFAs to secretion failure



Lipotoxicity is a mechanism implicated by Robbins; The excerpt does not give a single indispensable molecular intermediate for the islet.

Glucotoxicity creates a second pressure on β cells



Glucotoxicity as a factor; Detailed molecular intermediates not specified.

An abnormal incretin effect may impair insulin output

- GIP and GLP-1 are gut-derived hormones that promote insulin release.
- Disturbance of the incretin effect among β -cell defects.
- The supplied excerpt does not establish a uniform defect in hormone secretion for all T2D.

Islet amyloid is associated with long-standing T2D

- Amyloid accumulation in pancreatic islets is a characteristic morphologic association.
- It is typically considered in the context of chronic β -cell dysfunction.
- The source cautions that its causal status is uncertain.

Islet amyloid: Observation versus interpretation

Established observation

Characteristic in long-standing T2D

Often found in examined diabetic islets

Represents an islet morphologic correlate

Causal uncertainty

May accompany progressive β -cell impairment

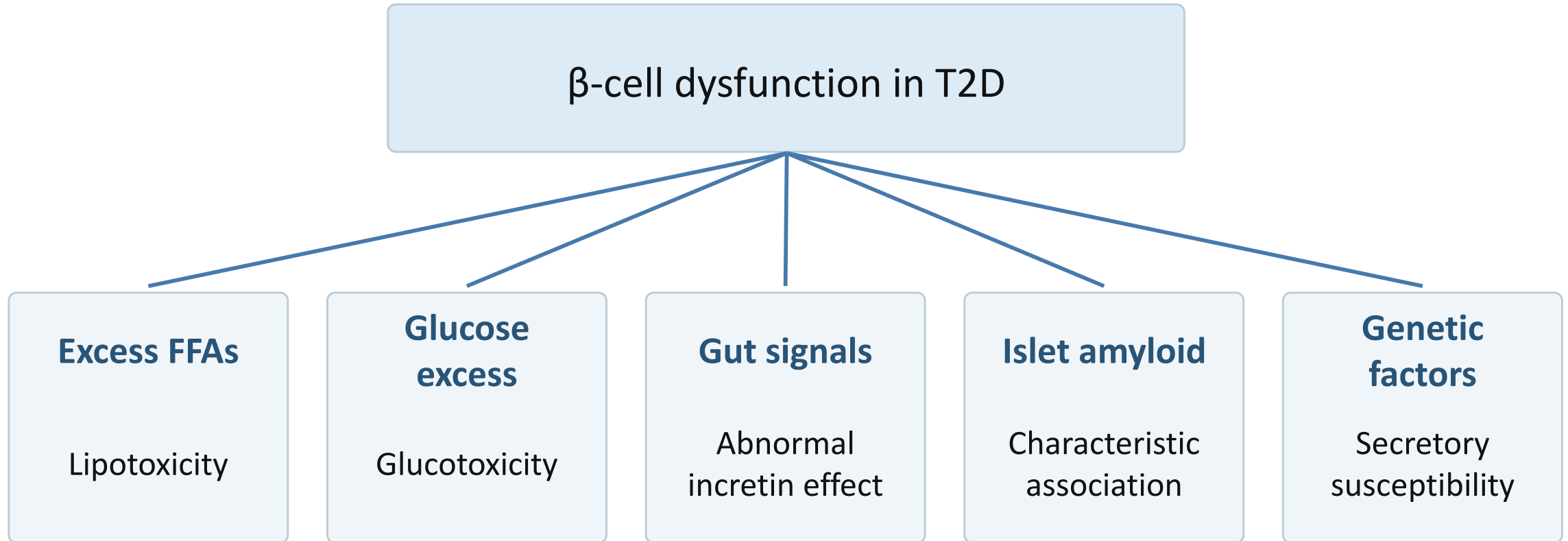
The source does not establish cause versus effect

Do not teach amyloid as the sole origin of β -cell failure

Genetic variation can affect secretory vulnerability

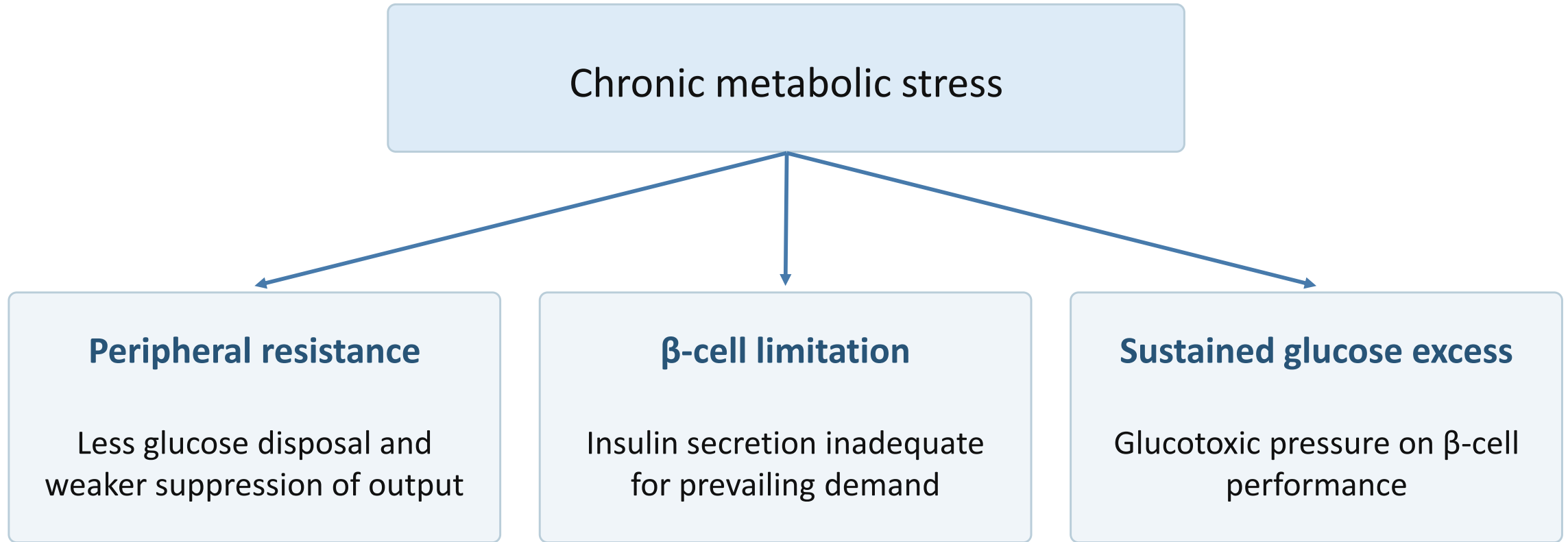
- Many risk-associated polymorphisms involve pathways governing insulin release.
- Genetic predisposition can influence capacity for β -cell adaptation.
- Sporadic T2D remains a complex interaction of genetic and acquired factors.

Factors implicated in β -cell dysfunction



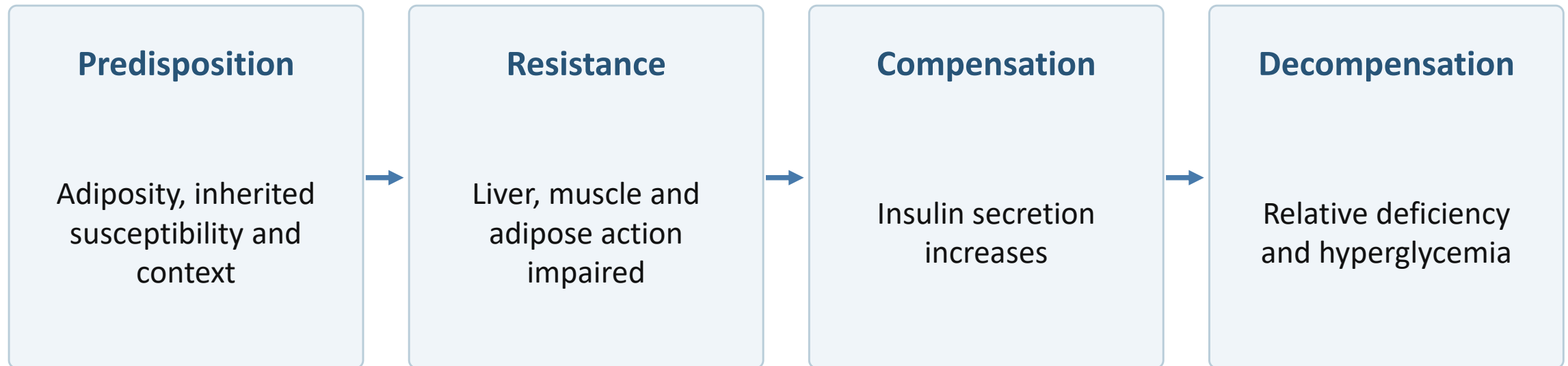
Islet amyloid is associated with T2D; A causal role is unconfirmed.

Insulin resistance and β -cell failure reinforce one another



Conceptual feedback synthesis supported by tissue mechanisms and named glucotoxicity.

A stage model for teaching the evolution of T2D



Conceptual stages; No clinical diagnostic cutoffs or precise times asserted.

T2D inflammation is not equivalent to T1D autoimmunity

T2D mechanism emphasized

Insulin resistance plus β -cell dysfunction

Nutrient-associated inflammatory signals

No established autoimmune basis

T1D mechanism contrasted

Immune-mediated β -cell destruction

Different upstream pathogenesis

Not the topic of this lecture

Clinicopathologic exercise: Elevated fasting glucose

Clinical observation

A person with central adiposity has elevated fasting glucose on repeated assessment.

Mechanistic interpretation

Which organ defect most directly explains fasting elevation?

Why?

Resistance to hepatic insulin action impairs suppression of endogenous glucose production. The liver continues to contribute glucose during fasting.

Clinicopathologic exercise: Exaggerated meal response

Clinical observation

An insulin-resistant person has a greater-than-expected glycemic rise after a meal.

Mechanistic interpretation

Which tissue response is deficient?

Why?

Skeletal-muscle glucose uptake and glycogen synthesis are not adequately stimulated by insulin. Post-meal glucose disposal is impaired.

Clinicopathologic exercise: Size alone is misleading

Clinical observation

An adult has no overt obesity by general appearance but has disproportionate visceral adiposity.

Mechanistic interpretation

Does a normal-looking body size exclude insulin resistance?

Why?

No. Visceral fat distribution is metabolically important, and BMI alone does not capture its location.

Clinicopathologic exercise: High insulin with dysglycemia

Clinical observation

An individual has insulin resistance and increased circulating insulin but already shows impaired glucose tolerance.

Mechanistic interpretation

How can insulin be elevated and still be inadequate?

Why?

Tissue responsiveness is reduced, so the amount of insulin required for normal glucose handling has increased.

Clinicopathologic exercise: Transition to overt diabetes

Clinical observation

After years of insulin resistance, glycemia becomes persistently elevated despite continued endogenous insulin production.

Mechanistic interpretation

Which second defect has become decisive?

Why?

β -cell output is now insufficient for metabolic requirements: Relative insulin deficiency.

Mechanistic recap: Identify the causal chain

- Liver: Inadequate suppression of glucose production → fasting hyperglycemia.
- Muscle: Reduced uptake / glycogen storage → postprandial hyperglycemia.
- Adipose tissue: Persistent lipolysis → elevated FFAs and downstream stress.
- β cells: Compensation eventually becomes inadequate → sustained diabetes.

Three distinctions that prevent diagnostic confusion

- Insulin resistance is impaired action, not automatically absent insulin.
- A high insulin concentration can coexist with inadequate metabolic effect.
- Islet amyloid is associated with T2D, but causation is unresolved.
- Central adiposity can be clinically relevant even without obvious obesity.

Core references and source boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).
- Chapter 24, The Endocrine System: Metabolic Defects in Type 2 Diabetes.
- Source text: printed pp. 1003–1004; no original chapter PDF or authorized histology images supplied.
- Related discussions of monogenic diabetes and complications are separate teaching units.