DIABETES MELLITUS

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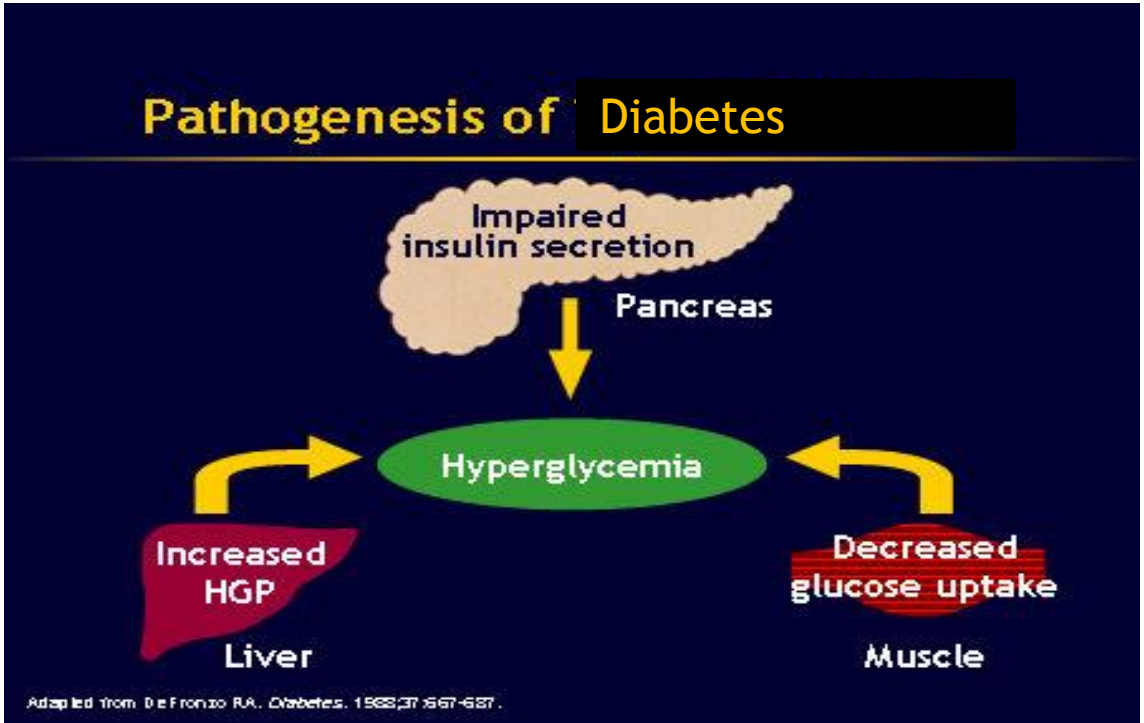
بسم الله الرحمن الرحیم

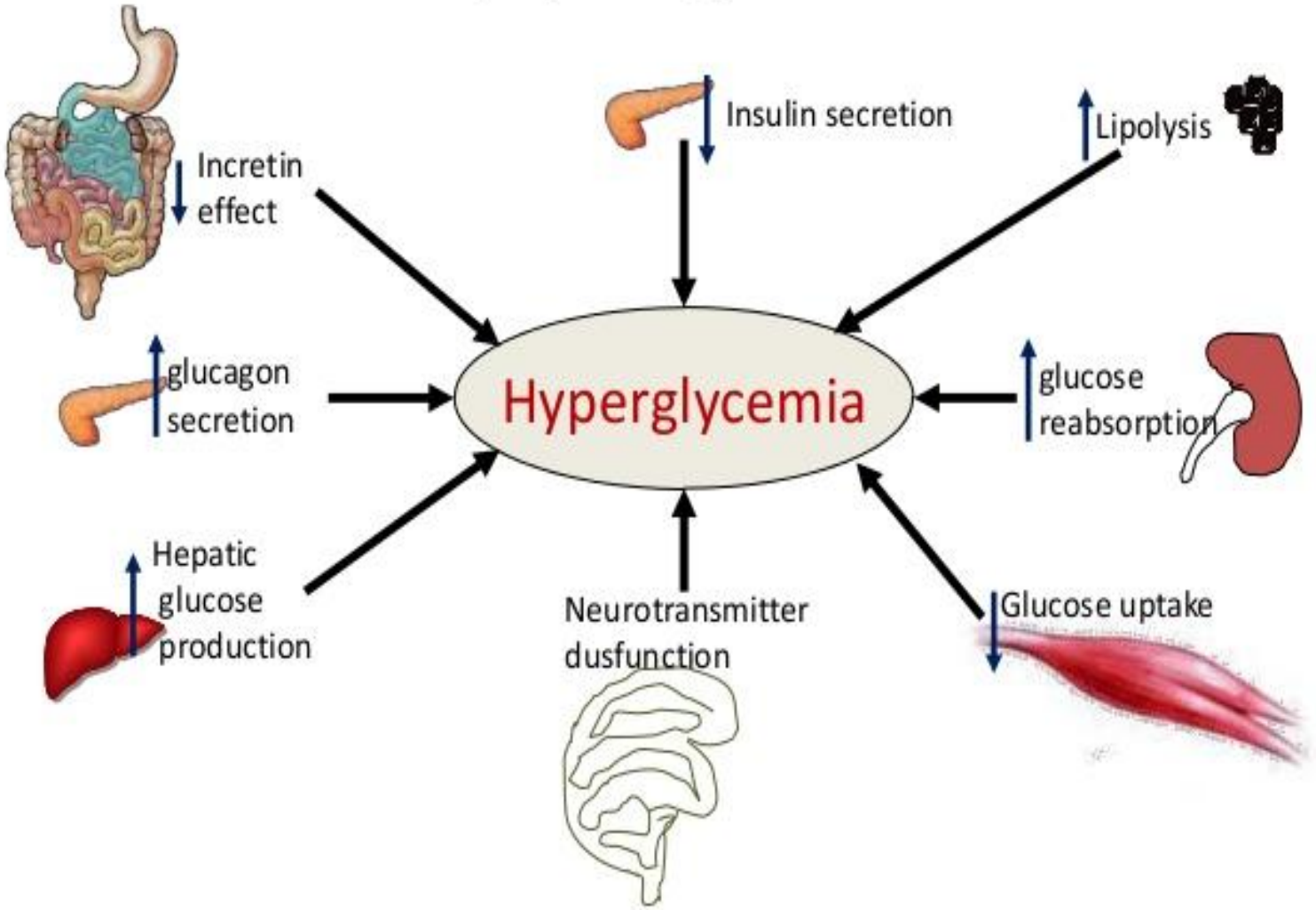
DEFINITION

- Hyperglycemia

- Due to reduced insulin secretion,
  decreased glucose utilization,
  and increased glucose production.



Pathophysiology of DM



DeFronzo R. Diabetes 2009;58:773-95.

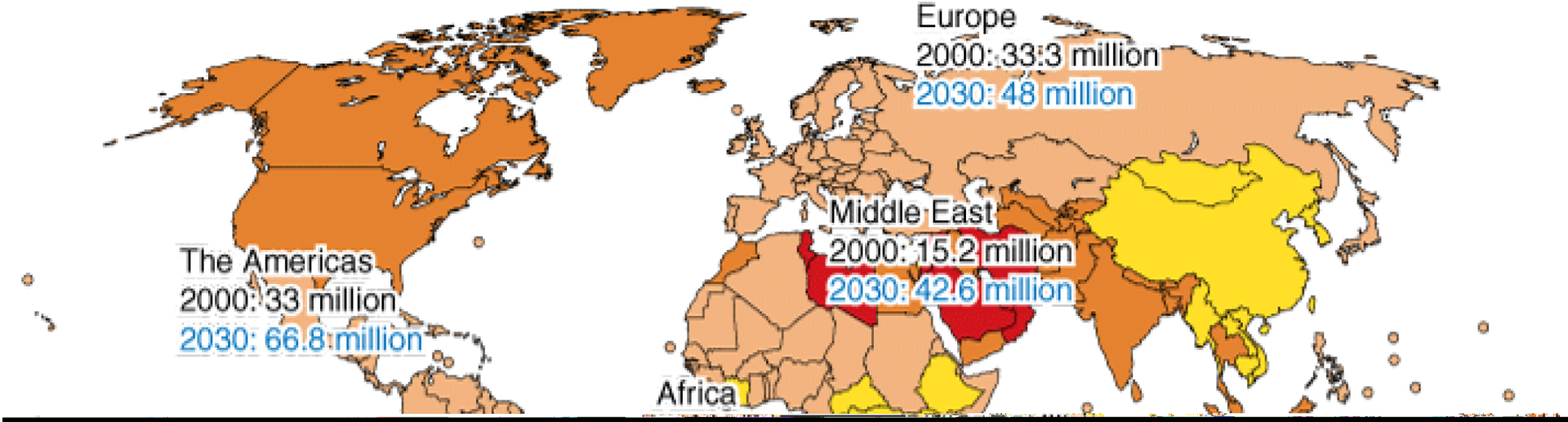
EPIDEMIOLOGY

- Based on current trends, 438 million individuals will have diabetes by the year 2030.
- The prevalence of type 2 DM is rising much more rapidly because of increasing obesity and reduced activity levels as countries become more industrialized.

EPIDEMIOLOGY

- Prevalence: 8.3% of the population
- DM increases with aging
- In individuals >60 years, the prevalence of DM was 26.9%.

Worldwide Prevalence of DM



- DM is the leading cause of
  end-stage renal disease (ESRD),
  lower extremity amputations,
  and adult blindness.
  It also predisposes to cardiovascular diseases.

Clinical Impact of Diabetes Mellitus

The leading cause of new cases of end-stage renal disease

A 2- to 4-fold increase in cardiovascular risk

Diabetes

The leading cause of new cases of blindness in working-aged adults

The leading cause of nontraumatic lower extremity amputations

Harris MI. In: *Diabetes in America.* 2nd ed. 1995. Washington, DC: National Institutes of Health; 1995. NIH publication 95-1468. Wingard DL et al. In: *Diabetes in America.* 2nd ed. 1995. NIH publication 95-1468. Kuller LH. In: *Diabetes in America.* 2nd ed. 1995. NIH publication 95-1468.

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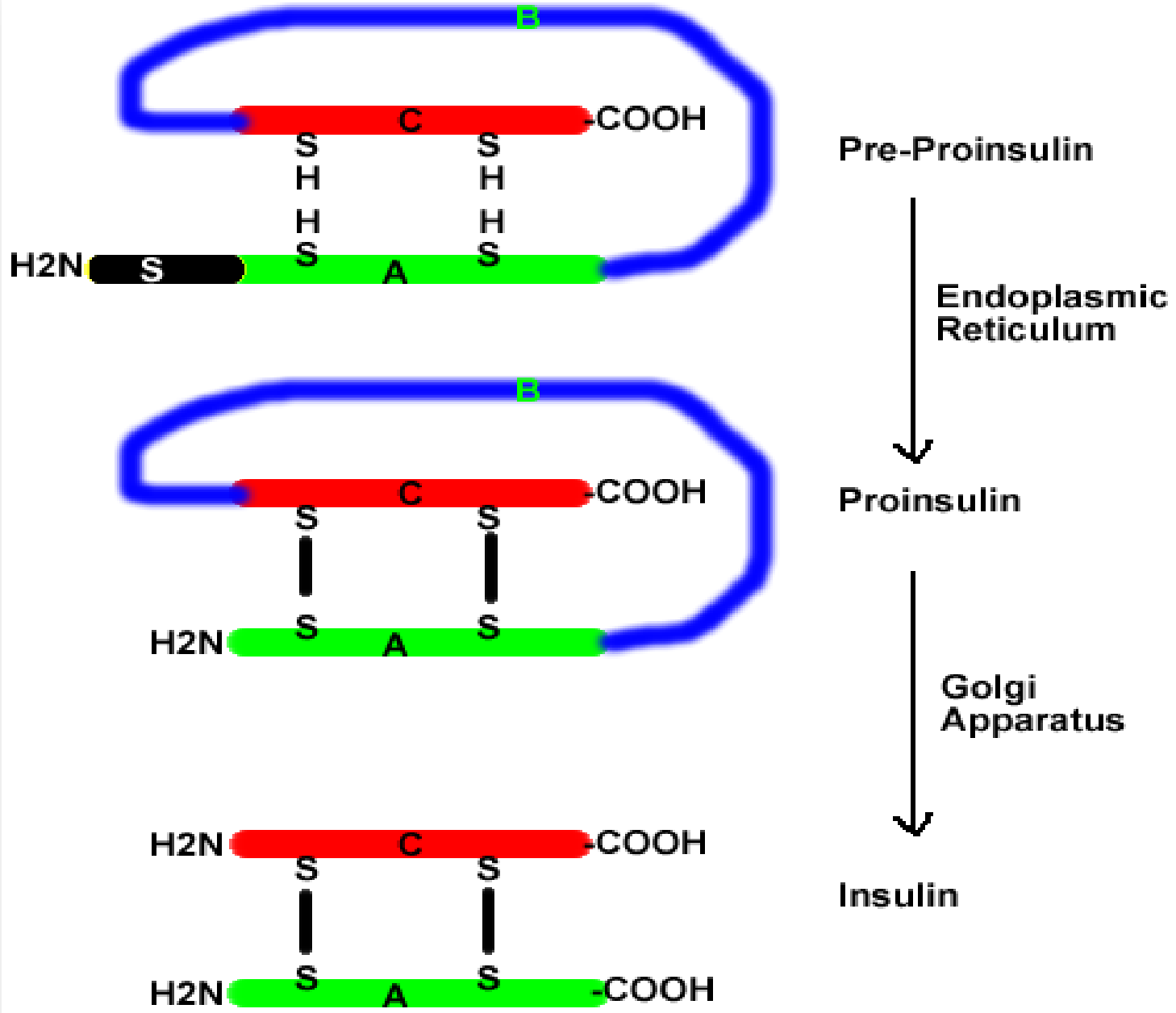
PATHOPHYSIOLOGY

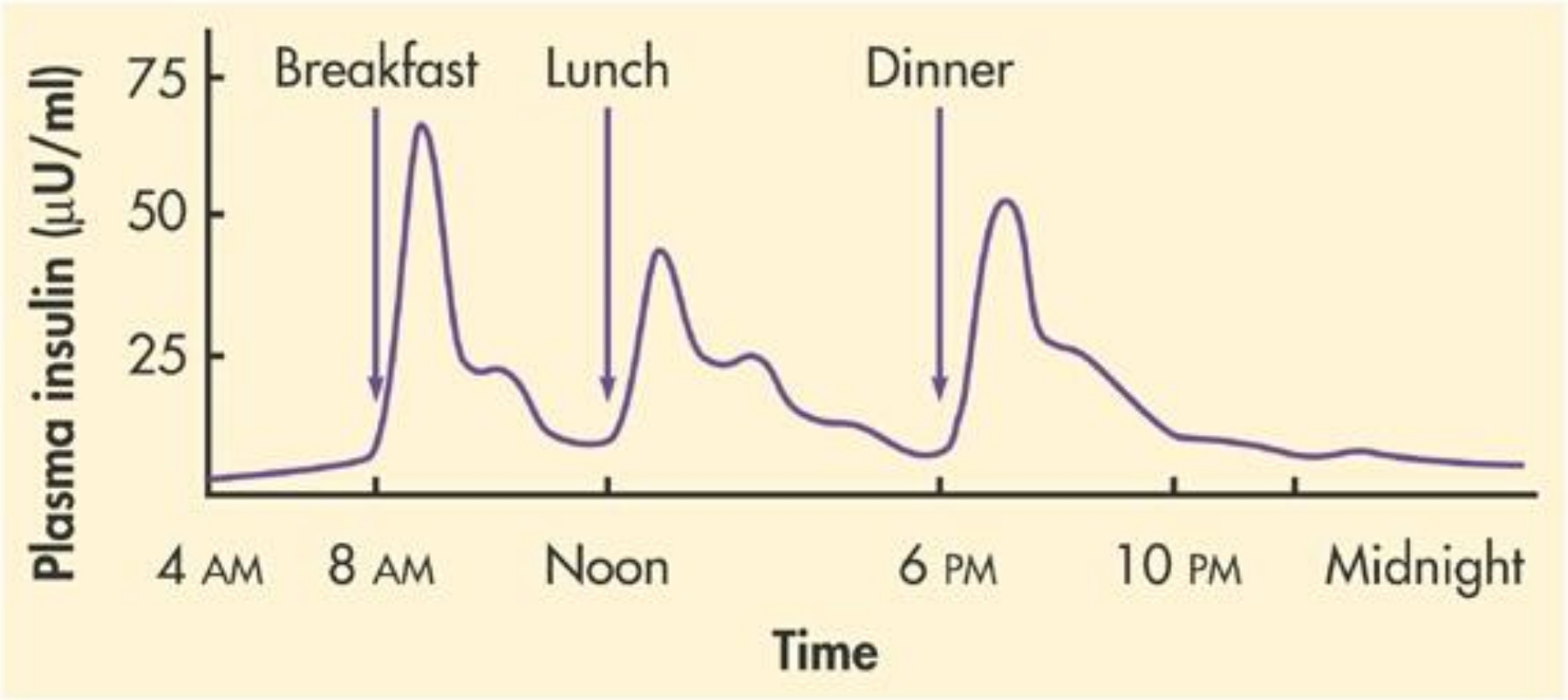
INSULIN BIOSYNTHESIS

- Insulin is produced in the beta cells of the pancreatic islets.
- It is initially synthesized as a single-chain 86-amino-acid precursor polypeptide,preproinsulin.
- Subsequent proteolytic processing removes the aminoterminal signal peptide, giving rise to proinsulin.
- Cleavage of an internal 31-residue fragment from proinsulin generates the C peptide and

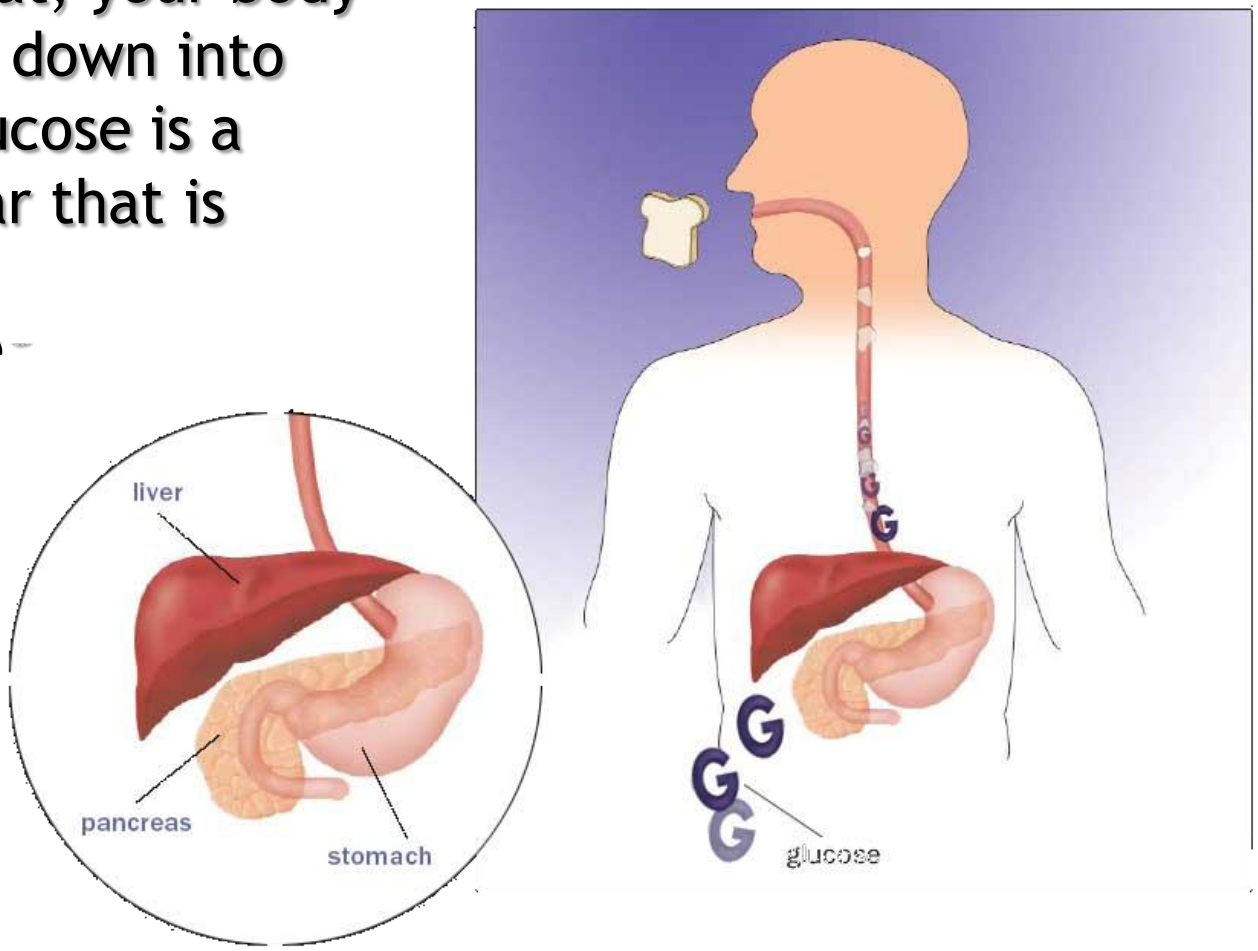
  the A (21 amino acids) and B (30 amino acids) chains of insulin, which are connected by disulfide bonds.


B
C
-COOH
S
H
H
S
S
H
H
S
H2N
S
A
S
Pre-Proinsulin
Endoplasmic Reticulum
B
C
-COOH
S
S
S
S
H2N
A
S
Proinsulin
Golgi Apparatus
H2N
C
-COOH
S
S
S
S
H2N
A
-COOH
S
Insulin

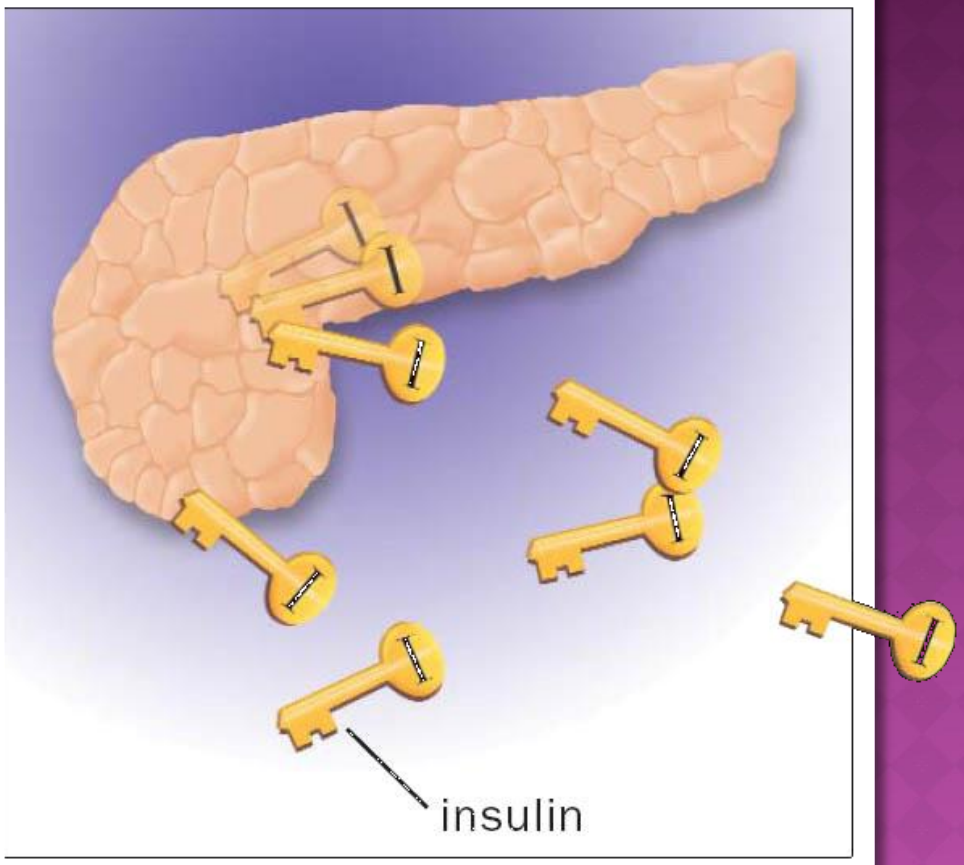
INSULIN SECRETION



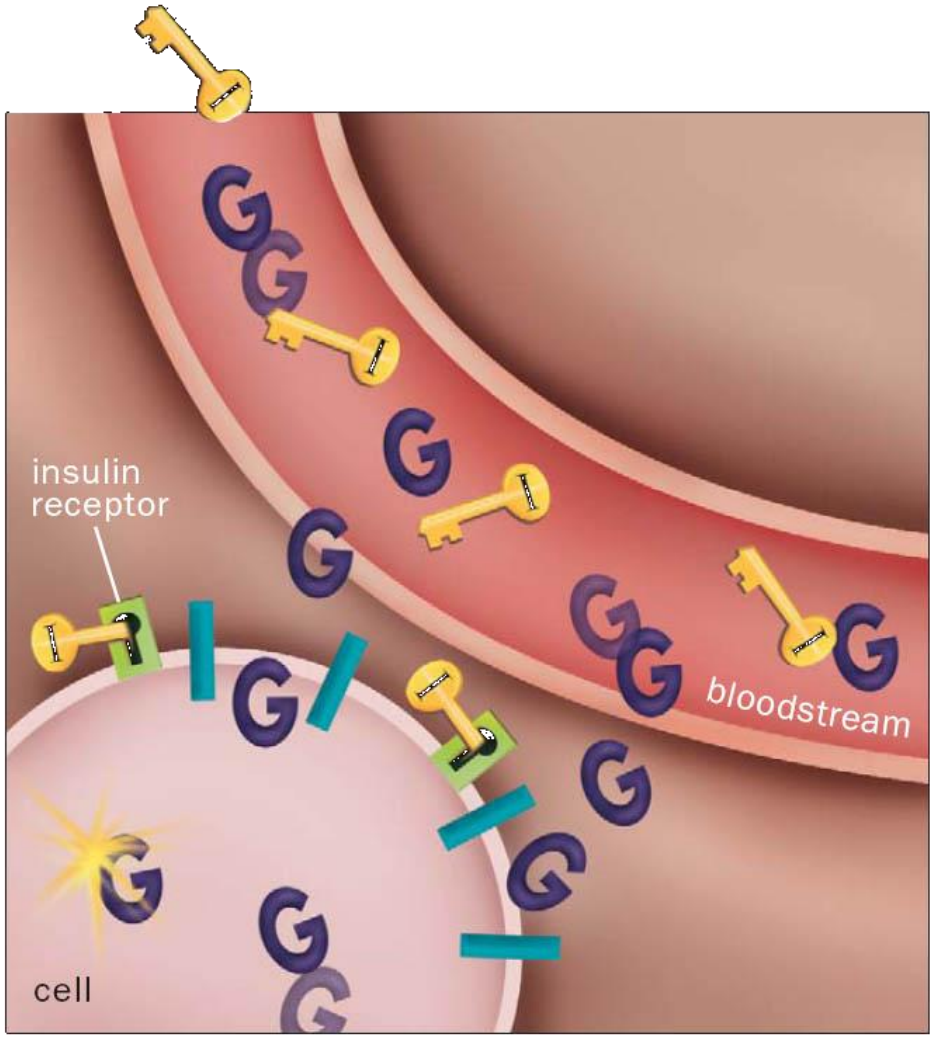
When you eat, your body breaks food down into glucose. Glucose is a type of sugar that is your body's main source of energy.



As blood glucose rises, the body sends a signal to the pancreas, which releases insulin.



Acting as a key, insulin binds to a place on the cell wall (an insulin receptor), unlocking the cell so glucose can pass into it. There, most of the glucose is used for energy right away.



REGULATION OF PLASMA GLUCOSE LEVEL

- Plasma glucose is tightly regulated by hormones:

Insulin: ↓ Plasma glucose

- **Glucagon**
  Epinephrine
  Cortisol
  Growth hormone

} **↑ Plasma glucose**

NORMAL INSULIN METABOLISM

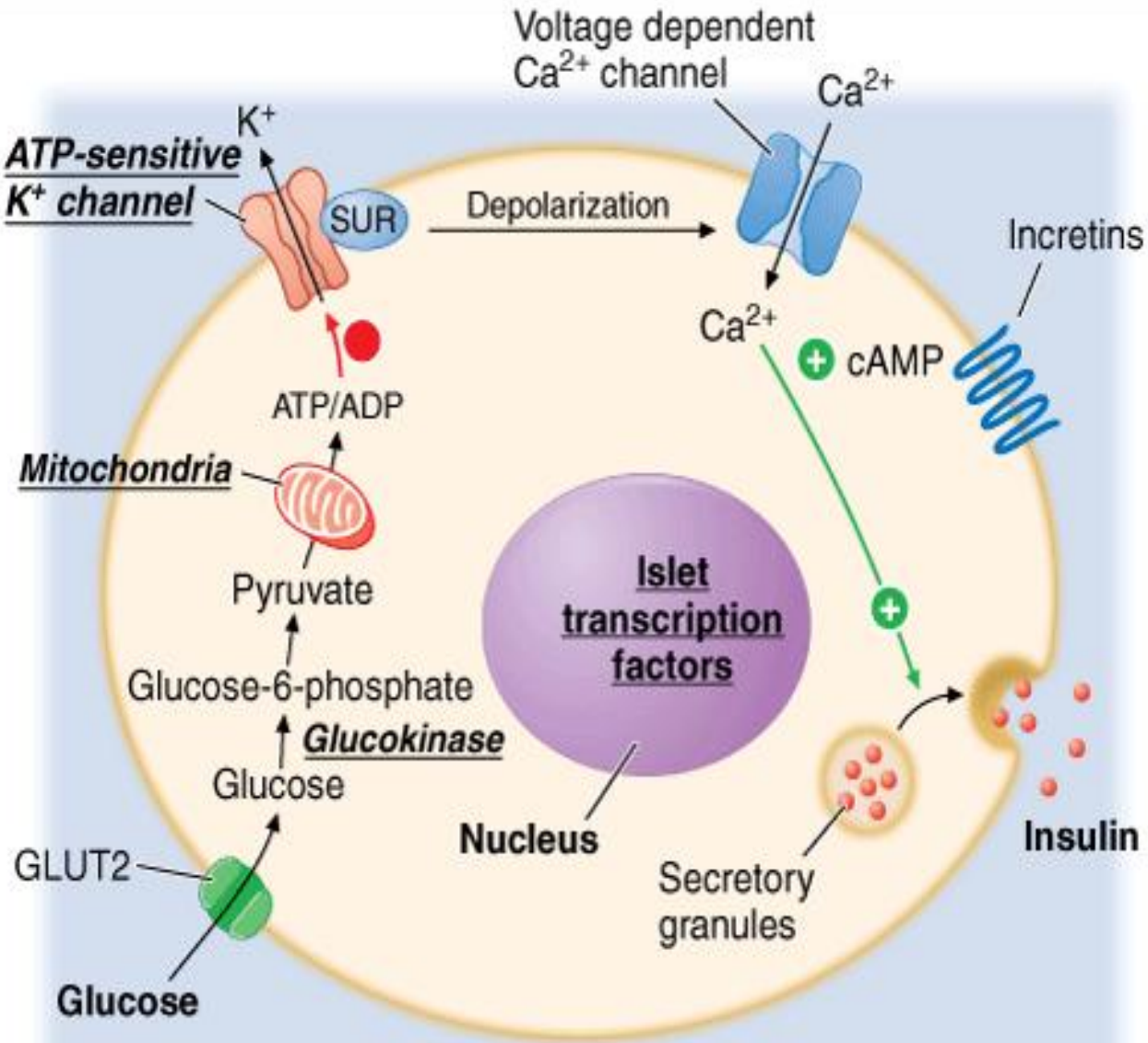
- ↑ Insulin after a meal:
  - stimulates storage of glucose as glycogen
  - inhibits gluconeogenesis
  - enhances fat deposition in adipose tissue
  - increases protein synthesis

NORMAL INSULIN METABOLISM

- [redacted]
  - Counter-regulatory hormones (especially glucagon) stimulate glycogen → glucose
- When glucose unavailable during fasting state
  - Lipolysis (fat breakdown)
  - Proteolysis (amino acid breakdown)

INSULIN SECRETION

- Glucose > 70 mg/dl is the key regulator of insulin secretion by the pancreatic beta cell.
- Although amino acids, ketones, various nutrients, gastrointestinal peptides, and neurotransmitters also influence insulin secretion.
- Glucose stimulation of insulin secretion begins with its transport into the beta cell by the GLUT2 glucose transporter .


Voltage dependent
Ca^{2+} channel
Ca^{2+}
K^+
ATP-sensitive
K^+ channel
SUR
Depolarization
Incretins
Ca^{2+}
cAMP
ATP/ADP
Mitochondria
Pyruvate
Islet
transcription
factors
Glucose-6-phosphate
Glucokinase
Glucose
Nucleus
Insulin
GLUT2
Secretory
granules
Glucose

INSULIN SECRETION

- Incretins are released from neuroendocrine cells of the GI tract following food ingestion and amplify glucose-stimulated insulin secretion and suppress glucagon secretion.
- Glucagon-like peptide 1 (GLP-1), the most potent incretin, is released from L cells in the small intestine and stimulates insulin secretion only when the blood glucose is above the fasting level.
- Incretin analogues, such as exenatide, are being used to enhance endogenous insulin secretion.

CLASSIFICATION

- I. Type 1 diabetes
  - A. Immune-mediated
  - B. Idiopathic
- II. Type 2 diabetes
- III. Secondary
  - A. MODY
  - B. Genetic defects in insulin action:
    1. Type A insulin resistance
    2. Leprechaunism
    3. Rabson Mendenhall syndrome
    4. Lipodystrophy syndromes
  - C. Diseases of the exocrine pancreas
  - D. Endocrinopathies
  - E. Drug- or chemical-induced
  - F. Infections
- IV. Gestational diabetes mellitus (GDM)

DM 1 AND DM 2

- Type 1 diabetes is the result of complete or near-total insulin deficiency.

- Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production.

TYPE 1 DIABETES MELLITUS ONSET OF DISEASE

- Weight loss
- Polydipsia (excessive thirst)
- Polyuria (frequent urination)
- Polyphagia (excessive hunger)
- Weakness and fatigue
- Ketoacidosis

CLINICAL MANIFESTATIONS TYPE 2 DIABETES MELLITUS

- Non-specific symptoms
- Fatigue
- Recurrent infections
- Prolonged wound healing
- Visual changes

PATHOGENESIS TYPE 1 DM

- Genetic factors
- Environmental factors
- Immunologic factors

- Identification of an environmental trigger has been difficult because the event may precede the onset of DM by several years.

Etiology of Type 1 Diabetes

Environmental Factors

Viruses

e.g.
- Coxsackie
- Mumps
- Rubella

Nutrients

↓

e.g. Cow milk

Babies → Cow milk → Antibodies against cow insulin

↓

Closely resembles human insulin

← May attack β cells

- Markers of the immune destruction include:
  - ✓islet cell auto-Ab (ICA)
  - ✓auto-Ab to insulin(AIA)
  - ✓auto-Ab to glutamic acid decarboxylase (GAD65)
  - ✓auto-Ab to the tyrosine phosphatases IA-2

- One and usually more of these auto-Ab are present in 85–90% of individuals when fasting hyperglycemia is initially detected.

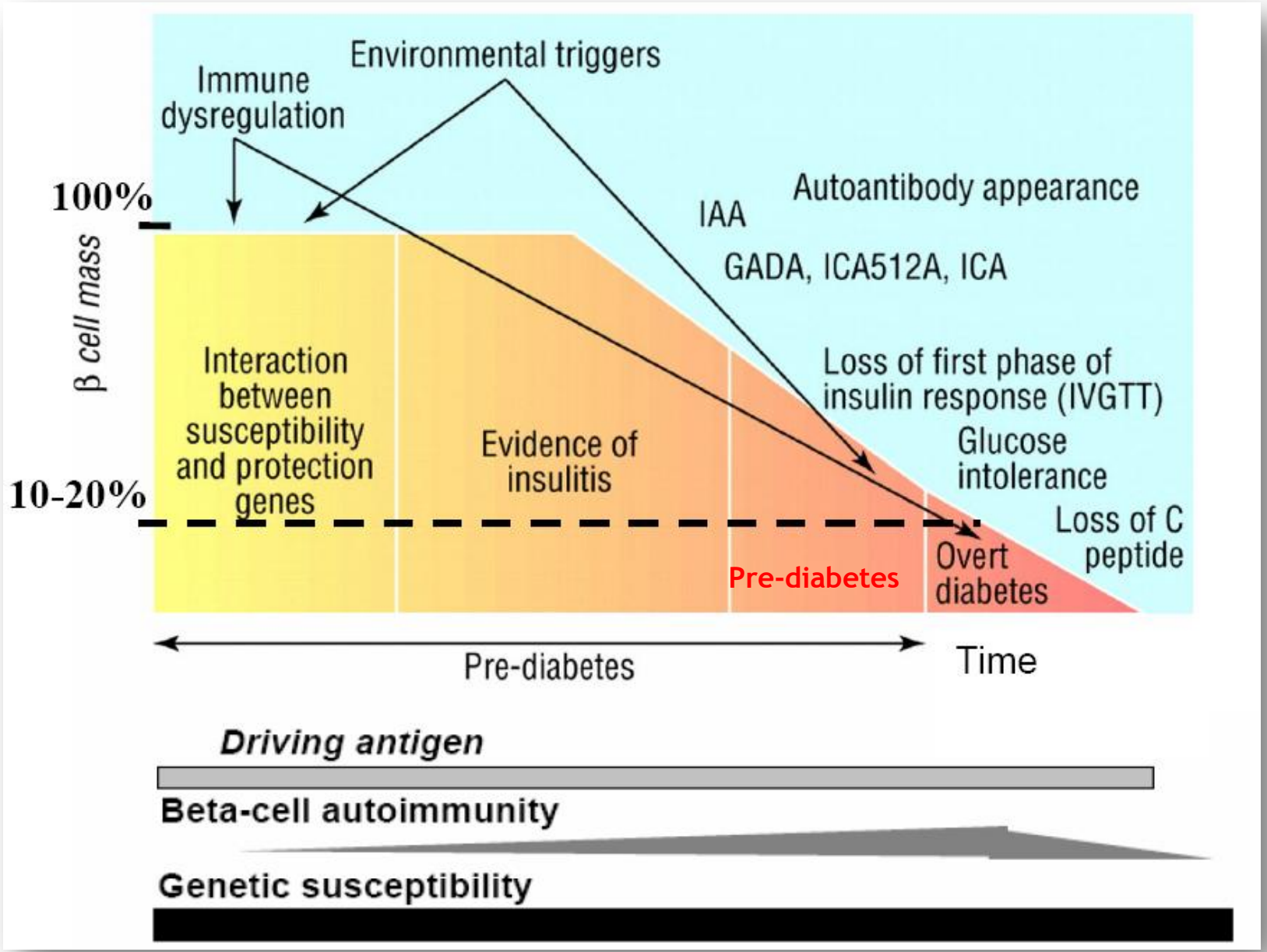
- At present, the measurement of ICAs in nondiabetic individuals is a research tool because no treatments have been approved to prevent the occurrence or progression to type 1 DM.

DIABETES TYPE 1B - IDIOPATHIC

- Some individuals who have the clinical phenotype of type 1 DM lack immunologic markers indicative of an autoimmune process involving the beta cells.

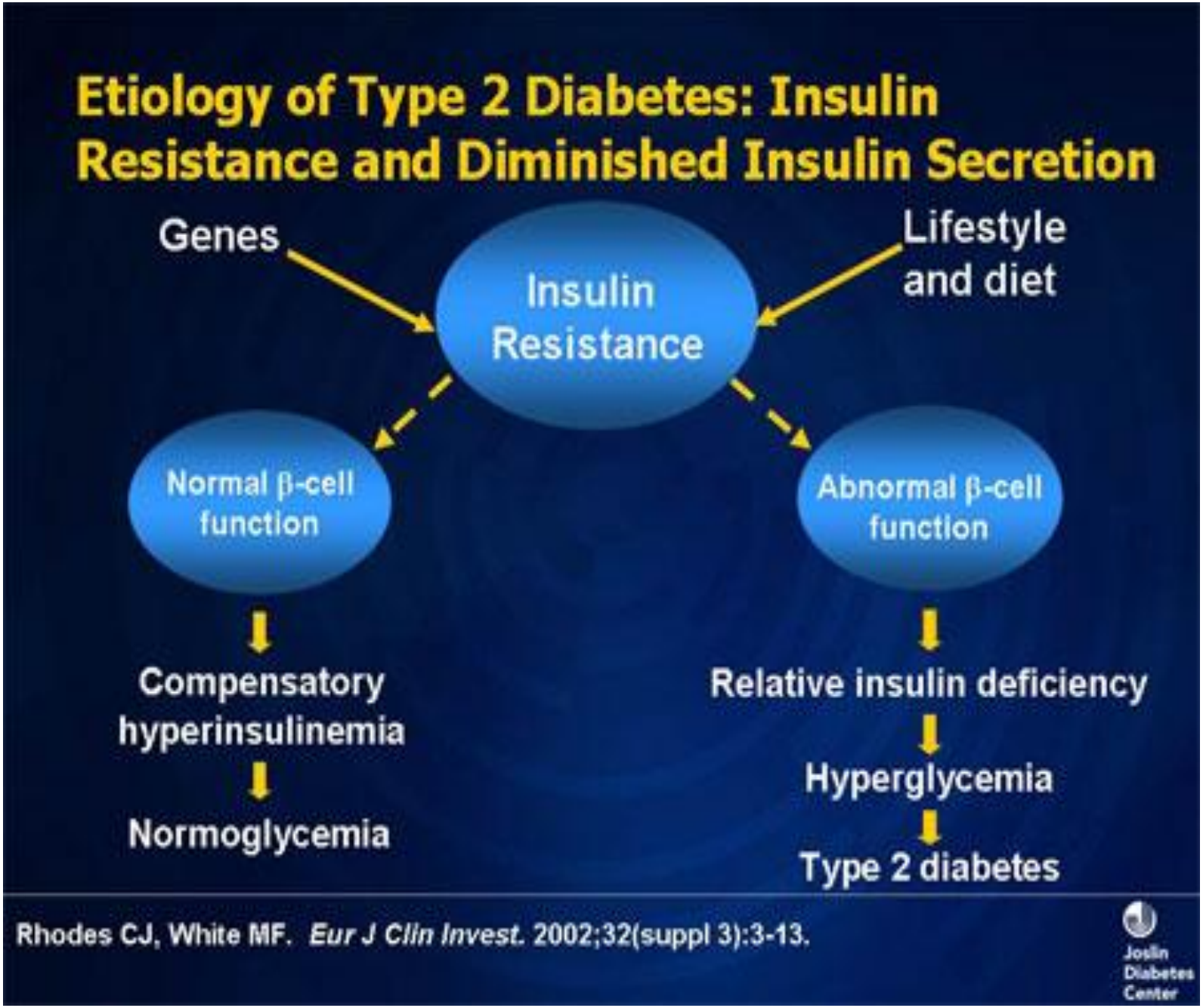
- These individuals are thought to develop insulin deficiency by unknown, nonimmune mechanisms and are ketosis prone; many are African American or Asian in heritage.

NATURAL HISTORY OF T1DM

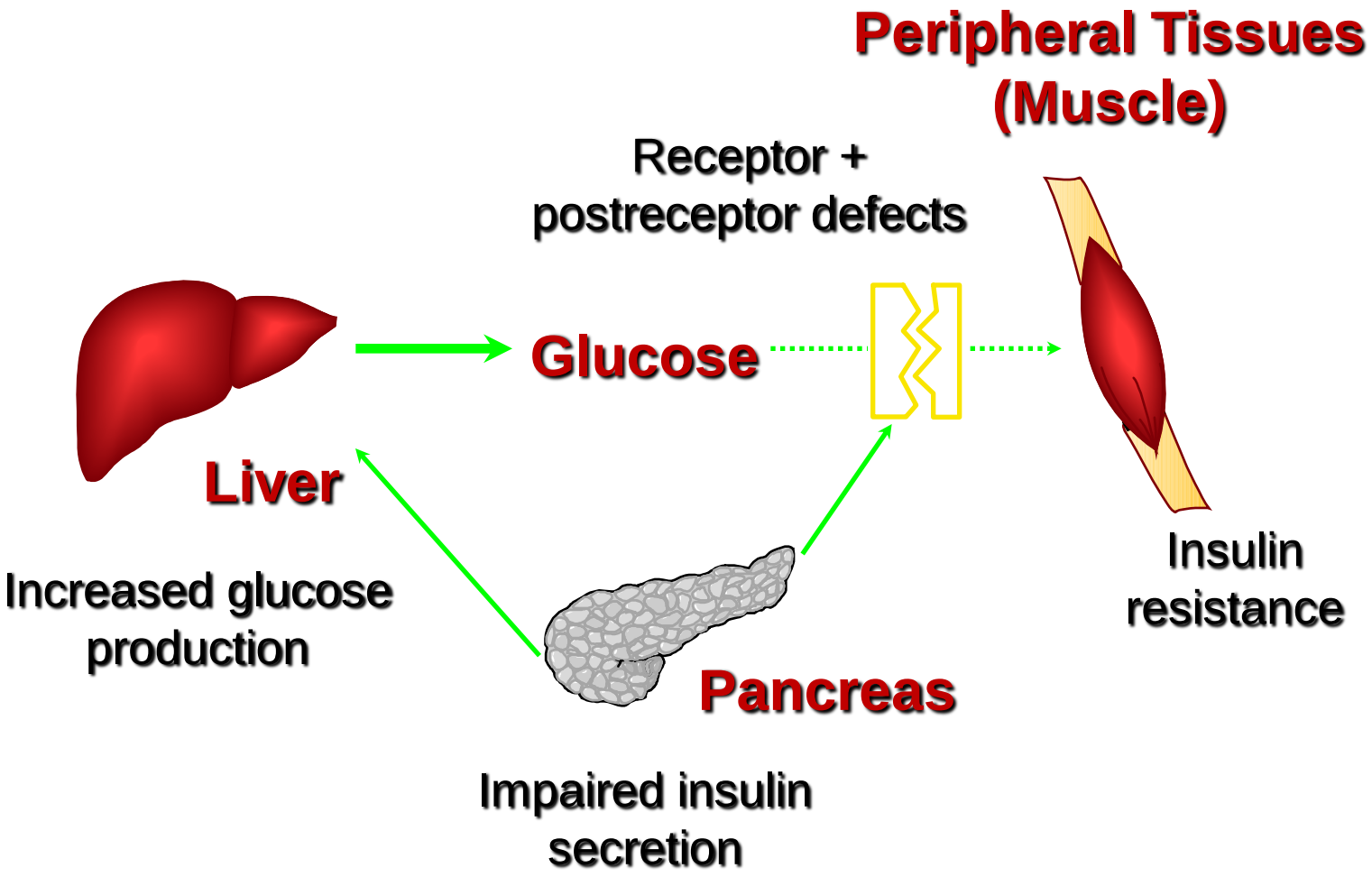


PATHOGENESIS TYPE 2 DM

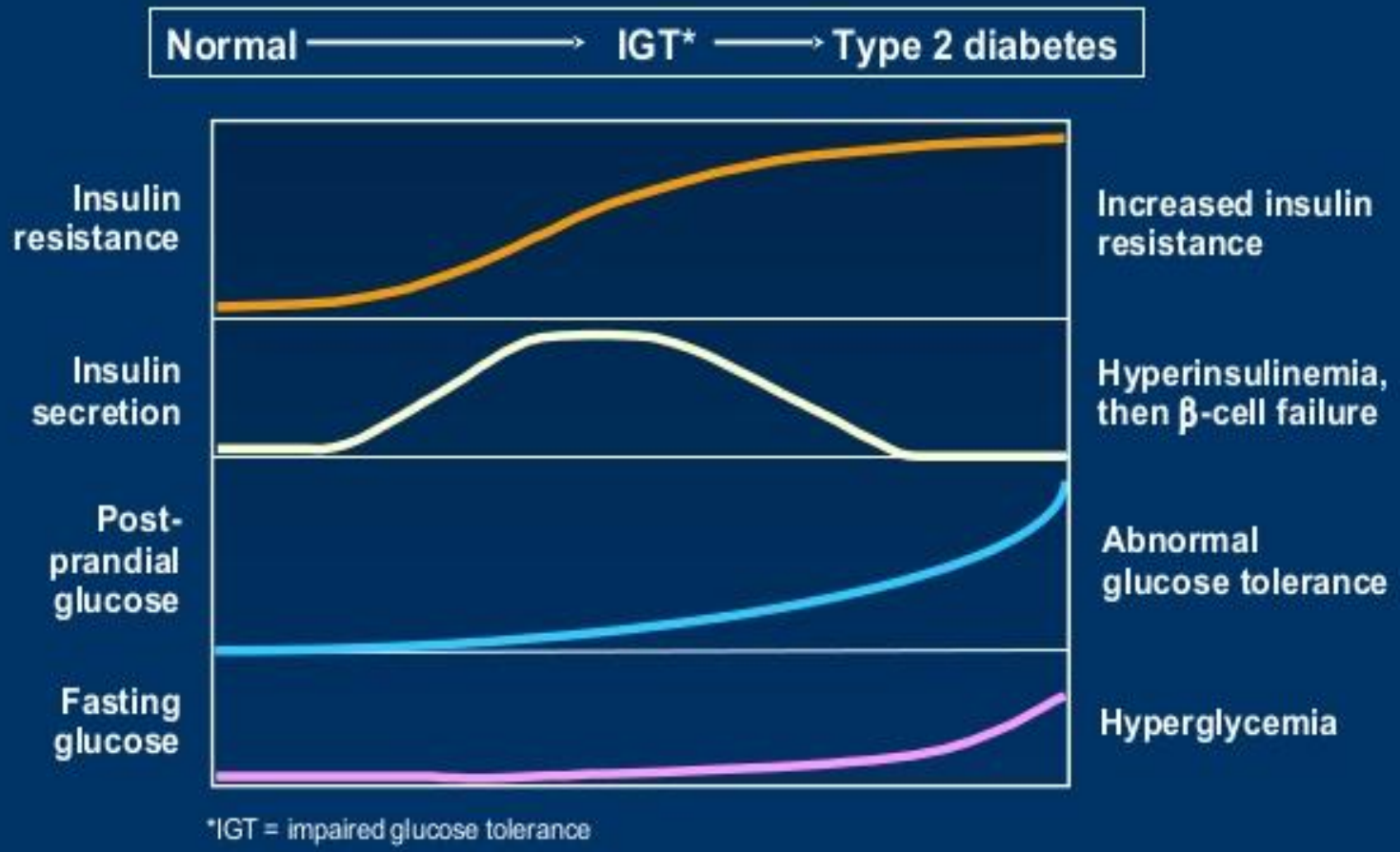
- Genetic Considerations
- Metabolic Abnormalities
  - Abnormal Muscle and Fat Metabolism
  - Impaired Insulin Secretion
  - Increased Hepatic Glucose and Lipid Production
- Insulin Resistance Syndromes


Etiology of Type 2 Diabetes: Insulin Resistance and Diminished Insulin Secretion
Genes
Lifestyle and diet
Insulin Resistance
Normal β-cell function
Abnormal β-cell function
Compensatory hyperinsulinemia
Normoglycemia
Relative insulin deficiency
Hyperglycemia
Type 2 diabetes
Rhodes CJ, White MF. Eur J Clin Invest. 2002;32(suppl 3):3-13.
Joslin Diabetes Center

PATHOPHYSIOLOGY OF T2DM



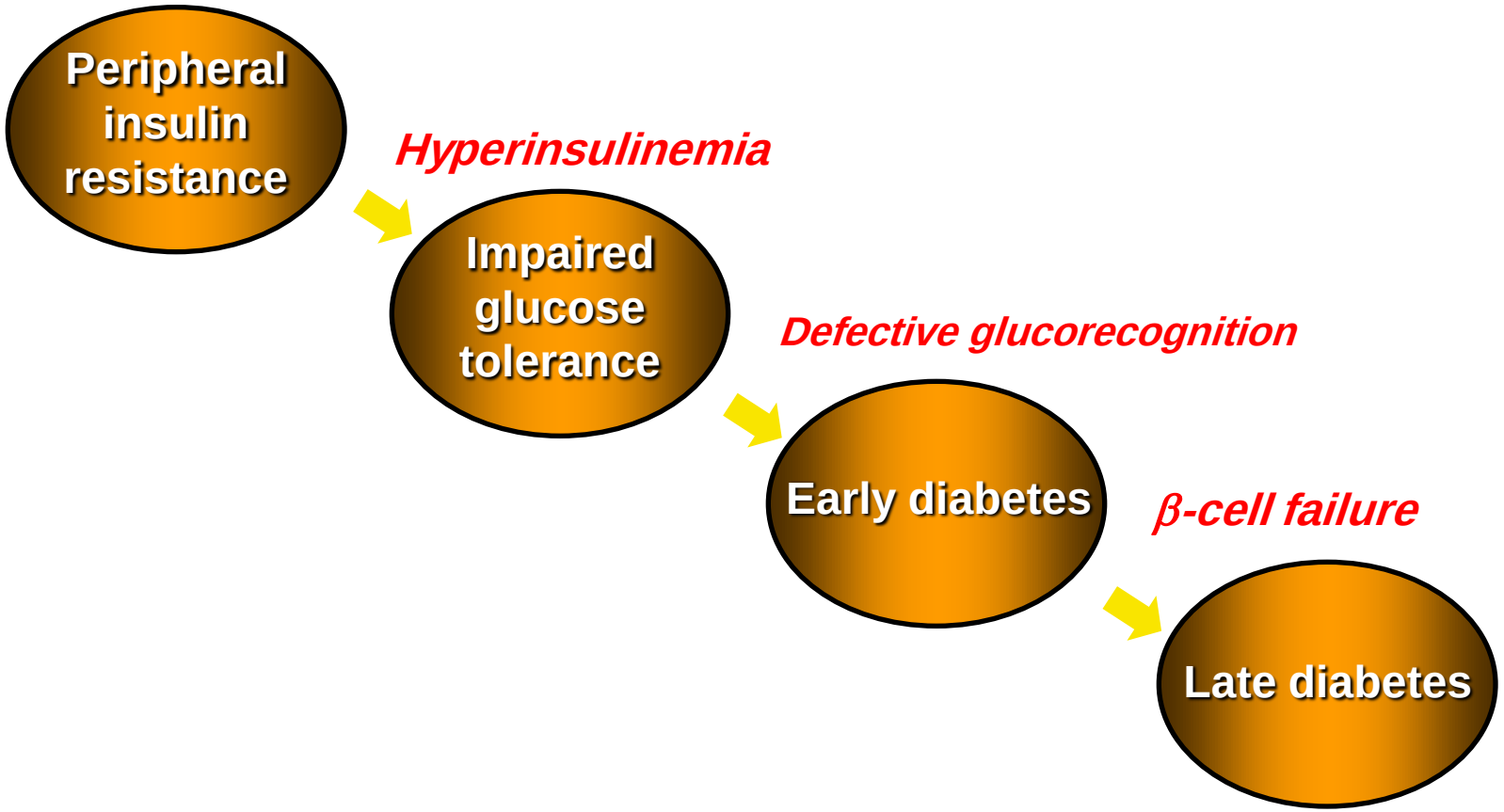
How do insulin resistance and β-cell dysfunction combine to cause type 2 diabetes?



*IGT = impaired glucose tolerance

Adapted from *Type 2 Diabetes BASICS*. International Diabetes Center (IDC), Minneapolis, 2000.

METABOLIC STAGING OF T2DM



Saltiel AR, Olefsky JM. Diabetes. 1996;45:1661-1669.

- The reason(s) for the decline in insulin secretory capacity in type 2 DM is unclear.
  - amyloid deposits
  - glucose toxicity
  - Lipotoxicity

- Beta cell mass is decreased in individuals with long-standing type 2 diabetes.

TYPE 1 DM PREVENTION

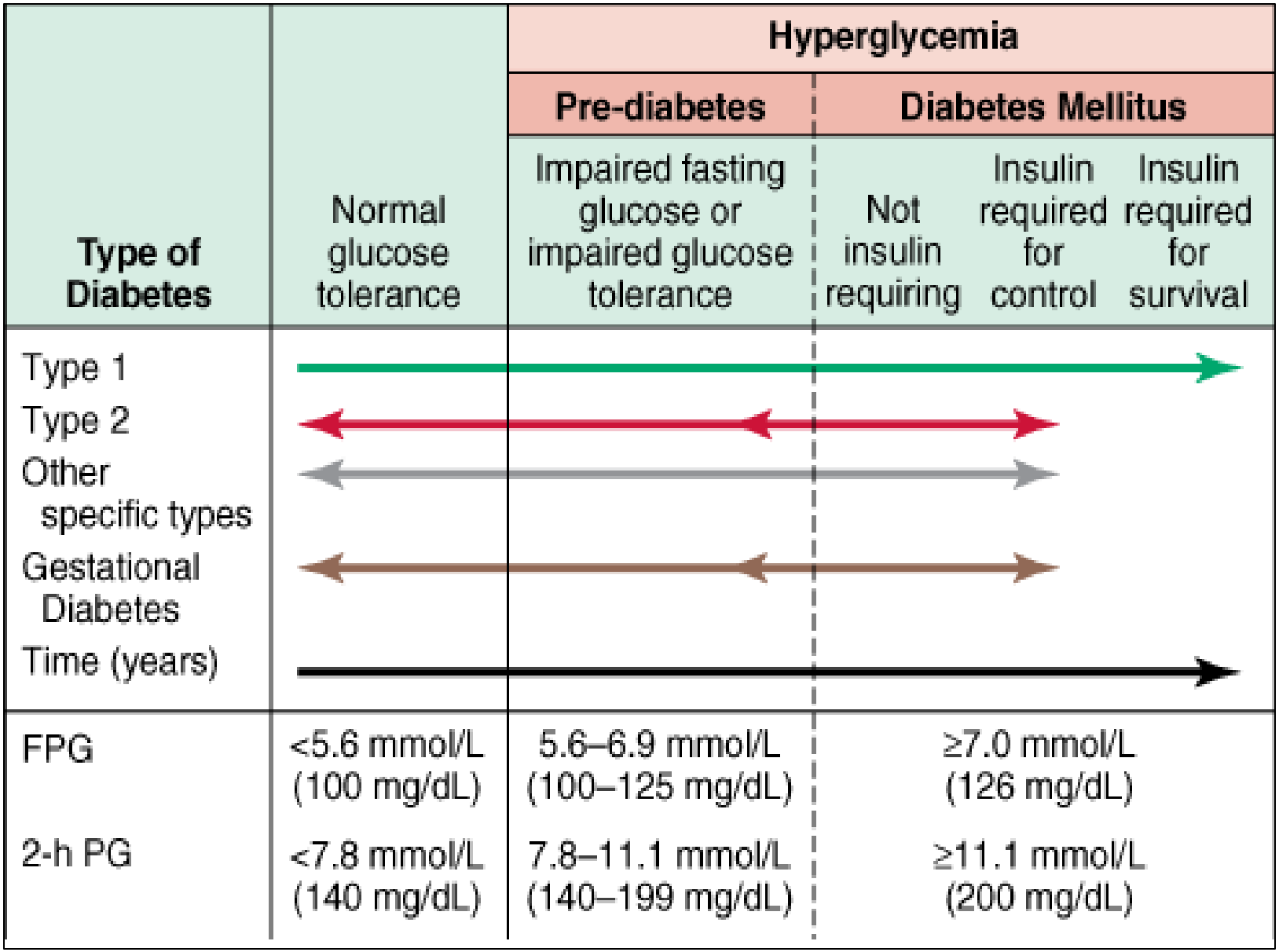
- Immunosuppression
- These interventions have not been successful in preventing type 1 DM in humans.
- In patients with new-onset type 1 diabetes, treatment with anti-CD3 monoclonal antibodies, a GAD vaccine, and anti-B lymphocyte monoclonal antibody has recently been shown to slow the decline in C-peptide levels.

TYPE 2 DM PREVENTION

- intensive changes in lifestyle (diet and exercise for 30 min/day five times/week) in individuals with IGT prevented or delayed the development of type 2 DM by 58% compared to placebo.
- In the same study, metformin prevented or delayed diabetes by 31% compared to placebo.
- acarbose, thiazolidinediones, and orlistat prevent or delay type 2 DM but are not approved for this purpose.

TYPE 2 DM PREVENTION

- Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for:
  - with BMI ≥35 kg/m2
  - aged<60 years
  - women with prior gestational diabetes mellitus
  - and/or those with rising A1C despite lifestyle intervention.


Hyperglycemia
Pre-diabetes
Diabetes Mellitus
Type of Diabetes
Normal glucose tolerance
Impaired fasting glucose or impaired glucose tolerance
Not insulin requiring
Insulin required for control
Insulin required for survival
Type 1
Type 2
Other specific types
Gestational Diabetes
Time (years)
FPG
<5.6 mmol/L (100 mg/dL)
5.6–6.9 mmol/L (100–125 mg/dL)
≥7.0 mmol/L (126 mg/dL)
2-h PG
<7.8 mmol/L (140 mg/dL)
7.8–11.1 mmol/L (140–199 mg/dL)
≥11.1 mmol/L (200 mg/dL)