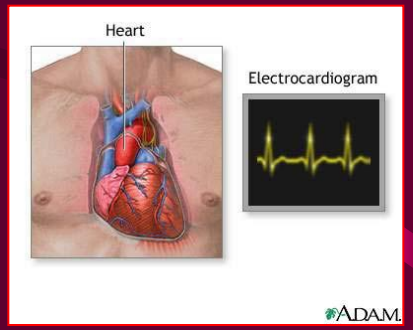
JSC «Astana Medical University»
Department of Internal Medicine №1

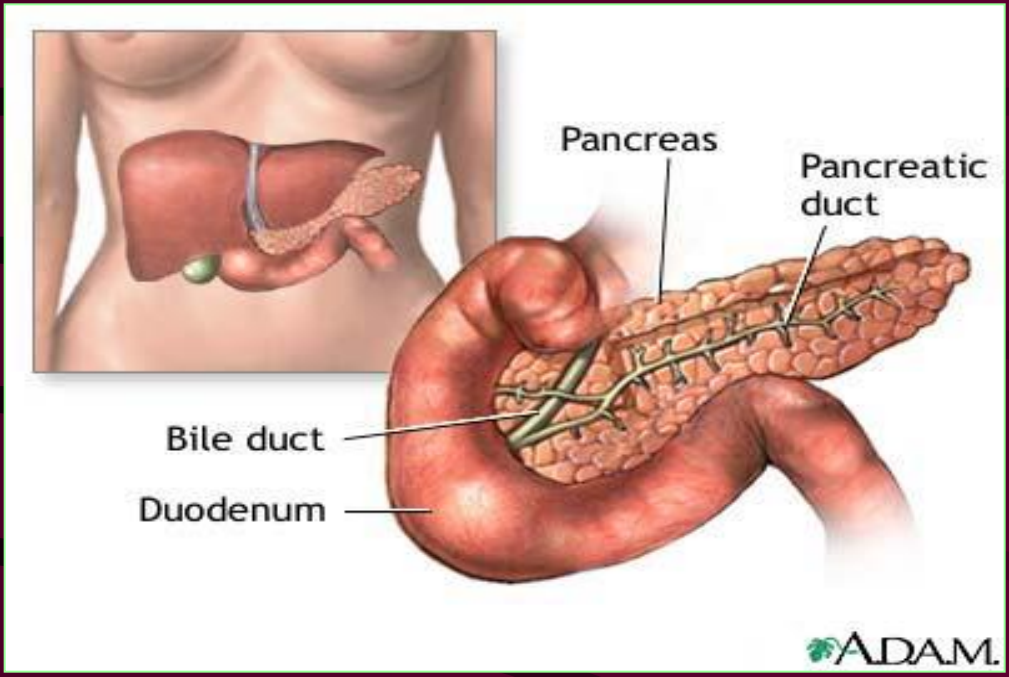


Done by Abduova L.M., 445 GM
Checked by Baidurin S.A.

Plan

- Introduction
- Regulation of Plasma Glucose Level
- Classification of DM
- Etiology
- Risk factors
- Pathophysiology
- Clinical presentation
- Gestational diabetes
- Other types of DM
- Bibliography

Introduction.
What is diabetes?



- **Diabetes mellitus (DM) is a chronic condition that is characterised by raised blood glucose levels (Hyperglycemia).**

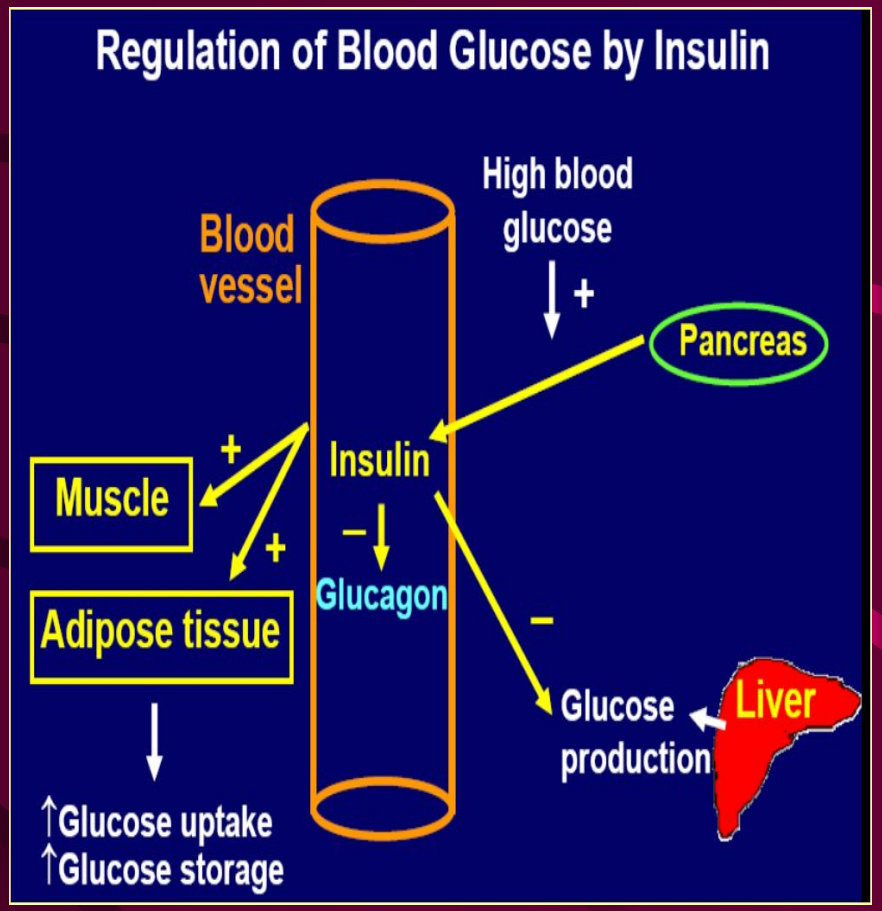
Regulation of Plasma Glucose Level

- Plasma glucose is tightly regulated by hormones:

Insulin: ↓ Plasma glucose

- Glucagon
  Epinephrine
  Cortisol
  Growth hormone

↑ Plasma glucose



Classification of DM

1. Type 1 DM

- It is due to insulin deficiency and is formerly known as.
  - Type I
  - Insulin Dependent DM (IDDM)
  - Juvenile onset DM

2. Type 2 DM

- It is a combined insulin resistance and relative deficiency in insulin secretion and is frequently known as.
  - Type II
  - Noninsulin Dependent DM (NIDDM)
  - Adult onset DM

3. Gestational Diabetes Mellitus (GDM):

- Gestational Diabetes Mellitus (GDM) developing during some cases of pregnancy but usually disappears after pregnancy.

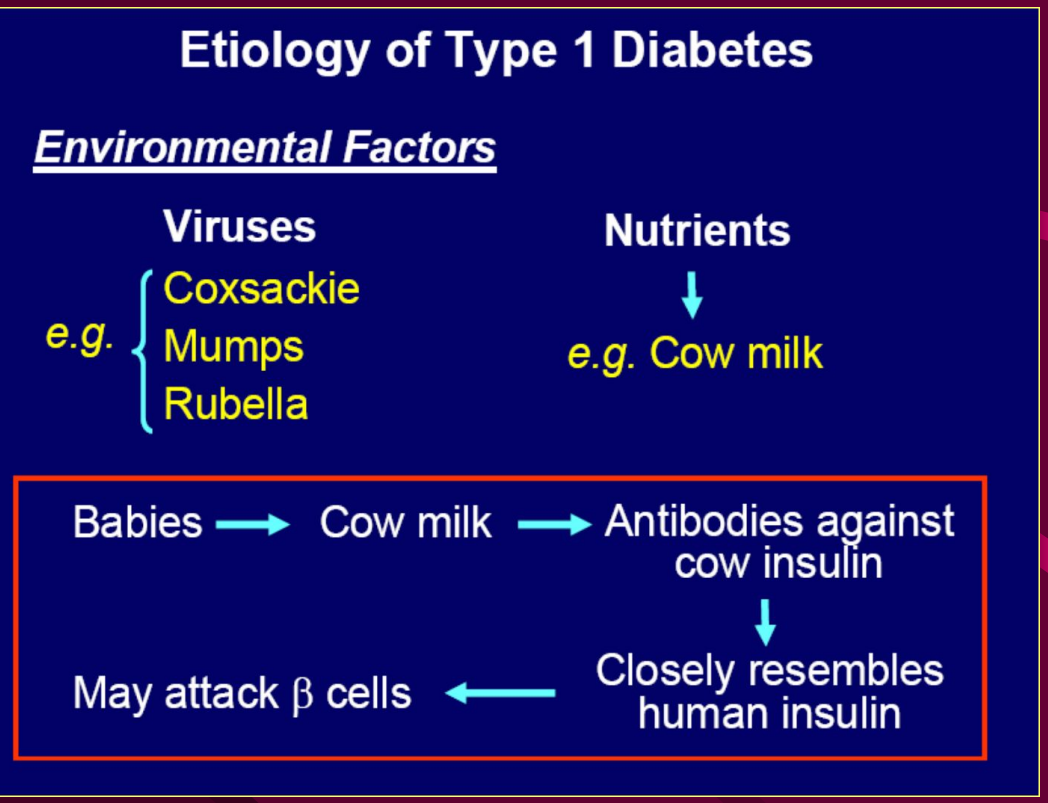
4. Other types:

- Secondary DM

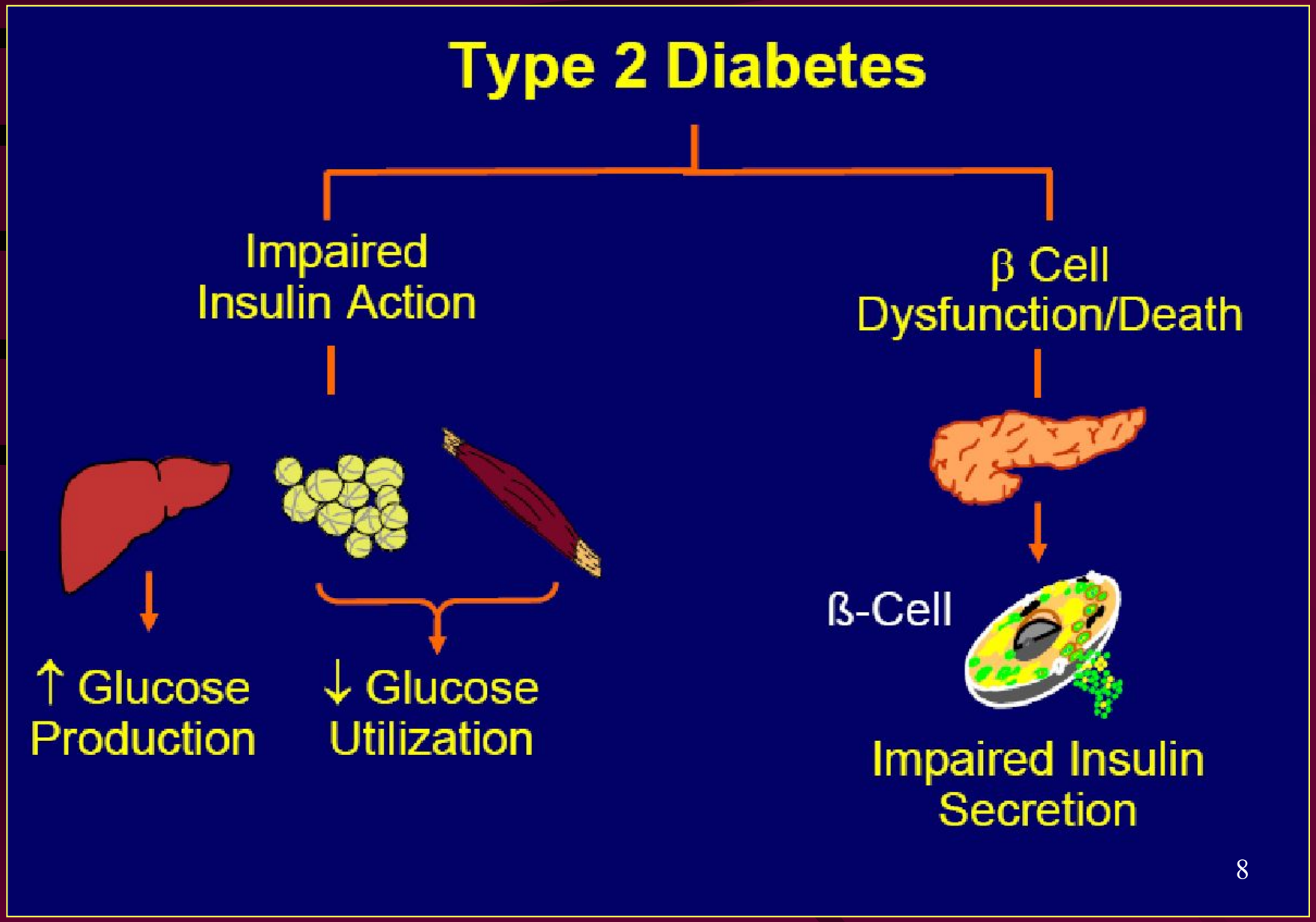
Etiology

1. Etiology of Type 1 Diabetes

- Autoimmune disease
- Selective destruction of β cells by T cells
- Several circulating antibodies against β cells
- Cause of autoimmune attack: unknown
- Both genetic & environmental factors are important



2. Etiology of Type 2 Diabetes



Etiology of Type 2 Diabetes

- Response to insulin is decreased
  - ↓glucose uptake (muscle, fat)
  - ↑glucose production (liver)
- The mechanism of insulin resistance is unclear
- Both genetic & environmental factors are involved
- Post insulin receptor defects

Characteristics	Type 1	Type 2
% of diabetic pop	5-10%	90%
Age of onset	Usually < 30 yr + some adults	Usually > 40 + some obese children
Pancreatic function	Usually none	Insulin is low, normal or high
Pathogenesis	Autoimmune process	Defect in insulin secretion, tissue resistance to insulin, increased HGO
Family history	Generally not strong	Strong
Obesity	Uncommon	Common
History of ketoacidosis	Often present	Rare except in stress
Clinical presentation	moderate to severe symptoms: 3Ps, fatigue, wt loss and ketoacidosis	Mild symptoms: Polyuria and fatigue. Diagnosed on routine physical examination
Treatment	Insulin, Diet Exercise	Diet ,Exercise Oral antidiabetics,Insulin

Risk Factors

- **Type 1 DM**
  - Genetic predisposition
    - In an individual with a genetic predisposition, an event such as virus or toxin triggers autoimmune destruction of β-cells probably over a period of several years.

Risk Factors

- **Type 2 DM**
  - Family History
  - Obesity
  - Habitual physical inactivity
  - Previously identified impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)
  - Hypertension
  - Hyperlipidemia

TABLE 72–5. Five Components of the Metabolic Syndrome (Individuals Having at Least Three Components Meet the Criteria for Diagnosis)

Risk Factor	Defining Level
Abdominal obesity	Waist circumference
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
High-density-lipoprotein C	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL

Reproduced from Expert Panel on Detection.[47]

Pathophysiology

- **Type 1 DM**
  - Type 1 DM is characterized by an absolute deficiency of insulin due to immune- mediated destruction of the pancreatic β-cells
  - In rare cases the β-cell destruction is not due to immune mediated reaction (idiopathic type 1 DM)

Pathophysiology

- **Type 1 DM**
  - **There are four stages in the development of Type 1 DM:**

1. **Preclinical period with positive β-cell antibodies**
2. **Hyperglycemia when 80-90% of the β- cells are destroyed.**
3. **Transient remission (honeymoon phase).**
4. **Establishment of the disease**

ALTERED CHO METABOLISM

↓ Insulin

↓

↓ Glucose Utilization

+

↑ Glycogenolysis

↓

Hyperglycemia

↓

Glucosuria

↓ (osmotic diuresis)

↓ Polyuria*

(and electrolyte imbalance)

↓

Polydipsia*

* Hallmark symptoms of diabetes

ALTERED PROTEIN METABOLISM

↓ Insulin

↓

↑ Protein Catabolism

↓

↑ Gluconeogenesis

(amino acids → glucose)

↓

Hyperglycemia

↓

Weight Loss and Fatigue

ALTERED FAT METABOLISM

↓ Insulin

↓

↑ Lipolysis

↓

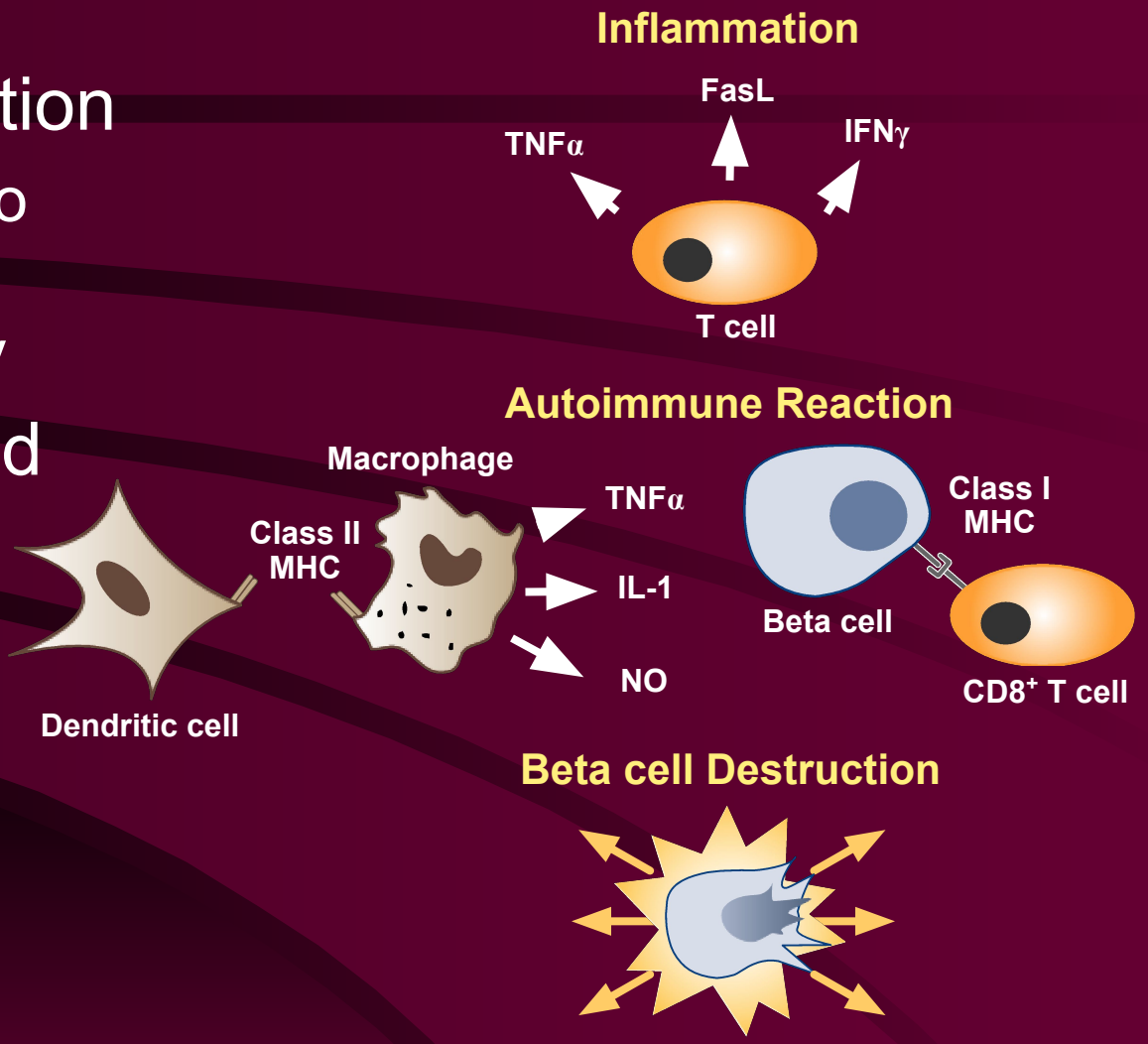
↑ Free fatty acids + ketones

↓

Acidosis + Weight Loss

Type 1 Diabetes

- Beta cell destruction
  - Usually leading to absolute insulin deficiency
- Immune mediated
- Idiopathic



Pathophysiology of T1DM

- Chronic autoimmune disorder occurring in genetically susceptible individuals
  - May be precipitated by environmental factors
- Immune system is triggered to develop an autoimmune response against
  - Altered pancreatic beta cell antigens
  - Molecules in beta cells that resemble a viral protein
- ~ 85% of T1DM patients have circulating islet cell antibodies
  - Majority also have detectable anti-insulin antibodies
- Most islet cell antibodies are directed against glutamic acid decarboxylase (GAD) within pancreatic beta cells

Pathophysiology

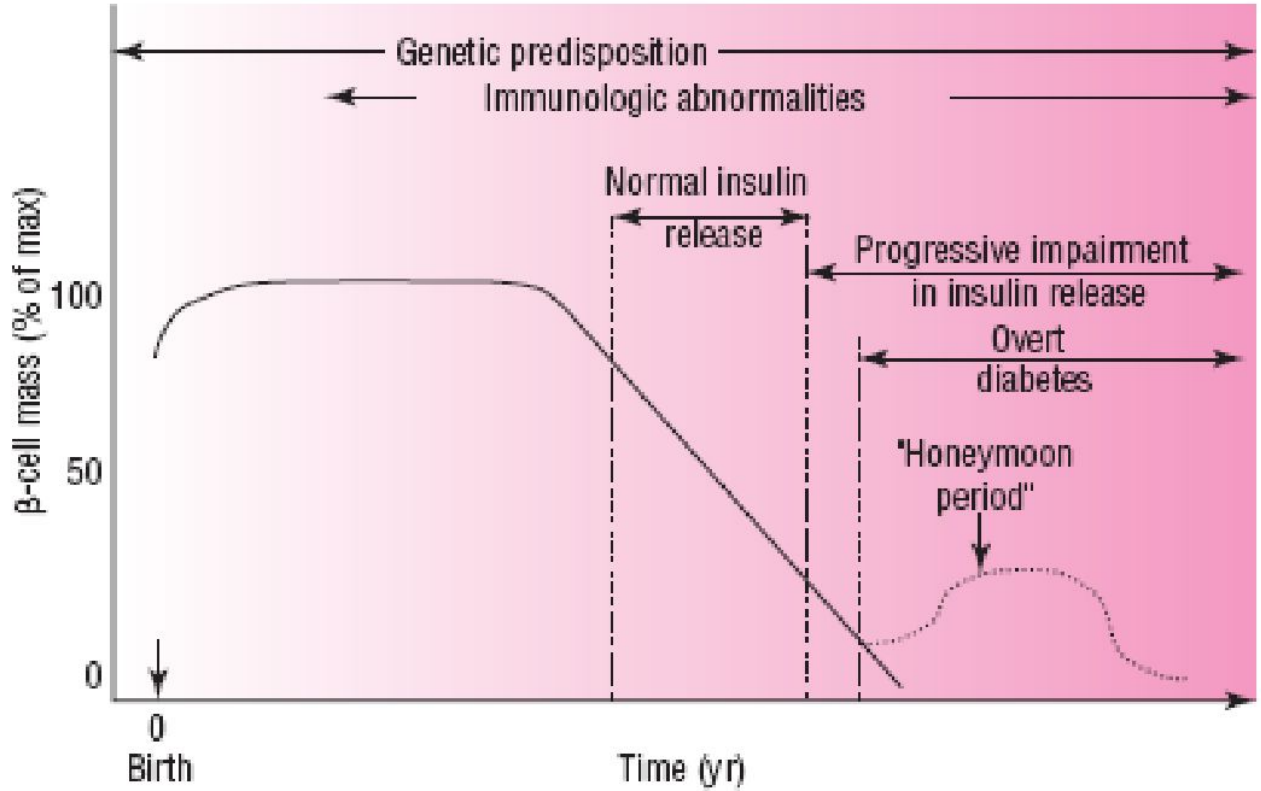
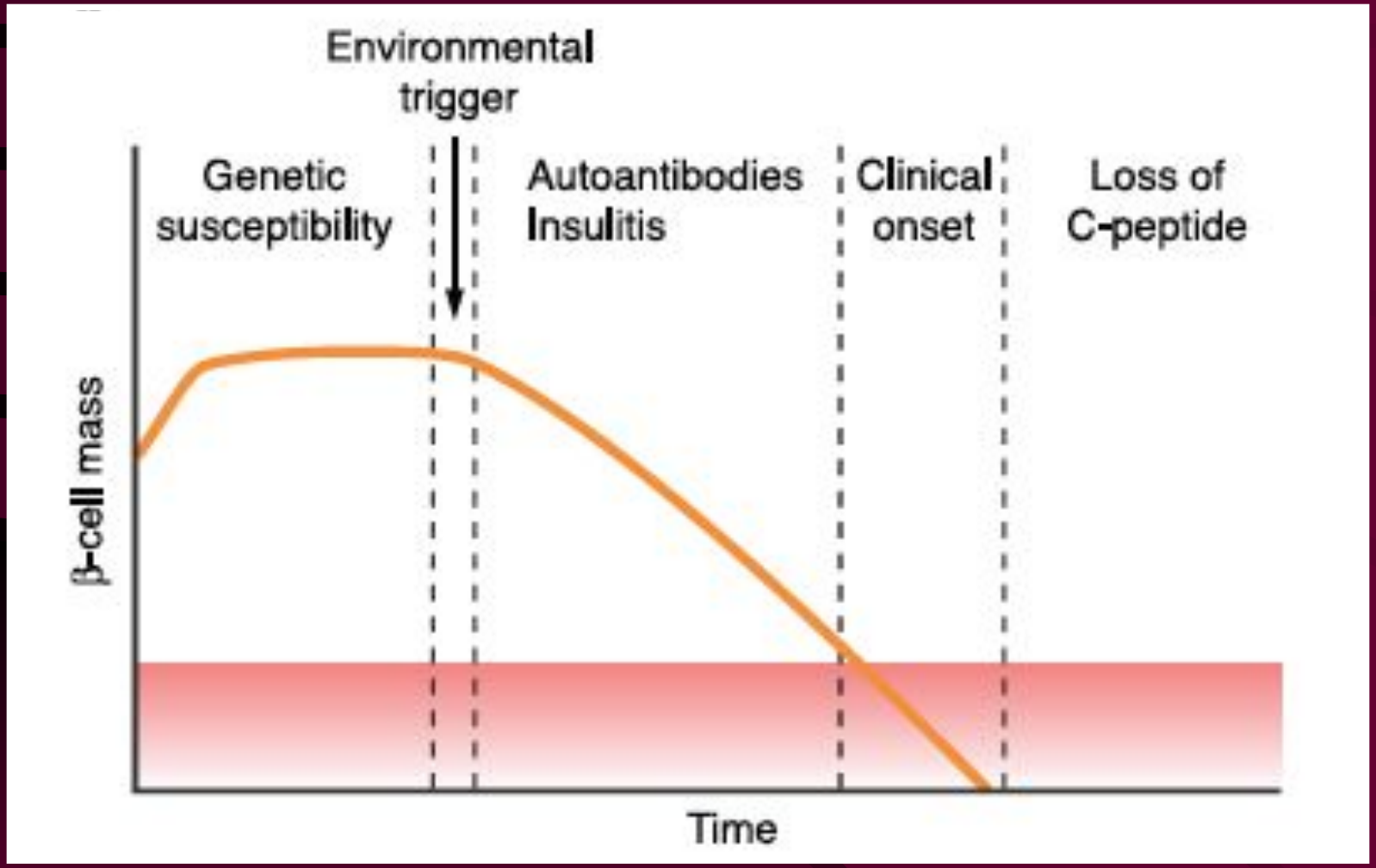


FIGURE 72–4. Scheme of the natural history of the β-cell defect in type 1 diabetes mellitus. (From ADA Medical Management of Type of 1 Diabetes, 3rd ed. 1998.)

Birth Time (years)

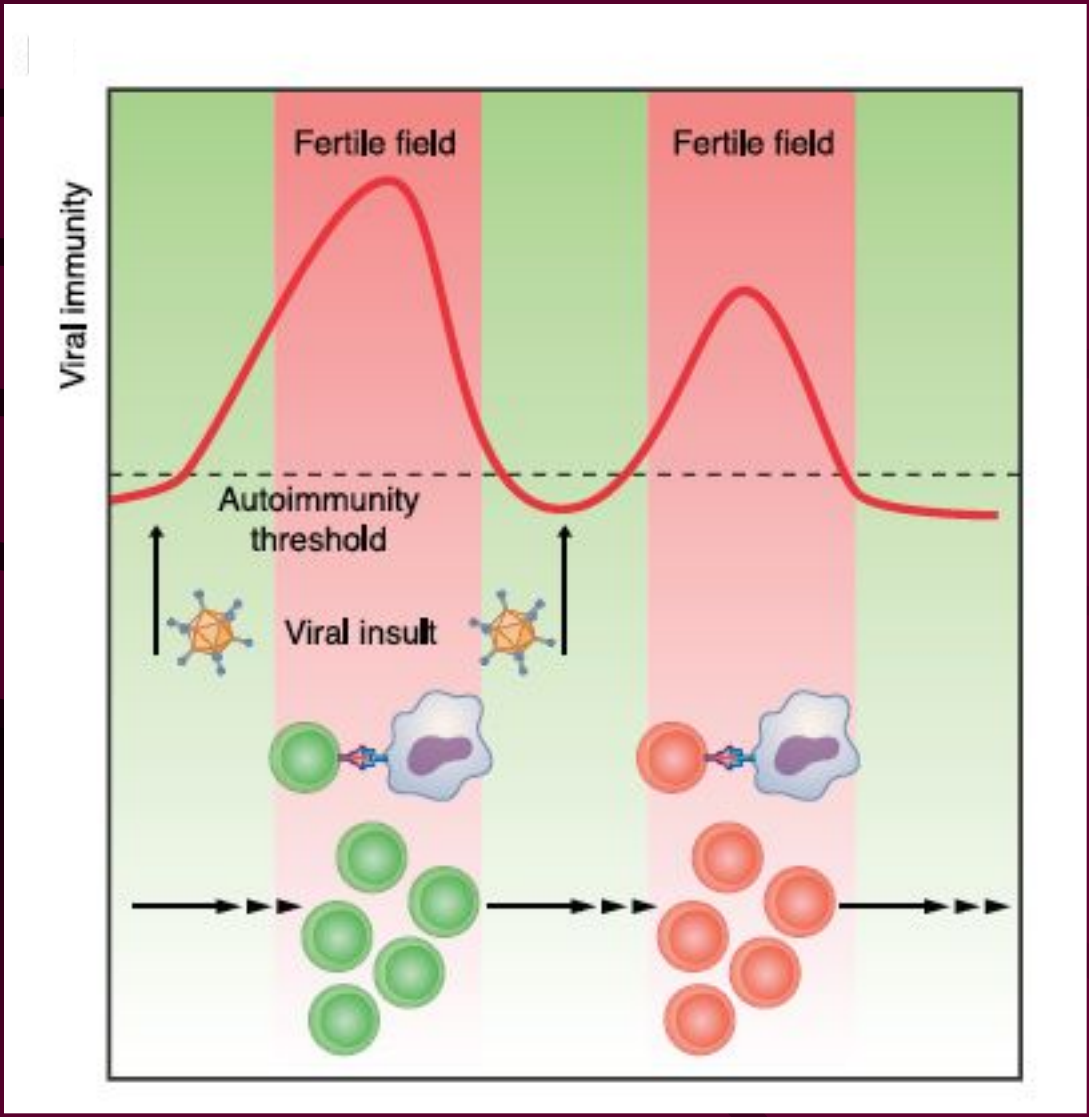
Models for Pathogenesis of T1DM



van Belle TL, et al. *Physiol Rev.*

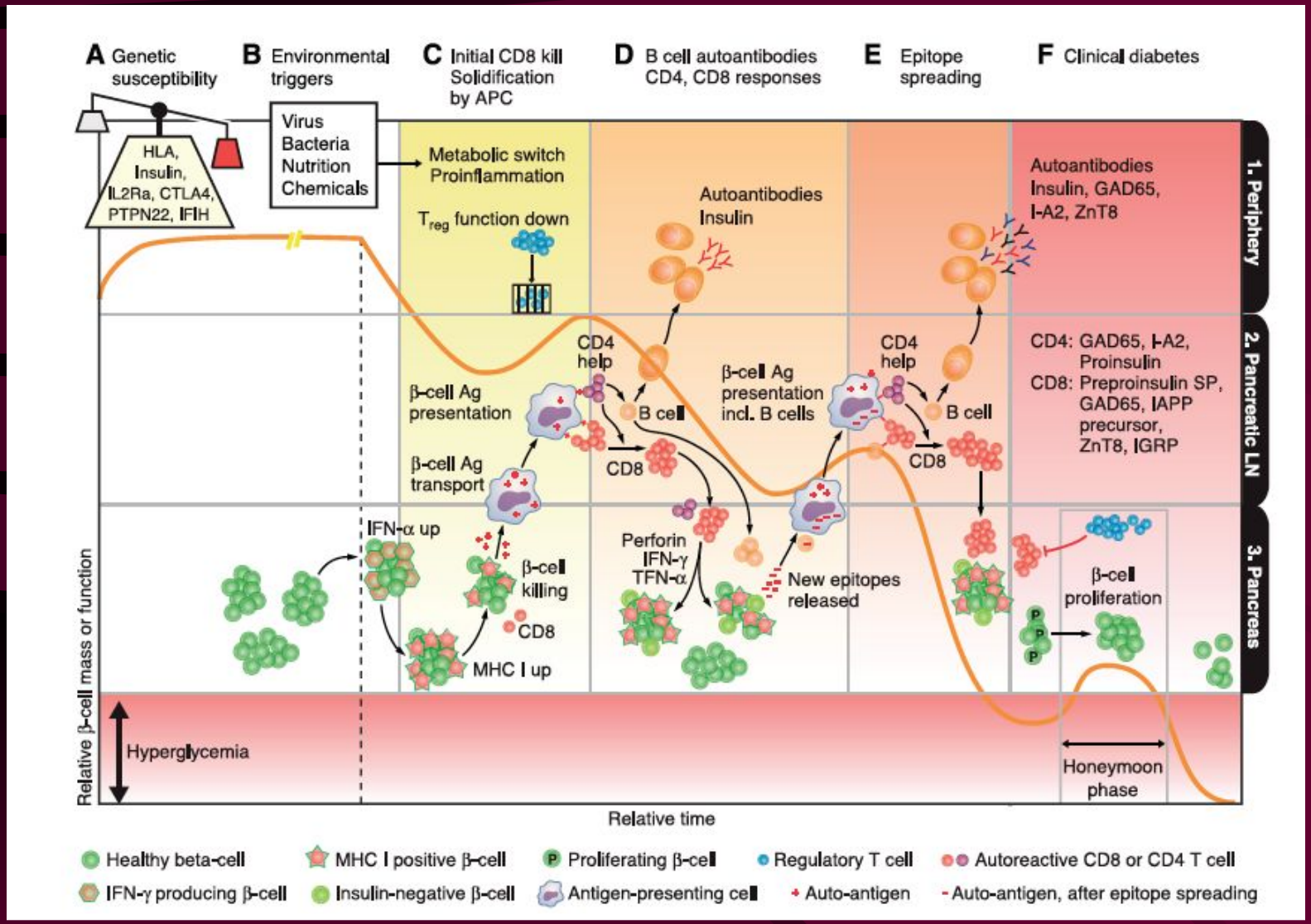
Models for Pathogenesis of T1DM

Fertile Field Hypothesis



van Belle TL, et al. *Physiol Rev.*

How Type 1 Diabetes Might Arise



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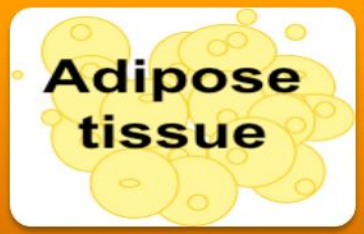
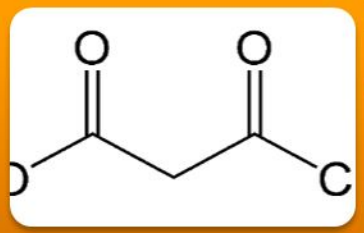
Major Metabolic Effects of Insulin and Consequences of Insulin Deficiency



Insulin effects: inhibits breakdown of triglycerides (lipolysis) in adipose tissue

- Consequences of insulin deficiency: elevated FFA levels



Insulin effects: Inhibits ketogenesis

- Consequences of insulin deficiency: ketoacidosis, production of ketone bodies

Insulin effects in muscle: stimulates amino acid uptake and protein synthesis, inhibits protein degradation, regulates gene transcription

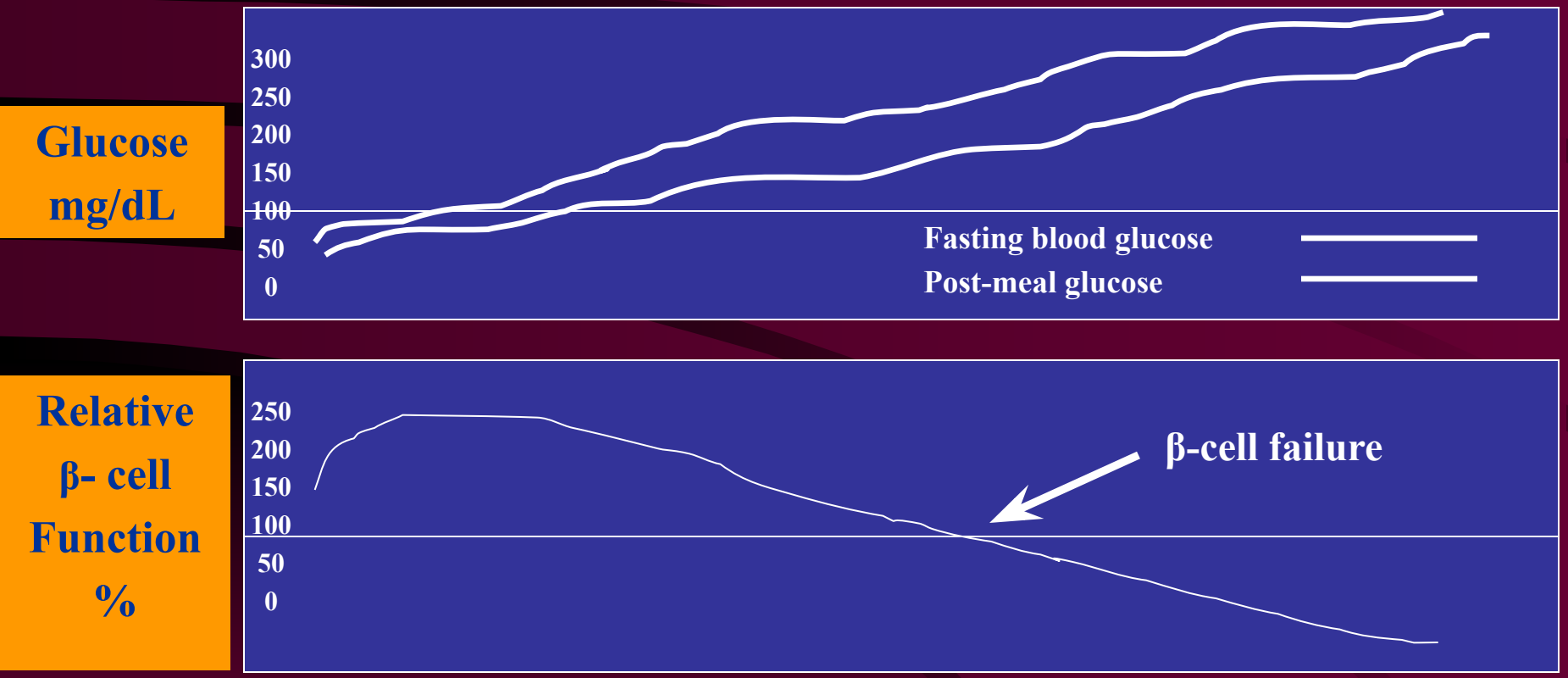
- Consequences of insulin deficiency: muscle wasting

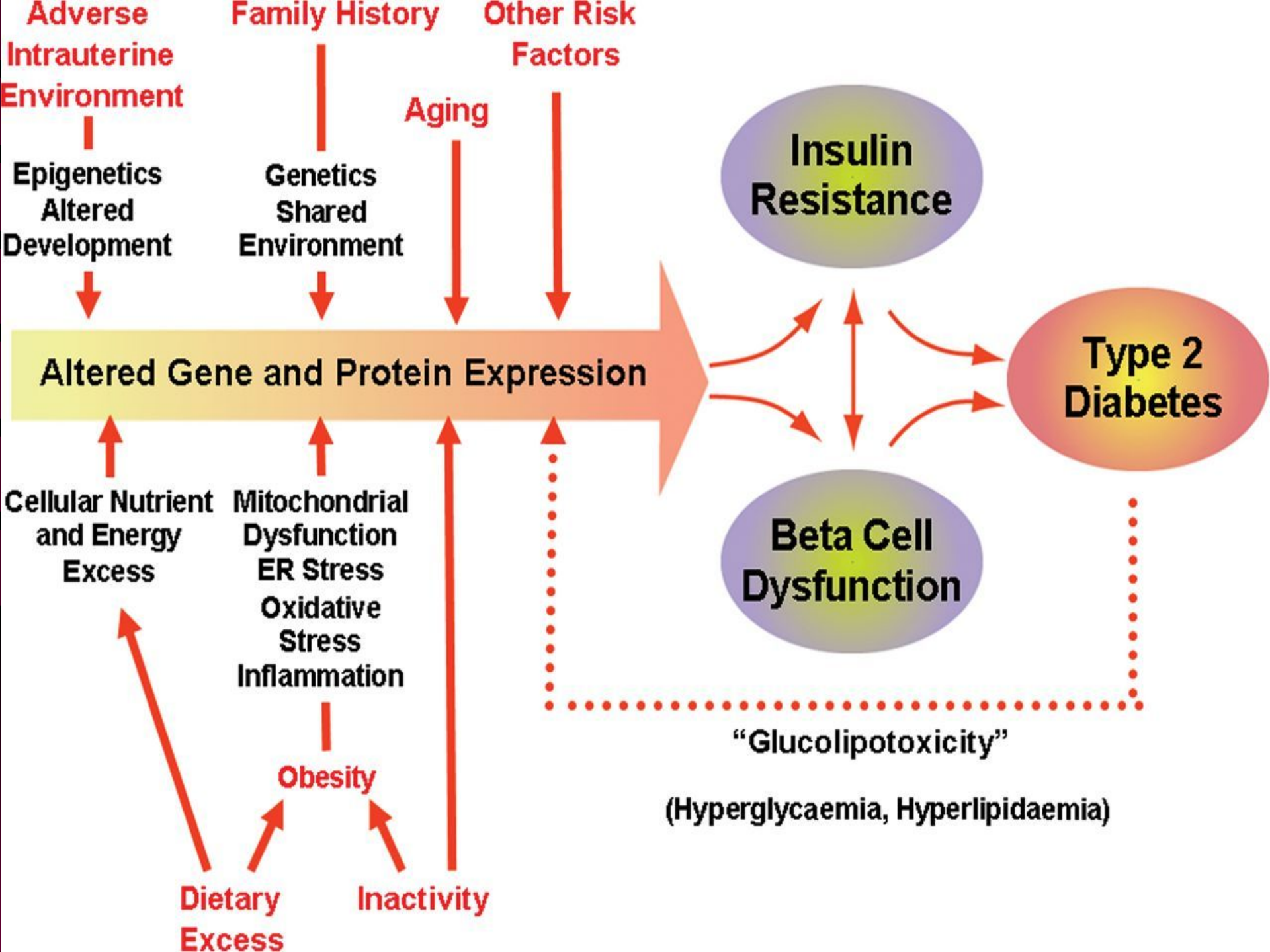
Pathophysiology

- **Type 2 DM**
  - Type 2 DM is characterized by the presence of both insulin resistance (tissue insensitivity) and some degree of insulin deficiency or β- cell dysfunction
  - Type 2 DM occurs when a diabetogenic lifestyle (excessive calories, inadequate caloric expenditure and obesity) is superimposed upon a susceptible genotype

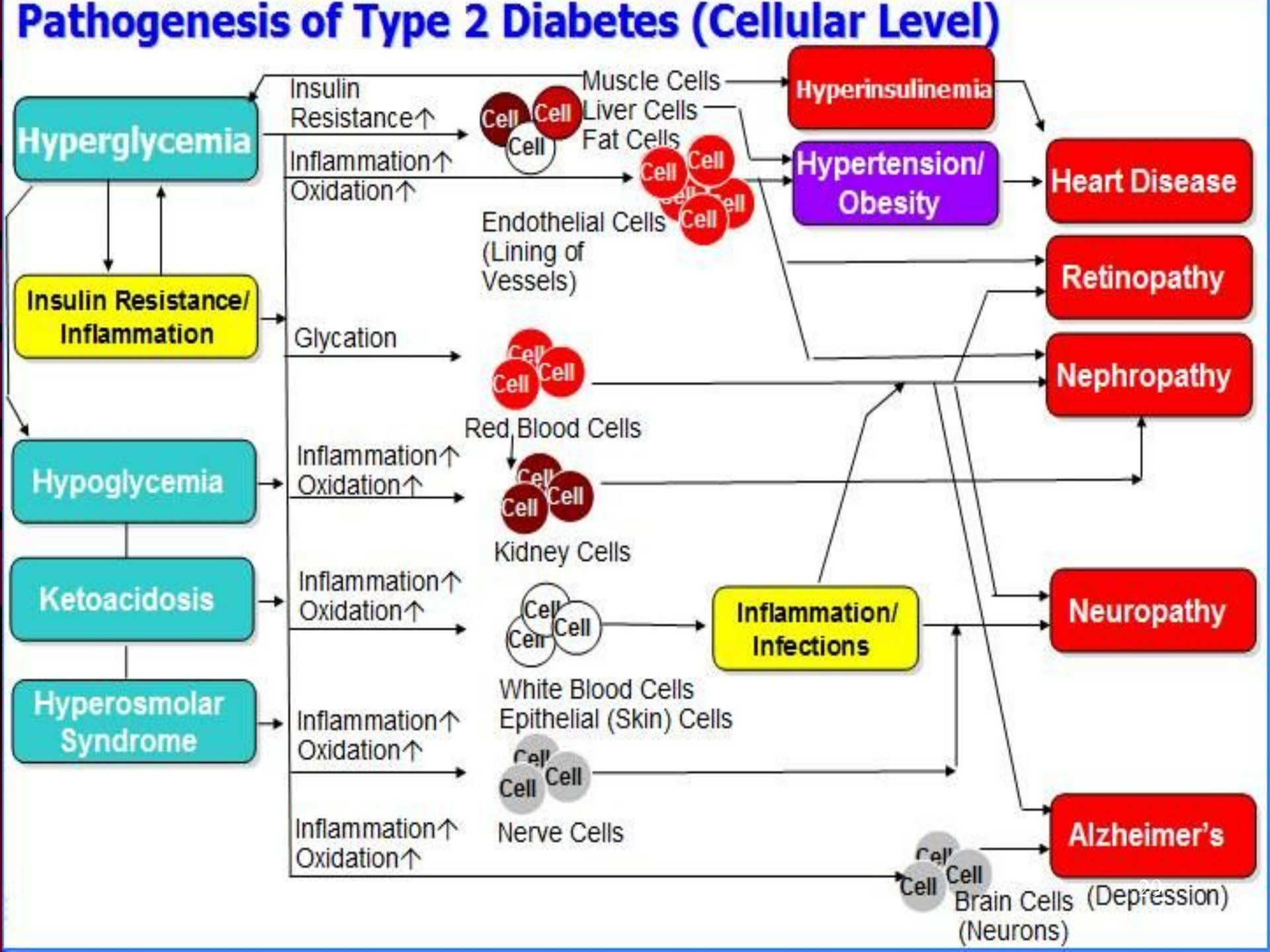
Pathophysiology

- **Type 2 DM**




Adverse Intrauterine Environment
Family History
Other Risk Factors
Aging
Epigenetics Altered Development
Genetics Shared Environment
Insulin Resistance
Altered Gene and Protein Expression
Type 2 Diabetes
Beta Cell Dysfunction
Cellular Nutrient and Energy Excess
Mitochondrial Dysfunction ER Stress Oxidative Stress Inflammation
"Glucolipotoxicity"
(Hyperglycaemia, Hyperlipidaemia)
Obesity
Dietary Excess
Inactivity

Pathogenesis of Type 2 Diabetes (Cellular Level)



Clinical Presentation

• Type 1 DM

- Polyuria
- Polydipsia
- Polyphagia
- Weight loss
- Weakness
- Dry skin
- Ketoacidosis

• Type 2 DM

- Patients can be asymptomatic
- Polyuria
- Polydipsia
- Polyphagia
- Fatigue
- Weight loss
- Most patients are discovered while performing urine glucose screening

Gestational diabetes

- A form of glucose intolerance that is diagnosed in some women during pregnancy.
- Gestational diabetes occurs more frequently among African Americans, Hispanic/Latino Americans, and American Indians. It is also more common among obese women and women with a family history of diabetes.
- During pregnancy, gestational diabetes requires treatment to normalize maternal blood glucose levels to avoid complications in the infant.
- After pregnancy, 5% to 10% of women with gestational diabetes are found to have type 2 diabetes.
- Women who have had gestational diabetes have a 20% to 50% chance of developing diabetes in the next 5-10 years.

DIABETES AND PREGNANCY

WHAT IS GESTATIONAL DIABETES (GDM)?

Gestational diabetes is the **onset of elevated blood sugar levels during pregnancy** and falls under the umbrella term hyperglycemia in pregnancy*

3/4 OF PEOPLE WITH DIABETES WORLDWIDE LIVE IN **LOW- AND MIDDLE-INCOME COUNTRIES.**

GDM IS **ON THE RISE** GLOBALLY, AFFECTING **1 IN 7 BIRTHS.**

SOME **INDIGENOUS WOMEN** ARE DISPROPORTIONATELY AFFECTED WITH AT LEAST **2X HIGHER RATES OF GDM.**

GDM IS ASSOCIATED WITH:

- The leading causes of **maternal deaths** and **disabilities**
- Increased **health complications for newborns**
- Increased **post-partum risk** for obesity, high blood pressure, and type 2 diabetes for both the woman, the child, and future generations

Pregnant women in low-and middle-income countries are **not consistently screened for GDM**, even though those regions account for **85%** of global deliveries and **88%** of GDM cases.

TESTING ALL PREGNANT WOMEN FOR ELEVATED BLOOD SUGAR PROVIDES A CHANCE TO:

Treat women right away

Improve inter-generational health

Promote prevention efforts like nutrition programs and physical activity

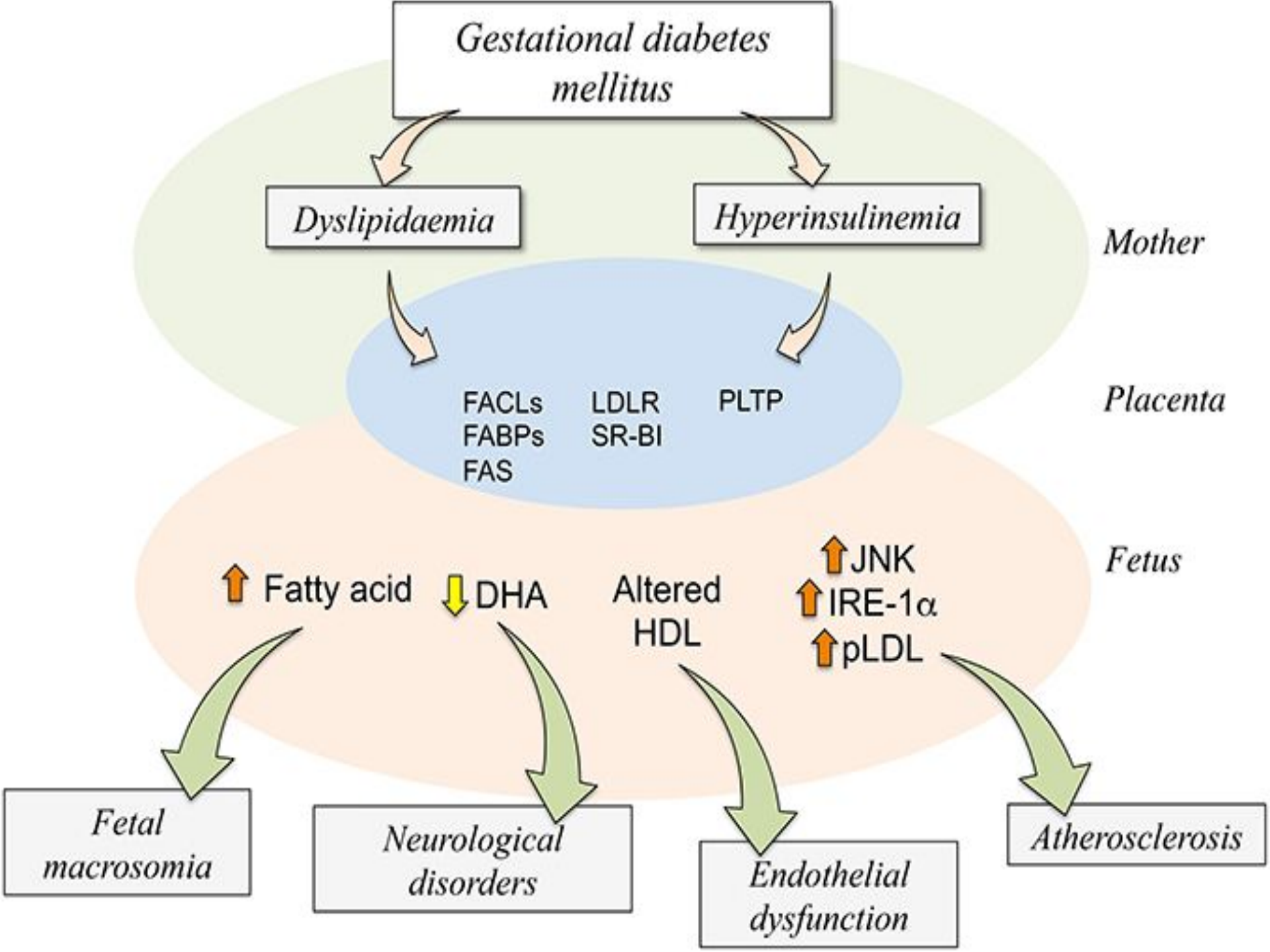
*"Hyperglycaemia in pregnancy" is the umbrella term for conditions including gestational diabetes mellitus (GDM), type 2 and type 1 diabetes in pregnancy.

WOMEN DELIVER

WORLD DIABETES FOUNDATION

WHO WINS? **EVERYBODY.**


Gestational Diabetes
High blood glucose levels in mother
Bring extra glucose to baby
Causes baby to put on extra weight


Gestational diabetes mellitus
Dyslipidaemia
Hyperinsulinemia
Mother
FACLs
FABPs
FAS
LDLR
SR-BI
PLTP
Placenta
Fatty acid
DHA
Altered HDL
JNK
IRE-1α
pLDL
Fetus
Fetal macrosomia
Neurological disorders
Endothelial dysfunction
Atherosclerosis

Other types of DM

- **Other specific types of diabetes result from specific genetic conditions (such as maturity-onset diabetes of youth), surgery, drugs, malnutrition, infections, and other illnesses.**

- **Such types of diabetes may account for 1% to 5% of all diagnosed cases of diabetes.**

Definition of LADA

Latent
Autoimmune
Diabetes in (of)
Adults

A form of autoimmune diabetes that resembles T1DM,but has a later onset and slower progression toward an absolute insulin requirement

LADA

- Latent Autoimmune Diabetes in Adults (LADA) is a form of ***autoimmune*** (***type 1 diabetes***) which is diagnosed in individuals who are older than the usual age of onset of type 1 diabetes.
- Alternate terms that have been used for "LADA" include Late-onset Autoimmune Diabetes of Adulthood, "Slow Onset Type 1" diabetes, and sometimes also "Type 1.5
- Often, patients with LADA are mistakenly thought to have ***type 2 diabetes***, based on their age at the time of diagnosis.

DIAGNOSTIC Δ :The Immunology of Diabetes Society

1. ≥ 30 years of age at diabetes onset
2. Positive for at least one of the four antibodies (ICAs and autoantibodies to GAD65*, IA-2, and insulin)
3. Insulin independence for at least 6 months after diagnosis

Features of LADA
Patients usually aged ≥ 25 years
Clinical presentation "masquerading" as non-obese type 2 diabetes
Initial control achieved with diet alone or diet and oral hypoglycaemic agents
Insulin dependency occurs within months but can take 10 years or more
Other features of type 1 diabetes
Low fasting and post-glucagon stimulated C-peptide
HLA susceptibility alleles
ICA+
GADA+

Clinical Types

- LADA-type 1 :Multiple antibodies or high titers of GADAb. More resembles T1DM
- LADA-type 2 :Single antibody positivity in low titers. More resembles T2DM

FEATURES	T1 DM	LADA	T 2 DM
Age at onset	Young/adult	Adult	Adult
HLA susceptibility	Yes (strong)	Yes	No
Autoantibodies	Yes (strong)	Yes (by definition)	No
Ketosis	Present	Absent	Absent
BMI	Normal	Normal/High	High
Insulin secretion	Absent/low	Present (but declines)	Present
Met.Syndrome	Infrequent	Variable	Frequent
IR	Absent/ infrequent	Variable	Present
Initial therapy	Insulin	Insulin/OHA	LSO/OHA

MODY

Maturity-**O**nset **D**iabetes of the **Y**oung

- In 1928, first noticed by Cammidge
- In 1975, first reported as MODY by Tattersall & Fajans ("Father of MODY")

MODY

- MODY – Maturity Onset Diabetes of the Young

- MODY is a monogenic form of diabetes with an autosomal dominant mode of inheritance:
  - Mutations in any one of several transcription factors or in the enzyme glucokinase lead to insufficient insulin release from pancreatic ß-cells, causing MODY.
  - Different subtypes of MODY are identified based on the mutated gene.

- Originally, diagnosis of MODY was based on presence of non-ketotic hyperglycemia in adolescents or young adults in conjunction with a family history of diabetes.

- However, genetic testing has shown that MODY can occur at any age and that a family history of diabetes is not always obvious.

Diagnostic criteria for MODY (Positive)

1.Onset of diabetes - before age 25 yrs

2.Not insulin-dependence - Absence of insulin treatment for at least 2 yrs after diagnosis

3. Autosomal-dominant inheritance. i.e. vertical transmission of diabetes through at least two (ideally three) generations with a similar phenotype in cousins or second cousins

4.β-cell dysfunction : insulin levels inappropriately low for the degree of hyperglycemia

Different subtypes of MODY

MODY type	Gene locus	Gene name	Prevalence	Diabetes
MODY 1	20q	HNF4A	2-5%	Severe
MODY 2	7p	GCK	**7-41%**	Mild
MODY 3	12q	HNF1A	**Up to 70%**	Severe
MODY 4	13q	PDX-1 (IPF)	<1%	Moderate
MODY 5	17q	HNF1B	2%	Severe
MODY 6	2q32 IDDM7	NEUROD1/Beta-cell E-box transactivator 2 (BETA2)	<1%	Severe

MODY vs. T1DM

Clinical Features	MODY	T1DM
Family history	AD	2-7%
Auto antibodies	**Negative**	**Positive**
C peptide reserve (nmol/l)	0.1-0.7	< 0.33
BMI	Normal/low	Low
Symptoms	Minimum	Maximum
Hyperglycemia	Mild to moderate	Severe
Doses of insulin	< 0.5 U/kg/d	> 0.5 U/kg/d
Onset	From birth or later	> 6 months of age
Extra-pancreatic features	May be present	Absent
Presentation	Insidious	Acute

Secondary DM

Secondary causes of Diabetes mellitus include:

- Acromegaly,
- Cushing syndrome,
- Thyrotoxicosis,
- Pheochromocytoma
- Chronic pancreatitis,
- Cancer
- Drug induced hyperglycemia:
  - Atypical Antipsychotics - Alter receptor binding characteristics, leading to increased insulin resistance.
  - Beta-blockers - Inhibit insulin secretion.
  - Calcium Channel Blockers - Inhibits secretion of insulin by interfering with cytosolic calcium release.
  - Corticosteroids - Cause peripheral insulin resistance and gluconeogensis.
  - Fluoroquinolones - Inhibits insulin secretion by blocking ATP sensitive potassium channels.
  - Naicin - They cause increased insulin resistance due to increased free fatty acid mobilization.
  - Phenothiazines - Inhibit insulin secretion.
  - Protease Inhibitors - Inhibit the conversion of proinsulin to insulin.
  - Thiazide Diuretics - Inhibit insulin secretion due to hypokalemia. They also cause increased insulin resistance due to increased free fatty acid mobilization.

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