DIABETES MELLITUS – TYPES AND PATHOGENESIS

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UNIWERSYTET MEDYCZNY W ŁODZI

DIABETES MELLITUS

Group of metabolic disorders with hyperglycemia:

1. reduced insulin secretion
2. decreased glucose utilization
3. increased glucose production

CLASSIFICATION

- DM is classified on the basis of pathogenic process that causes hyperglycemia
- Common feature: transversion from

Normal glucose tolerance

Pre-diabetes

Diabetes Mellitus

NORMOGLYCEMIA ←→ HYPERGLYCEMIA

	Normal glucose tolerance	Impaired fasting glucose or impaired glucose tolerance	Diabetes Mellitus
Fasting plasma glucose	< 5.6 mmol/L (100mg/dL)	5.6 – 6.9 mmol/L (100 –125 mg/dL)	≥7.0 mmol/L (126 mg/dL)
2-h-plasma glucose	<7.8 mmol/L (140 mg/dL)	7.8 – 11.1 mmol/L (140 – 199 mg/dL)	≥11.1mmol/L (200 mg/dL)

These values do not apply to gestational DM!!!

Etiologic classification of DM

I. Type 1 diabetes (destruction of beta cells)

II. Type 2 diabetes

III. Other specific types of diabetes

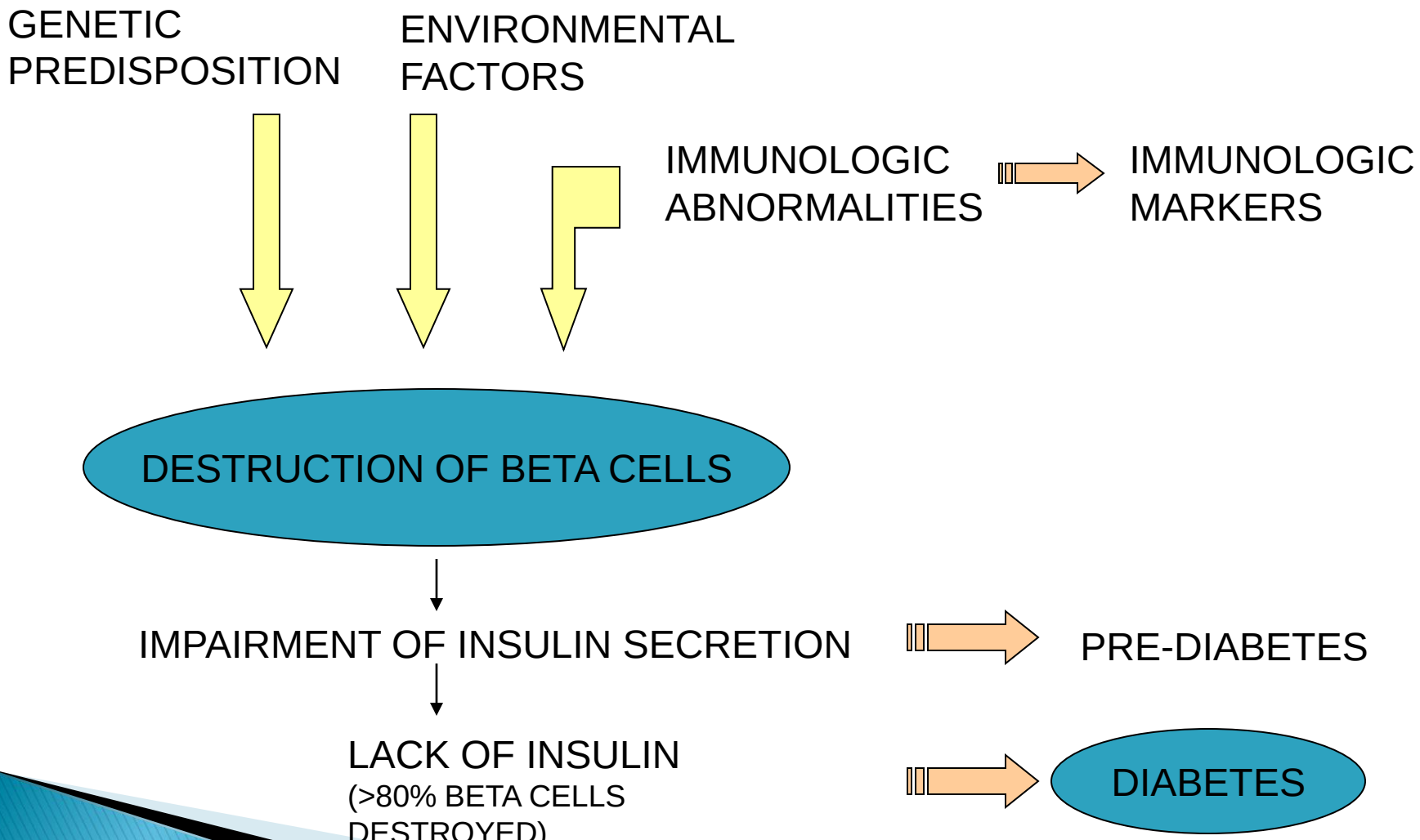
IV. Gestational diabetes mellitus (GDM)

- Other types of DM include specific genetic defects in insulin secretion, action, metabolic disorders that impair insulin secretion or glucose tolerance, mitochondrial abnormalities

- **MODY** – *maturity onset diabetes of the young,* subtype of DM, autosomal dominant inheritance, early onset of hyperglycemia (<25 years), impaired of insulin secretion

- **GDM** – gestational DM, caused by insulin resistance during pregnancy, may revert to normal glucose tolerance; risk of developing DM later in life.

TYPE 1 DM – pathogenesis

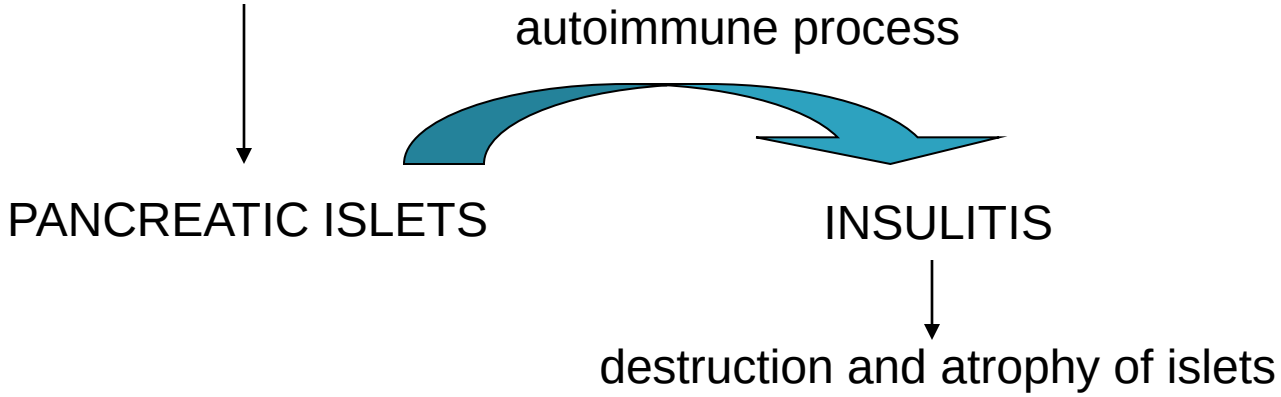


GENETIC PREDISPOSITION

- Involves multiple genes
- Major susceptibility gene located in the HLA region on chromosome 6
- Polymorphisms in the HLA complex account for about 50% of the genetic risk factors of developing DM1
- Haplotype DQA1*0301, DQB1*0302, DQB1*0201 are strongly associated with type 1 DM.
- Concordance of type 1 DM in identical twins is variable (30 – 70%) – role of environmental factors

Pathophysiology of type 1 DM

Infiltration with lymphocytes T



Immunologic abnormalities – islet cell autoantibodies (ICAs):

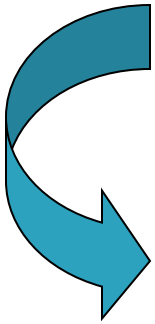
1. Insulin
2. Glutamic acid decarboxylase (GAD)
3. Tyrosine phosphatases (ICA-512/IA-2)
4. Phogrin (insulin secretory granule protein)

} immunologic markers present in >75% new-onset type 1 DM disapear after all beta cells are distroyed

Environmental factors

- Trigger an autoimmune process in genetically susceptible individuals
- Viral infections (coxsackie, rubella)
- Bovine milk proteins
- Nitrosourea compounds
- Event may precede the onset of DM by several years

Pathogenesis of type 2 DM



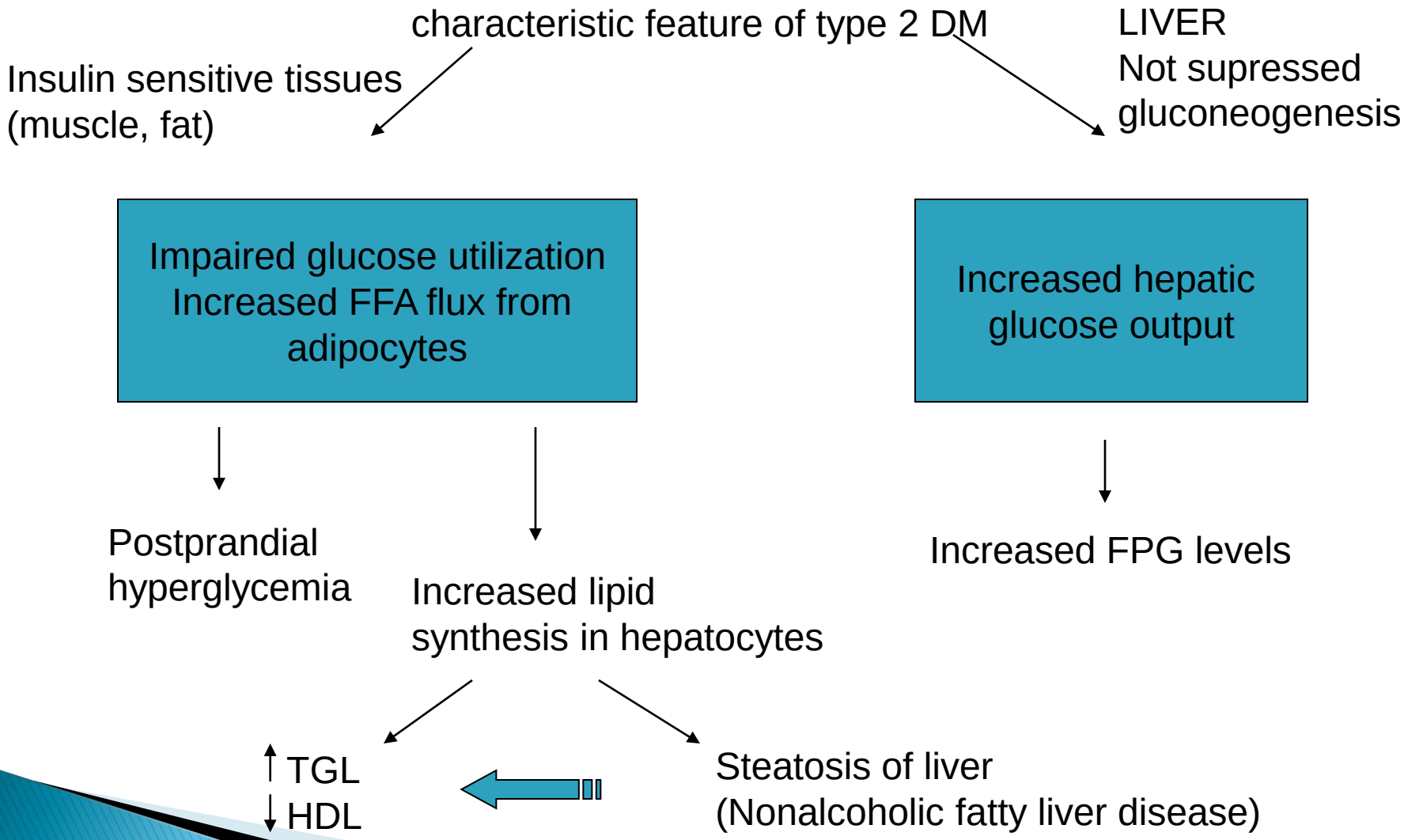
INSULIN RESISTANCE WITH HYPERINSULINEMIA
Obesity (visceral) → insulin resistance → compensatory increased insulin output

INSULIN SECRETORY DEFECT
Decline in insulin secretion – beta cells failure
(islet amyloid deposits and decreased beta cell mass in long-standing DM type2)

DIABETES DEVELOPES WHEN INSULIN SECRETION IS INADEQUATE

1. Strong genetic component (concordance in identical twins 70 – 90%)
2. Both parents with type 2 DM = 40% risk of DM !
3. Resonsible genes are not completely specified
4. DM type 2 is polygenic and multifactorial (environmental factors: obesity, nutrition, physical activiy)

INSULIN RESISTANCE



Genetically defined, monogenic forms of DM

- 6 variants of **MODY** – mutation in genes encoding islet-enriched transcription factors (e.g. HNF – *hepatic nuclear transcription factors*) or glucokinase
- These factors affect islet development or the expression of genes responsible for glucose-stimulated insulin secretion
- Clinical features:

  progressive decline in insulin secretion and control of glycemia, in some types they respond to **sulfonyloureas**
- Mutation in MODY-associated genes are rare (<5% of type 2 DM)