Diabetes mellitus

Etiology and pathogenesis
Clinical forms

Nóra Hosszúfalusi

27.03.2017.
Prevalence of diabetes mellitus type 2 in various racial and ethnic groups in the US (2007 estimates)
Chronic complications of diabetes

Diabetic autonomic neuropathy

Clinical features
- Sudden death
- Hypoglycaemic warning loss
- Abnormal sweating
  - Postural hypotension
- Gastric stasis
- Diarrhoea and constipation
- Urinary retention
- Impotence
- Oedema

Asymptomatic
- Neuroendocrine abnormalities
- Pupillary dysfunction
- Bronchoconstrictor defects
- Heart rate abnormalities
- Gastrointestinal motility disturbances
- Abnormal renal sodium handling
- Bladder emptying impairment
- Vasomotor dysfunction
• Etiology, pathomechanism, diagnosis, classification
• Diabetic complications
• Treatment
Diabetes mellitus

• Sustained elevation of blood sugar (blood glucose, BG)
• Cause: lack of insulin action
  - missing or impaired insulin production
  - impaired insulin effect

• Acute and chronic complications
Effects of insulin on blood glucose (liver, muscle, fat)
Major effects of insulin

• Metabolic effects of insulin
  - inhibition of glycogenolysis and gluconeogenesis (liver)
  - enhance peripheral glucose uptake and utilization (muscle, fat)
  - restrain lipolysis and proteolysis (fat, muscle)

• Mitogenic effect
Mechanisms of hyperglycemia in diabetes
Histology of normal pancreas

Pancreatic islet (islet of Langerhans)

~ 3,000 cells
75% beta-cells
25% other (A,D,PP) cells

Micrograph: Lelio Orci, Geneva
Beta cell

10 µm ~ 10,000 granules

Micrograph: Lelio Orci, Geneva
Putative mechanisms of insulin secretion
The molecular basis of insulin resistance
Symptoms of diabetes

The blood sugar level exceeds the renal threshold of glucose (BG ≥ 10.0 mmol/l):

- frequent urination with increased amount of urine = polyuria
- intense thirst = polydipsia
- loss of body weight

fatigue, skin and mucosal infections, blurred vision (osmotic swelling of lenses)

- Acute hyperglycemic crisis: diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS)
### Diagnostic criteria of disturbances of carbohydrate metabolism

*(WHO 1998, ADA 2015)*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Fasting blood glucose (mg/dl, mmol/l)</th>
<th>OGTT 120’ (mg/dl, mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal carbohydrate tolerance</strong></td>
<td>(\leq 110, \leq 6.0) (ADA (&lt; 100, 5.6))</td>
<td>(&lt; 140, &lt; 7.8)</td>
</tr>
<tr>
<td></td>
<td>(HbA1c (&lt; 5.7%))</td>
<td></td>
</tr>
<tr>
<td><strong>Impaired fasting glucose (IFG)</strong></td>
<td>(\leq 110 \text{ and } \leq 125) 6.1-6.9 (ADA 100-125)</td>
<td>(&lt; 140, &lt; 7.8)</td>
</tr>
<tr>
<td><strong>Prediabetes HbA1c: 5.7-6.4 %</strong></td>
<td>(&lt; 126, &lt; 7.0)</td>
<td>(\geq 140 \text{ and } &lt; 200 \geq 7.8-11.0)</td>
</tr>
<tr>
<td><strong>Impaired glucose tolerance (IGT)</strong></td>
<td>(&lt; 126, &lt; 7.0)</td>
<td>(\geq 200, \geq 11.1)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus HbA1c (\geq 6.5%)</strong></td>
<td>(\geq 126, \geq 7.0)</td>
<td></td>
</tr>
</tbody>
</table>
Diagnostic criteria of diabetes mellitus (WHO)

Symptoms
(polyuria, polydipsia, weight loss, DKA, HHS)

+ 
• Random blood glucose level \( \geq 11.1 \) mmol/l 
  \( (\geq 200 \) mg/dl) 

  or

• Fasting blood glucose level \( \geq 7.0 \) mmol/l 
  \( (\geq 126 \) mg/dl), (no caloric intake 8 h) 

  or

• 120 min blood glucose in OGTT \( \geq 11.1 \) mmol/l \( (\geq 200 \) mg/dl) 

  or

• HbA1c \( \geq 6.5 \) %
Diagnostic criteria of diabetes mellitus (WHO)/2.

- Without typical symptoms (screening) abnormal blood sugar value must be present on two occasions (on different days)
- Personal blood sugar measuring devices are not allowed for diagnostic purposes: laboratory measurement is necessary.
Diagnostic criteria of diabetes mellitus (ADA, 2015)

- HbAc1 \( \geq 6.5\% \)
  
or
- Fasting blood glucose level \( \geq 7.0\) mmol/l
  \((\geq 126\) mg/dl)
  
or
- 120 min blood glucose in OGTT \( \geq 11.1\) mmol/l \((\geq 200\) mg/dl)

Same test repeat immediately

- Symptoms (polyuria, polydipsia, weight loss, DKA, HHS)
  
  +

- Random blood glucose level \( \geq 11.1\) mmol/l
  \((\geq 200\) mg/dl)
Screening for undiagnosed type 2 diabetes (ADA, 2015)

- BMI ≥ 25 kg/m² (Asian Americans ≥ 23 kg/m²) and one or more additional risk factors for diabetes at any age without risk factors testing should begin at age 45 years
- Normal test → repeat at 3-year intervals
- A1C, FPG, or 2-h OGTT
- Diagnosis of DM → identify other CV risk factors
- Children and adolescents overweight or obese and ≥ 2 risk factors for diabetes
Classification of diabetes

• Type 1 diabetes
  results from beta cell destruction, leading to absolute insulin deficiency
• Type 2 diabetes
  results from a progressive insulin secretion defect on a background of impaired insulin function
  impaired incretin function
• Gestational diabetes mellitus (diagnosed during pregnancy)
• Other specific types of diabetes (due to other known causes)
<table>
<thead>
<tr>
<th>Stages/Types</th>
<th>Normoglycaemia</th>
<th>Hyperglycaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal glucose tolerance</td>
<td>IGT and/or IFG</td>
</tr>
<tr>
<td></td>
<td>Not insulin requiring</td>
<td>Insulin requiring for control</td>
</tr>
</tbody>
</table>

**Type I**
- Autoimmune
- Idiopathic

**Type II**
- Predominantly insulin resistance
- Predominantly insulin secretory defects

**Other specific types**
- Genetic defects of beta-cell function
- Genetic defects of insulin action
- Diseases of exocrine pancreas
- Endocrinopathies
- Drug or chemical induced
- Others

**Gestational hyperglycaemia**
CLASSIFICATION of diabetes (ADA 2017)

CLASSIFICATION
Diabetes can be classified into the following general categories:

• 1. **Type 1 diabetes** (due to autoimmune b-cell destruction, usually leading to absolute insulin deficiency)
• 2. **Type 2 diabetes** (due to a progressive loss of b-cell insulin secretion frequently on the background of insulin resistance)
• 3. **Gestational diabetes mellitus** (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
• 4. **Specific types of diabetes** due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
Type 1 diabetes mellitus

• A. Autoimmune:
  autoimmune destruction of beta cells
  - rapid progression
  - slow progression (latent autoimmune diabetes in adults, LADA)

• B. Idiopathic
Type 1 Diabetes Mellitus

- Genetic susceptibility
- Triggering effect
- Period of immunologic abnormalities
- Manifestation of diabetes mellitus
Islet of Langerhans

Normal

Insulitis
## Genetic susceptibility

<table>
<thead>
<tr>
<th>Prevalence of T1DM</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average population before then age of 30 years</td>
<td>0,1-0,4</td>
</tr>
<tr>
<td>In case of diabetic sibling</td>
<td>6</td>
</tr>
<tr>
<td>In case of diabetic parent</td>
<td>3-6</td>
</tr>
<tr>
<td>If the father is diabetic by the age of 20 years</td>
<td>6-9</td>
</tr>
<tr>
<td>If the mother is diabetic by the age of 20 years</td>
<td>1-4</td>
</tr>
<tr>
<td>In identical twins is diabetic by the age of 30 years</td>
<td>34</td>
</tr>
<tr>
<td>In identical twins 12 years later after the diagnosis of the proband</td>
<td>43</td>
</tr>
<tr>
<td>In identical twins 40 years later after the diagnosis of the proband</td>
<td>50</td>
</tr>
<tr>
<td>In non-identical twins</td>
<td>10-12</td>
</tr>
<tr>
<td>HLA identical sibling</td>
<td>15</td>
</tr>
<tr>
<td>HLA haploidentical sibling</td>
<td>9</td>
</tr>
<tr>
<td>HLA non-identical sibling</td>
<td>29 1-2</td>
</tr>
<tr>
<td>Lokusznév</td>
<td>Kapcsolt marker vagy gén</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>IDDM1*</td>
<td>HLA DRB1-DQA1-DQB1</td>
</tr>
<tr>
<td>IDDM2*</td>
<td>insulin gén 5' VNTR</td>
</tr>
<tr>
<td>IDDM3</td>
<td>D15S107 microsatellita</td>
</tr>
<tr>
<td>IDDM4*</td>
<td>FGF3/D11S1337 régió</td>
</tr>
<tr>
<td>IDDM5*</td>
<td>D6S476-D6S448 régió</td>
</tr>
<tr>
<td>IDDM6</td>
<td>D18S487 microsatellita</td>
</tr>
<tr>
<td>IDDM7</td>
<td>D2S152 microsatellita</td>
</tr>
<tr>
<td>IDDM8*</td>
<td>D6S281 microsatellita</td>
</tr>
<tr>
<td>IDDM9</td>
<td>D3S1303</td>
</tr>
<tr>
<td>IDDM10</td>
<td>D10S193-D10S588 régió</td>
</tr>
<tr>
<td>IDDM11</td>
<td>D14S67 microsatellita</td>
</tr>
<tr>
<td>IDDM12*</td>
<td>CTLA-4 gén</td>
</tr>
<tr>
<td>IDDM13</td>
<td>IGFBP-2, -5 génrégió</td>
</tr>
<tr>
<td>IDDM15</td>
<td>D6S283 microsatellita</td>
</tr>
<tr>
<td>1q</td>
<td>D1S1644</td>
</tr>
<tr>
<td>GCK</td>
<td>glukokináz gén</td>
</tr>
<tr>
<td>Xp</td>
<td>DXS1068</td>
</tr>
</tbody>
</table>
Predisposing HLA haplotypes and genotypes for T1DM

- HLA DR4-DQ8
- HLA DR3-DQ2
- HLA DR4-DQ8/HLA DR3-DQ2
- HLA DR4-DQ8/HLA DR4-DQ8
Putative autoantigens

- insulin (proinsulin)
- GAD65 (glutamic acid decarboxylase)
- IA-2 (homology with tyrosine phosphatases)
Environmental factors

- Enteroviruses (Coxsackie-B4, polio,)
  Antibody titer anti-CB4 is higher in DR3/DR4 > DR2,
  it means a lower cellular reaction to the virus,
  it could mean a persistent virus carrier status
- CMV
- Bovine milk proteins (?)
- Nitrosourea compounds (?)
- Insufficient D3 vitamin supply(?)
Autoantibodies in T1DM Markers

- ICA (islet-cell/cytoplasmatic/autoantibodies)
- GADA (autoantibody to glutamic acid decarboxylase)
- IA-2A (autoantibody to IA-2)
- IAA (insulin autoantibodies)
- ZnT8A (cink transzporter ZnT8 elleni antitest, kation pumpa/efflux/család)
Insulin response to IVGTT in healthy subjects and in subjects with ongoing beta cell damage

Temporal model for development of T1DM
Characteristics of T1DM

• Classical clinical symptoms
• Ketonuria
• (Lack of obesity)
• Low C-peptide level
• Presence of autoantibodies
• Presence of other organ specific autoimmune disorders (thyroid, celiac, Addison)
• Family history of T1DM,
  (predisposing HLA haplotypes)
Type 2 Diabetes Mellitus

Two simple questions:

Why do people get it (etiology)?
What goes wrong (pathophysiology)?

The answers are not simple!
Reports of high and low rates of T2DM

Low rates

Poor of London and Berlin before 1900
Eskimos
Rural poor of India
Affluent societies during famine and war
Rural Africans on traditional diet

High rates

Rich Indian men of Bengal
Pima Indians
Sephardic Jews of Zimbabwe
Sumo wrestlers of Japan
Royal families of Zululand

Genetic influence (inter bred societies); environmental influences (poverty and affluence); combination of the those (Pima Indians on poor western diet)
Type 2 Diabetes Mellitus

- Genes
  - Insulin resistance (Skeletal muscle, Adipose tissue, Liver)
  - Beta-cell dysfunction/failure (Pancreas)
- Environment
  - IGT
- Type 2 Diabetes
  - Metabolic toxicity
  - ↑FFA, ↑Glucose
  - Metabolic toxicity
Risk factors for T2DM

- Family history of T2DM (parent or sibling with T2DM)
- Obesity (BMI 25 kg/m²)
- Sedentary lifestyle
- Race/ethnicity (African/Hispanic/Native/Asian Americans)
- Previously identified IFG or IGT
- History of GDM or delivery of baby > 4 kg
- Hypertension
- Dyslipidemia
- Polycystic ovary syndrome or acanthosis nigricans
- History of vascular disease
Obesity is a risk factor of T2DM
Diet with decreased carbohydrate and increased fat content is characteristic for patients with T2DM.

<table>
<thead>
<tr>
<th></th>
<th>Daily calories</th>
<th>Carbohydrate</th>
<th>Protein</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIABETICS (143)</td>
<td>2997</td>
<td>50.9</td>
<td>12.1</td>
<td>37.0</td>
</tr>
<tr>
<td>NORMALS (137)</td>
<td>2478</td>
<td>55.9</td>
<td>12.3</td>
<td>31.8</td>
</tr>
</tbody>
</table>

Table 3: CALORIE INTAKE
Males & Females 16–75 yrs

Himsworth & Marshall 1935(6)
UKPDS showed that obesity predominate at the diagnosis of T2DM.

Fig 3: The distribution of body weight in normal (---) and NIDDM (----) subjects.
Table 4: CONCORDANCE AND DISCORDANCE FOR DIABETES.

200 pairs of identical twins:

<table>
<thead>
<tr>
<th></th>
<th>Number of pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concordant</td>
</tr>
<tr>
<td>IDDM:</td>
<td>80 (54%)</td>
</tr>
<tr>
<td>NIDDM:</td>
<td>48 (91%)</td>
</tr>
<tr>
<td>Total:</td>
<td>128 (64%)</td>
</tr>
</tbody>
</table>

from: Barnett et al. 1981(8)
Skin abnormalities in insulin resistance

- Acanthosis nigricans
- Fibroma
Pathophysiology of T2DM

- Peripheral insulin resistance
- Excessive hepatic glucose production
- Impaired insulin secretion
- Impaired incretin effect

Copyright 2006 by Elsevier, Inc.
Fasting and postload glucose levels, insulin sensitivity and insulin secretion before the diagnosis of T2DM (Whitehall II study)

At fasting plasma glucose >6.4 mmol/l first phase insulin response is absent.

FBG: 6.4 mmol/l
115 mg/dl

FIG. 2. Mean relative incremental insulin levels following intravenous glucose in arbitrarily divided subgroups of subjects based on fasting glucose levels. Note presence of acute insulin response in subjects with fasting glucose levels below 115 mg/dl, and absence of response above 115 mg/dl.

Brunzell JD, J Clin. Endoc Metab 42:22, 1976
The molecular basis of insulin resistance (2007)
a, Serine residues of IRS-1(S)
b, Tyrosine residues of IRS-1 and (Y)
Factors of insulin sensitivity

- Genetics (50%, ethnic difference)
- Visceral obesity (25%; adipocytokines: TNF-α, IL-6; NEFA, AG; PPAR-γ)
- Physical activity (25%; acute, chronic)
- Age
- Food (CH↑, fat↓, cytokine production↓)
- AT II
<table>
<thead>
<tr>
<th>System</th>
<th>Effect</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids</td>
<td>Lipolysis ↑</td>
<td>NEFA ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Liver</td>
<td>VLDL ↑</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td></td>
<td>HGP ↑</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Muscle</td>
<td>Glucose uptake ↓</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Endothel</td>
<td>NO production ↓</td>
<td>Endothel dysfunction</td>
</tr>
<tr>
<td>Heart</td>
<td>Glucose uptake ↓</td>
<td>Metabolic disturbance</td>
</tr>
</tbody>
</table>
Effects of ectopic fat deposition
Fig. 1 Contribution of type 1 and type 2 diabetes to all cases of diabetes. At about 35 years of age the incidence of type 2 diabetes increases sharply. Most cases with LADA are aged >35 years.
### Difference between T1 and T2DM

<table>
<thead>
<tr>
<th></th>
<th>T1DM</th>
<th>T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive family history</td>
<td>- (+)</td>
<td>+</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>thin, symptoms +, ketonuria +</td>
<td>obes, symptoms –, ketonuria -</td>
</tr>
<tr>
<td>Other diseases</td>
<td>autoimmune (thyroid, celiac)</td>
<td>metabolic syndrome, CVD</td>
</tr>
<tr>
<td>Antibodies (GADA)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>C-peptide- (insulin-) level</td>
<td>low/normal</td>
<td>normal/high/low</td>
</tr>
<tr>
<td>HLA association</td>
<td>DR3-DQ2; DR4-DQ8</td>
<td>no (T2F7L2)</td>
</tr>
<tr>
<td>Stages/Types</td>
<td>Normoglycaemia</td>
<td>Hyperglycaemia</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td></td>
<td>Normal glucose tolerance</td>
<td>IGT and/or IFG</td>
</tr>
</tbody>
</table>

**Type I**
- Autoimmune
- Idiopathic

**Type II**
- Predominantly insulin resistance
- Predominantly insulin secretory defects

Other specific types
- Genetic defects of beta-cell function
- Genetic defects of insulin action
- Diseases of exocrine pancreas
- Endocrinopathies
- Drug or chemical induced
- Others

Gestational hyperglycaemia
Other types of diabetes mellitus
Monogenic forms

- **MODY** (maturity onset diabetes of the young): mutations of the glucokinase, the HNF genes – beta cell failure, autosomal dominant inheritance early onset of diabetes (< 25 years) family accumulation (3 generations).


- **Neonatal diabetes**: diabetes onset in the first 6 months (up to 1 year)
Genetic classification of neonatal diabetes

Neonatal diabetes

- Transient (TNDM) 45%
  - 6q ZAC 71%
  - KCNJ11 11%
- Permanent (PNDM) 45%
  - ABCC8 31%
  - INS 13%
  - GCK 16%
  - 3%
- Syndromes & Pancreatic aplasia 10%
  - PTF1A 45%
  - FOXP3
  - EIF2AK3
  - HNF1B
  - IPF1

(Kir6.2) (SUR1)
GLP1 receptor
Adenyl cyclase
CAMP
PKA

KCNJ11
ABCC8

Glucose transporter (GLUT2)

Glucose

ATP-sensitive K⁺ channel

K⁺

Depolarisation

GLP1

Adenyl cyclase
CAMP
PKA

K⁺

Ca²⁺

Insulin secretion

Insulin receptor

Glucose 6-phosphate

Glycolysis

Krebs cycle

Mitochondrion

mtA3243G
MIDD

GCK
MODY

NDM

SLC30A8

intracellular Ca²⁺ stores

Insulin containing granules

WFS1
Endoplasmic reticulum

CDKAL1
CDKN2A/B

TCF1
TCF2
HNF4A
HHEX
TCF7L2

Promoter

MODY

<table>
<thead>
<tr>
<th>None</th>
<th>Wild type</th>
<th>0.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal diabetes alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G53R</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>G53S</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>I182V</td>
<td>5.3</td>
<td>ATP-binding</td>
</tr>
<tr>
<td>H46Y</td>
<td>7.3</td>
<td>Gating</td>
</tr>
<tr>
<td>N48D</td>
<td>16</td>
<td>ATP-binding</td>
</tr>
<tr>
<td>R201H</td>
<td>8</td>
<td>ATP-binding</td>
</tr>
<tr>
<td>E227K</td>
<td>10</td>
<td>Gating</td>
</tr>
<tr>
<td>E229K</td>
<td>3.7</td>
<td>Gating</td>
</tr>
<tr>
<td>R50Q</td>
<td>8.2</td>
<td>ATP-binding</td>
</tr>
<tr>
<td>V252A</td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td>iDEND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V59M</td>
<td>13</td>
<td>Gating</td>
</tr>
<tr>
<td>R201C</td>
<td>15</td>
<td>ATP-binding</td>
</tr>
<tr>
<td>H46L</td>
<td>17</td>
<td>Gating</td>
</tr>
<tr>
<td>DEND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R50P</td>
<td>33</td>
<td>ATP-binding</td>
</tr>
<tr>
<td>Q52R</td>
<td>27</td>
<td>Gating</td>
</tr>
<tr>
<td>V59G</td>
<td>40</td>
<td>Gating</td>
</tr>
<tr>
<td>I167L</td>
<td>28</td>
<td>Gating</td>
</tr>
<tr>
<td>I296L</td>
<td>32</td>
<td>Gating</td>
</tr>
<tr>
<td>Gene</td>
<td>Inheritance</td>
<td>Clinical features</td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>MODY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCK</td>
<td>AD</td>
<td>GCK-MODY: stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (&lt;54 mg/dL [3 mmol/L])</td>
</tr>
<tr>
<td>HNF1A</td>
<td>AD</td>
<td>HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (&gt;90 mg/dL [5 mmol/L]); sensitive to sulfonylureas</td>
</tr>
<tr>
<td>HNF4A</td>
<td>AD</td>
<td>HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas</td>
</tr>
<tr>
<td>HNF1B</td>
<td>AD</td>
<td>HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout</td>
</tr>
<tr>
<td>Neonatal diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KCNJ11</td>
<td>AD</td>
<td>Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas</td>
</tr>
<tr>
<td>INS</td>
<td>AD</td>
<td>Permanent: IUGR; insulin requiring</td>
</tr>
<tr>
<td>ABCC8</td>
<td>AD</td>
<td>Transient or permanent: IUGR; rarely developmental delay; responsive to sulfonylureas</td>
</tr>
<tr>
<td>6q24 (PLAGL1, HYMA1)</td>
<td>AD for paternal duplications</td>
<td>Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication or maternal methylation defect; may be treatable with medications other than insulin</td>
</tr>
<tr>
<td>GATA6</td>
<td>AD</td>
<td>Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring</td>
</tr>
<tr>
<td>EIF2AK3</td>
<td>AR</td>
<td>Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring</td>
</tr>
<tr>
<td>FOXP3</td>
<td>X-linked</td>
<td>Permanent: immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome: autoimmune diabetes; autoimmune thyroid disease; exfoliative dermatitis; insulin requiring</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction.
Other types of diabetes mellitus
Monogenic forms

• **MODY** (maturity onset diabetes of the young): mutations of the glucokinase, the HNF genes – beta cell failure, autosomal dominant inheritance early onset of diabetes (< 25 years) family accumulation (3 generations).

• **MIDD** (maternally inherited diabetes and deafness): mutation of the mitochondrial gene, mostly A3243G (adenin-guanin change at position 3243). Progressive beta-cell failure. Metformin contraindicated!

• **Neonatal diabetes (NDM)**
Genetic classification of MODY
(Diabetes 57:2889, 2008)
### Table 2.7—Most common causes of monogenic diabetes (68)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Inheritance</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MODY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCK</td>
<td>AD</td>
<td>GCK-MODY: stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (&lt;54 mg/dL [3 mmol/L])</td>
</tr>
<tr>
<td>HNF1A</td>
<td>AD</td>
<td>HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (&gt;90 mg/dL [5 mmol/L]); sensitive to sulfonylureas</td>
</tr>
<tr>
<td>HNF4A</td>
<td>AD</td>
<td>HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas</td>
</tr>
<tr>
<td>HNF1B</td>
<td>AD</td>
<td>HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout</td>
</tr>
<tr>
<td><strong>Neonatal diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KCNJ11</td>
<td>AD</td>
<td>Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas</td>
</tr>
<tr>
<td>INS</td>
<td>AD</td>
<td>Permanent: IUGR; insulin requiring</td>
</tr>
<tr>
<td>ABCC8</td>
<td>AD</td>
<td>Transient or permanent: IUGR; rarely developmental delay; responsive to sulfonylureas</td>
</tr>
<tr>
<td>6q24 (PLAG1, HYMA1)</td>
<td>AD for paternal duplications</td>
<td>Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication or maternal methylation defect; may be treatable with medications other than insulin</td>
</tr>
<tr>
<td>GATA6</td>
<td>AD</td>
<td>Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring</td>
</tr>
<tr>
<td>EIF2AK3</td>
<td>AR</td>
<td>Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring</td>
</tr>
<tr>
<td>FOXP3</td>
<td>X-linked</td>
<td>Permanent: immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes; autoimmune thyroid disease; exfoliative dermatitis; insulin requiring</td>
</tr>
</tbody>
</table>

*AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction.*
Other types of diabetes mellitus  
Monogenic forms

- **MODY** (maturity onset diabetes of the young): mutations of the glucokinase, the HNF genes – beta cell failure, autosomal dominant inheritance early onset of diabetes (< 25 years) family accumulation (3 generations).
- **Neonatal diabetes**
1. Family with MIDD

2. Family

Hosszúfalusi…Pánczél, DMRR 25:127, 2009
Other specific types

- Diseases of pancreas → insulin treatment
- Endocrinopathies: Cushing syndrome, acromegaly, hyperthyroidism, phaeocromocytoma
- Drug or chemical induced:
  - steroid induced diabetes!
Clinical features

T1DM                             T2DM

Etiology

autoantibodies, C-peptide, genetics

T2DM                Other types         T1DM

1-2 % (known genetics)        (> 5 %)
Gestational diabetes (GDM)  
(ADA 2015)

- Diagnosed during pregnancy
- Test for undiagnosed DM at first prenatal visit in those with risk factors (HbA1c)
- Screen!: 24-28 weeks of gestation, 75 g OGTT
- Screen women with GDM for persistent diabetes 6-12 weeks postpartum
- GDM, T1DM, T2DM, other
- Lifelong screening for diabetes at least every 3 years
- GDM + prediabetes → metformin
Diagnostic criteria for GDM
One-step strategy (ADA, 2015)

• 24-28 weeks, without previous DM diagnosis
• OGTT, 75 g, any of the following values
  • FBG ≥ 5.3 mmol/l (95 mg/dl)
  • 1 hour BG: ≥ 10.0 mmol/l (180 mg/dl)
  • 2 hour BG: ≥ 8.5 mmol/l (153 mg/dl)