Typing diabetes mellitus

Dominique Maiter
UCL St Luc
ADA classification

1. Type 1 diabetes (β-cell destruction, leading to absolute insulin deficiency)
   1. Immune mediated
   2. Idiopathic
2. Type 2 diabetes (from insulin resistance with relative insulin deficiency to predominantly secretory defect with insulin resistance)
3. Others specific diabetes
   1. Genetic defects of β-cell function
   2. Genetic defects in insulin action
   3. Diseases of the exocrine pancreas
   4. Endocrinopathies (acromegaly, cushing’s syndrome, hyperthyroidism, …)
   5. Drugs- or chemical-induced
   6. Infections (congenital rubella, cytomegalovirus, …)
   7. Uncommon forms of immune-mediated diabetes
   8. Other genetic syndromes sometimes associated with diabetes
4. Gestational diabetes mellitus (GDM)
Useful parameters for classification of a diabetes

- Familial history
- Personal history and co-existing diseases
- History of the diabetes mellitus
- History of treatment of the DM
- Clinical examination: weight, BMI, waist circumference
- Biology: glycaemia at admission, HbA₁C, C-peptide, ketosis, lipids, antibodies
- HOMA test: β function, insulin sensitivity, hyperbolic product
- Anti GAD, IA2 antibodies, other Abs
- Evolution
Clinical case 1  Ms. AV, 39 yrs

- Personal history: -
- Familial history: -
- Treatment: -

- History of the DM:
  Symptoms ++ since 1 month
  Weight loss 10 kg
  Visual problems (accomodation) +
  Fatigue ++
Clinical examination:
56 kg, 1m73, BMI 18.7 kg/m²

Biology:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycaemia</td>
<td>mg/dl</td>
<td>304</td>
</tr>
<tr>
<td>HbA₁C</td>
<td>%</td>
<td>15</td>
</tr>
<tr>
<td>ketonuria</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>c-peptide</td>
<td>pmol/ml</td>
<td>0.15</td>
</tr>
<tr>
<td>Cholesterol total</td>
<td>mg/dl</td>
<td>230</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>mg/dl</td>
<td>169</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>mg/dl</td>
<td>39</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>mg/dl</td>
<td>110</td>
</tr>
<tr>
<td>Ab TPO, Tg</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>
Ms. AV, 39 yrs

- **HOMA Test**:

<table>
<thead>
<tr>
<th>Glucose</th>
<th>mg/dl</th>
<th>0'</th>
<th>5'</th>
<th>10'</th>
</tr>
</thead>
<tbody>
<tr>
<td>267</td>
<td>262</td>
<td>260</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Insulin</th>
<th>µU/ml</th>
<th>3</th>
<th>4</th>
<th>3</th>
</tr>
</thead>
</table>

- **β Cell function**: 8.3%
- **Sensitivity**: 122%
- **Hyperbolic product**: 10%

**Antibodies**: GAD + (87.6 U/ml), IA2 + (2.93 U/ml)

→ **Type 1 diabetes**
Clinical case 2  Mr. HO, 41 yrs

- **Personal history:**
  Hypertension

- **Familial history:**
  diabetes in the mother’s family

- **Treatment:**
  Aldactazine

- **History of the DM:**
  Symptoms ++ since 6 months
  Weight loss 4 kg
  Visual problems (accomodation) +
  Fatigue ++
Mr. HO, 41 yrs

- **Clinical examination:**
  87 kg, 1m74, BMI 28.7 kg/m², waist 104 cm

- **Biology:**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycaemia</td>
<td>mg/dl</td>
<td>367</td>
</tr>
<tr>
<td>HbA₁C</td>
<td>%</td>
<td>10.8</td>
</tr>
<tr>
<td>ketonuria</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>c-peptide</td>
<td>pmol/ml</td>
<td>0.56</td>
</tr>
<tr>
<td>Cholesterol total</td>
<td>mg/dl</td>
<td>195</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>mg/dl</td>
<td>156</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>mg/dl</td>
<td>39</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>mg/dl</td>
<td>349</td>
</tr>
<tr>
<td>Ab TPO, Tg</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>
Mr. HO, 41 yrs

- **HOMA Test:**

<table>
<thead>
<tr>
<th></th>
<th>0'</th>
<th>5'</th>
<th>10'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose mg/dl</td>
<td>212</td>
<td>214</td>
<td>212</td>
</tr>
<tr>
<td>Insulin µU/ml</td>
<td>11</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

- **β Cell function**: 33%
- **Sensitivity**: 38%
- **B x S**: 13%

Antibodies: **GAD -**, **IA2 -**

→ **Type 2 diabetes (insulinopenic)**
Clinical case 3  Mr. OP, 28 yrs

- Personal history: -

- Familial history: -

- Treatment: -

- History of the DM:
  Symptoms ++ since 2 months
  Weight loss 12 kg
  But previous weight gain of 30 kg in 6 years
Mr. OP, 28 yrs

- **Clinical examination:**
  94 kg (- 12kg), 1m86, BMI 27.2 kg/m$^2$, Tour de taille 104 cm

- **Biology:**

<table>
<thead>
<tr>
<th></th>
<th>Unit</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycaemia</td>
<td>mg/dl</td>
<td>322</td>
</tr>
<tr>
<td>HbA$_1$C</td>
<td>%</td>
<td>12.6</td>
</tr>
<tr>
<td>ketonuria</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>c-peptide</td>
<td>pmol/ml</td>
<td>0.17</td>
</tr>
<tr>
<td>Cholesterol total</td>
<td>mg/dl</td>
<td>142</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>mg/dl</td>
<td>64</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>mg/dl</td>
<td>34</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>mg/dl</td>
<td>220</td>
</tr>
</tbody>
</table>
Mr. OP, 28 yrs

- **HOMA Test:**

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/dl</td>
<td>µU/ml</td>
</tr>
<tr>
<td>0’</td>
<td>5’</td>
</tr>
<tr>
<td>277</td>
<td>274</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

- β cell function: 9.8%
- Sensitivity: 86.4%
- B X S: 8.5%

Antibodies: GAD + (16 U/ml), IA2 + (4.4 U/ml)

→ type 1 diabetes
Clinical case 4  Mrs. AM, 55 yrs

- **Personal history:** Hypothyroidism

- **Familial history:** -

- **Treatment:**
  - L-T4

- **History of the DM:**
  - June 2005: mycosis, no weight loss (58 kg, 1m55), Glycaemia 200 mg/dl, HbA$_1$C 10.5 %, R/ Metformin $\Rightarrow$ 6.5 %
  - August 2006: HbA$_1$C 8.8 %, R/ + Gliclazide
  - June 2007: HbA1c 8.1%
Mrs. AM, 55 yrs

- **Clinical examination:**
  59 kg, 1m55, BMI 24.5 kg/m²

- **Biology:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Unit</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycaemia</td>
<td>mg/dl</td>
<td>128</td>
</tr>
<tr>
<td>HbA\textsubscript{1C}</td>
<td>%</td>
<td>8.1</td>
</tr>
<tr>
<td>Insulin</td>
<td>\mu U/ml</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>c-peptide</td>
<td>pmol/ml</td>
<td>0.41</td>
</tr>
<tr>
<td>Cholesterol total</td>
<td>mg/dl</td>
<td>217</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>mg/dl</td>
<td>159</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>mg/dl</td>
<td>44</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>mg/dl</td>
<td>69</td>
</tr>
<tr>
<td>Ab TPO, Tg</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
Mrs. AM, 55 yrs

Test HOMA:

<table>
<thead>
<tr>
<th></th>
<th>0'</th>
<th>5'</th>
<th>10'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose mg/dl</td>
<td>128</td>
<td>129</td>
<td>128</td>
</tr>
<tr>
<td>Insulin µU/ml</td>
<td>3</td>
<td>&lt; 3</td>
<td>3</td>
</tr>
</tbody>
</table>

β cell function : 27.9 %
Sensitivity: 197.8 %
B X S : 55 %

Antibodies: GAD + (38.2 U/ml)
⇒ Type 1 diabetes « slow onset » or LADA
Clinical case 5  Mr. NK, 62 yrs

- **Personal history:**
  - Biliary pancreatitis in 2006 (R/ sphincterotomy)
  - Hypertension
  - Hypercholesterolemia

- **Familial history:** -

- **Treatment:**
  - Creon 5/day, Simvastatin 20mg, Nexiam 20mg

- **History of the DM:**
  - Symptoms -
  - Weight: stable
Mr. NK, 62 yrs

Clinical examination:
56 kg, 1m61, BMI 21.6 kg/m², waist 80 cm

Biology:

<table>
<thead>
<tr>
<th>Test</th>
<th>Unit</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycaemia</td>
<td>mg/dl</td>
<td>300</td>
</tr>
<tr>
<td>HbA₁C</td>
<td>%</td>
<td>8.9</td>
</tr>
<tr>
<td>Ketonuria</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>C-peptide</td>
<td>pmol/ml</td>
<td>0.57</td>
</tr>
<tr>
<td>Cholesterol total</td>
<td>mg/dl</td>
<td>179</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>mg/dl</td>
<td>106</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>mg/dl</td>
<td>63</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>mg/dl</td>
<td>50</td>
</tr>
</tbody>
</table>
Mr. NK, 62 yrs

- **Test HOMA:**

<table>
<thead>
<tr>
<th></th>
<th>0'</th>
<th>5'</th>
<th>10'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>mg/dl</td>
<td>190</td>
<td>189</td>
</tr>
<tr>
<td>Insuline</td>
<td>µU/ml</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

- β Cell function : 13 %
- Sensitivity : 180 %
- B x S : **23.4 %**

- **Abdomen CT Scan:** atrophy of the corpus and tail of the pancreas, pseudo-cysts, calcifications
  - Diabetes secondary to chronic pancreatitis
Clinical case 6  Mrs. MG, 54 yrs

- 54 year-old woman sent for
  - muscle weakness and fatigue
  - Polyuria-polydipsia
  - fasting glycaemia 273 mg/dl
Mrs. MG, 54 yrs

- Personal history

- Peripheral arteritis R/plavix
- Recurrent mycosis of the GI tract
- Sideropenic anemia (gastritis)
- Rectal ulcers (analgesics)
- Auto-immune hypothyroidism R/thyroxine
- Hypercholesterolaemia
- Chronic renal insufficiency < benign nephroangio-sclerosis
- Chronic sinusitis since 2000
Mrs. MG, 54 yrs

Treatment:

- Plavix
- L-thyroxine 125 µg
- Adalat 5mg
- Pravasine 10 mg
- Befact, Folavit
- Movicol
1/ Confirm diabetes mellitus:

- fasting glucose - OGGT if glucose < 150
- HOMA Test
- HbA1c
**HOMA Test**

<table>
<thead>
<tr>
<th></th>
<th>0'</th>
<th>5'</th>
<th>10'</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose (mg/dl)</strong></td>
<td>155</td>
<td>156</td>
<td>161</td>
</tr>
<tr>
<td><strong>Insulin (µU/ml)</strong></td>
<td>12</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>

- Sensitivity : 40 %
- β-cell function : 57 %
- B x S = 23 %
Mrs. MG, 54 yrs

HbA$_{1c}$ : 8.3 % (3-6)
2/ Etiology of diabetes?
Mrs. MG, 54 yrs

☐ Type 1 ? No
  ▪ Clinically no argument
  ▪ Homa test: quite good β-cell function
  ▪ Antibodies: anti GAD65 (-), IA2 (-)
  ▪ (Auto immune thyroiditis)

☐ Type 2 ?
  ▪ No familial history
  ▪ No overweight, no metabolic syndrome
  ▪ But insulin resistance
Other specific diabetes?

- No sign of pancreatitis - Imaging (-)

**Other signs and symptoms**

- Weight gain 10 Kg in 1 yr, HTA
- Moon face, easy bruising of the skin, ecchymoses .. (Plavix ?)
- Mycosis and gastritis
- General weakness
- Leucocytosis (neutrophilic) observed since months

→ diagnosis?
Cushing’s syndrome

What would you ask to confirm CS?

- 24 h - Urinary free cortisol (< 100 µg)
- Dexamethasone suppression test (1 mg overnight or Liddle’s test over 2 days)
- Cortisol rhythm (+ ACTH)
- If available: midnight salivary cortisol
Cortisol rhythm

ACTH low 3-10 pg/ml (20-60)
Mrs. MG, 54 yrs

- 24 h UFC: 147 µg (nl < 100)

- Low dose dexamethasone suppression test (4 x 0.5 mg 2 days): no suppression!

- Cortisol 355 nM (< 140 nmol/L)
- ACTH 4 pg/ml (< 20 pg/ml)
- 24 h UFC 247 µg (< 25 µg)

→ CONFIRMED CUSHING'S SYNDROME
Cushing syndrome

- What would you ask to search for aetiology?

- High dose dexamethasone suppression test
- CRH test
- Imaging (Pituitary MRI - Adrenal CT)
- (Inferior petrosal sinus sampling?)
MG, 54 yrs

- High dose dexamethasone suppression test (4 x 2 mg 2 days): no suppression!
  - Cortisol: 477 nM
  - ACTH: 2 pg/ml
  - 24 h UFC: 587 µg

→ ADRENAL CUSHING?
Adrenal CT Scan

No tumor - No hyperplasia
Other diagnosis?

Proven Cushing’s syndrome $\rightarrow$ diabetes

ACTH-independent

with normal adrenal (and pituitary) imaging

...??
Chronic exogenous glucocorticoid intake

Complaints of chronic sinusitis ...

Daily use of nasal drops of Sofrasolone®
- = prednisolone acetate 2.5 mg/ml – 10 ml (over-the-counter medication!)
- admitted use of 3 to 4 vials per week!
- = 75 - 100 mg prednisolone/week or 10-14 mg/day
- since 4 years
Conclusion

- Specific diabetes induced by iatrogenic Cushing

- Iatrogenic Cushing due to exogenous abuse of corticoids in nasal drops (Sofrasolone)