Rethinking the Classification of Diabetes

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Classification of Diabetes

The concept of insulin sensitivity in diabetes is attributed to Sir Harold Himsworth because he first distinguished between two main types of diabetes, an insulin-sensitive and an insulin-insensitive diabetes, now known as type 1 diabetes and type 2 diabetes respectively.

Himsworth HP. The Lancet, 1936; 227:127-30

Classification of Diabetes

In 1997 an Expert Committee on the Diagnosis and Classification of Diabetes Mellitus working under the sponsorship of the American Diabetes Association revised the diagnostic and classification criteria for diabetes mellitus.

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus
Diabetes Care, 1997; 20: 1183-1197.

Diagnosis and Classification:
Etiologic classification of diabetes mellitus

I. Type 1 DM
II. Type 2 DM
III. Other specific types
IV. Gestational DM

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus
Diabetes Care, 1997; 20: 1183-1197.

Disclosure to Participants

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  – Consultant for Janssen, Novo Nordisk, Eli Lilly, Sanofi, AstraZeneca
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  – Speaker fees from Novo Nordisk, Janssen
I. Type 1 diabetes
(beta-cell destruction, usually leading to absolute insulin deficiency)

A. Immune mediated
B. Idiopathic

II. Type 2 diabetes
(may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types

A. Genetic defects of beta-cell function
   1. Chromosome 12, HNF-1 α (MODY3)
   2. Chromosome 7, glucokinase (MODY2)
   3. Chromosome 20, HNF-4 α (MODY1)
   4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY6)
   5. Chromosome 17, HNF-1 β (MODY5)
   6. Chromosome 2, NeuroD1 (MODY6)
   7. Mitochondrial DNA
   8. Others

B. Genetic defects in insulin action
   1. Type A insulin resistance
   2. Leprechaunism
   3. Rabson-Mendenhall syndrome
   4. Lipoatrophic diabetes
   5. Others

C. Diseases of the exocrine pancreas
   1. Pancreatitis
   2. Trauma/pancreatectomy
   3. Necrosis
   4. Cystic fibrosis
   5. Hemochromatosis
   6. Fibrocalculous pancreatopathy
   7. Others

D. Endocrinopathies
   1. Acromegaly
   2. Cushing’s syndrome
   3. Gissoadrenoma
   4. Paraganglioma
   5. Hyperparathyroidism
   6. Somatostatinoma
   7. Aldosteronoma
   8. Others

E. Drug or chemical-induced
   1. Vasoressin
   2. Pantamine
   3. Neutrin acid
   4. Glucocorticoids
   5. Thyroid hormone
   6. Dazoxidone
   7. E-adrenergic agonists
   8. Theophyllines
   9. Diamine
   10. a-interferon
   11. Others

F. Infections
   1. Congenital rubella
   2. Cytomegalovirus
   3. Others

G. Uncommon forms of immune-mediated diabetes
   1. “Still-male” syndrome
   2. Anti-insulin receptor antibodies
   3. Others

H. Other genetic syndromes sometimes associated with diabetes
   1. Down’s syndrome
   2. Klinefelter’s syndrome
   3. Turner’s syndrome
   4. Wolfram’s syndrome
   5. Friedreich’s ataxia
   6. Huntington’s chorea
   7. Laurence-Moon-Biedl syndrome
   8. Myotonic dystrophy
   9. Polydactyly
   10. Prader-Willi syndrome
   11. Others

IV. Gestational diabetes mellitus (GDM)

Disorders of glycemia: etiologic types and stages

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus
Diabetes Care, 1997; 20: 1183-1197.
Percentage of Adults with Diagnosed Diabetes in the US, by State, in 2008

Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2008

Darwin’s theory of evolution

Classification of Diabetes

- Lots of attention have been given to the recent and rapid quantitative changes in diabetes
- Little attention has been paid to qualitative changes - the expansion or emergence of forms of diabetes that do not fit the traditional categories defined by the ADA or WHO

Diabetes Mellitus in the US according to the ADA

U.S. Diabetes Prevalence

All Ages, 2005

- 20.8 million people have diabetes
  - Diagnosed: 14.6 million people
    - Type 1 diabetes accounts for 5 – 10%
    - Type 2 diabetes accounts for 90 – 95%
    - Other types of DM probably account for ~ 1 – 2%
  - Undiagnosed: 6.2 million people

References:
Type 2 Diabetes Mellitus

"Type 2 diabetes:
This form of diabetes, which accounts for 90-95% of those with diabetes...encompasses individuals who have insulin resistance and usually have relative insulin deficiency."

The Classification of Diabetes Mellitus: a Clinician’s Perspective

- 64 y/o WM
- T2DM dx’d 14 years ago
- Gastric By-Pass 22 yrs ago
- HTN, Dyslipidemia, CAD
- Human Insulin 70/30 - 130 units per day
- Metformin 1000 mgs bid
- Byetta 10 mcg bid

Type 1 Diabetes Mellitus

"Type 1 diabetes
Immune-mediated diabetes
This form of diabetes, which accounts for only 5-10% of those with diabetes...results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas."

The Classification of Diabetes Mellitus: a Clinician’s Perspective

- Family Hx of Diabetes: Multiple Family Members with T2DM
- Wt: 235; Ht: 5’10”
- BP: 123/68
- High LDL, Low HDL, High Trig
- Glucose 238 mg/dl
- C-Peptide 6.8 ng/ml
- Anti-GAD Antibody (-)
The Classification of Diabetes Mellitus: a Clinician’s Perspective

- 27 y/o WM
- T1DM dx’d 19 yrs ago
- No HTN, No Dyslipidemia
- Humalog 27 units/day
- (Insulin Pump)

Fam Hx of Diabetes (-)

Wt: 173 lbs; Ht: 5’11”
BP: 115/60

LDL: 115; HDL: 46; Trig: 62
Glucose 197 mg/dl
C-Peptide < 0.5 ng/ml
Anti-GAD Ab (+)

Heterogeneous Clinical Features of Type 2 DM

Slowly Progressive → Rapidly Progressive
Lean → Obese
Abnormal Fasting Glucose → Abnormal Fasting and Postprandial Glucose
Abnormal Postprandial Glucose → Abnormal Fasting and Postprandial Glucose
Non-DKA Prone → DKA-Prone
Insulin Non-Requesting → Insulin-Requesting
High Insulin Sensitivity → Low Insulin Sensitivity
High Insulin Secretion → Low Insulin Secretion
Oral Agent Responsive (by drug class?) → Oral Agent Unresponsive
Low Risk Ethnicity (genetic and cultural?) → High Risk Ethnicity
Low Risk Behaviors (genetic and cultural?) → High Risk Behaviors
Low Risk Environment → High Risk Environment
Low Specific Genetic Risk Factors → High Specific Genetic Risk Factors

Smith, R. J. et al. J Clin Endocrinol Metab, 2010;95:1566-1574

The Spectrum of Diabetes in Northern Europe

The list of unusual types of diabetes which have been described is rather long:
- LADA, T 1 ½ DM, T2DM, MODY, T2DM, LADY
- Prandie Diabetes, Flatbush Diabetes, T3DM, T2DM
- ACMI → Non-autoimmune Fulminant DM
- T1D, T2D, T3DM
- MODY, MHCIA, LINDDIA, PDPD, FCPD
- T2D
- LADA, T1D, T2D

MODY subtype prevalence and treatment

Glucokinase
MODY1 (22%)
HNF4α
MODY1 (10%)
HNF1α
MODY2 (16%)
HNF1β
MODY3 (8%)
HNF1α + HNF1β (16%)
Unknown (15%)

No new except in pregnancy
Low-dose Sulfonylureas
Low-dose Sulfonylures
Insulin
Tea tree
Tea tree

Smith, R. J. et al. J Clin Endocrinol Metab, 2010;95:1566-1574
Atypical Diabetes Mellitus

Most notably in the US the following “atypical” types of diabetes have been noted:

– Ketosis Prone Type 2 Diabetes (KP-T2DM)
– Atypical Diabetes Mellitus (ADM)
– Latent Autoimmune Diabetes of the Adult (LADA)

Ketosis-Prone Type 2 Diabetes Mellitus and Human Herpesvirus 8 Infection in Sub-Saharan Africans

<table>
<thead>
<tr>
<th>Ketosis-Prone DM-2 DM-N</th>
<th>Numatic DM-2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: women</td>
<td>41/7 (55.8%)</td>
<td>36/58 (62.1)</td>
</tr>
<tr>
<td>West African origin</td>
<td>50/78 (63.3%)</td>
<td>75/108 (69.4%)</td>
</tr>
<tr>
<td>Central African origin</td>
<td>22/27 (81.5%)</td>
<td>36/58 (62.1)</td>
</tr>
<tr>
<td>Carbohydrate metabolism</td>
<td>46 (16)</td>
<td>50 (15)</td>
</tr>
<tr>
<td>Diabetes duration, men</td>
<td>5.3 (4.6)</td>
<td>5.0 (4.6)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.7 (2.6)</td>
<td>25.4 (3.7)</td>
</tr>
<tr>
<td>HbA1c, mmol/L</td>
<td>7.7 (1.2)</td>
<td>7.4 (1.7)</td>
</tr>
<tr>
<td>Hypertension prevalence</td>
<td>36/57 (63.2%)</td>
<td>42/68 (61.8)</td>
</tr>
<tr>
<td>Hypothyroidism prevalence</td>
<td>6/62 (9.7%)</td>
<td>11/16 (6.8)</td>
</tr>
<tr>
<td>Insulin treated</td>
<td>1/14 (7.1%)</td>
<td>2/26 (7.7)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>13/16 (8.1)</td>
<td>20/45 (4.4)</td>
</tr>
</tbody>
</table>

Ketosis-Prone in Sub-Saharan context

Age, mean (SD) | 50 (11) | 45 (10) | .29
BMI, kg/m²     | 25.4 (4.3) | 26.5 (3.6) | .20
Blood glucose, mmol/L | 7.1 (2.0) | 7.3 (1.9) | .01
HbA1c, mmol/L  | 7.7 (1.2) | 7.4 (1.7) | .31
Hypertension, mmol/L | 36 (59) | 42 (51) | .71
Hypothyroidism, mmol/L | 6 (10) | 11 (10) | .63
Insulin treated, mmol/L | 1 (7) | 2 (18) | .63

The Classification of Diabetes Mellitus: a Clinician’s Perspective

- 50 y/o BM
- T2DM dx’d 16 yrs ago
- HTN, Dyslipidemia
- Metformin
- Insulin 200 units/day
The Classification of Diabetes Mellitus: a Clinician’s Perspective  

70 y/o Asian Male  
T2DM dx’d 1 yr ago  
HTN, Dyslipidemia  
Diet & Exercise only  

53 y/o WM  
T2DM dx’d 8 yrs ago  
HTN, No Dyslipidemia  
Insulin 35 units/day  

45 y/o BF  
T2DM dx’d 19 yrs ago  
HTN, No Dyslipidemia  
Insulin 75 units/day
The Classification of Diabetes Mellitus:
a Clinician’s Perspective

47 y/o Indian Male
- T2DM dx’d 8 yrs ago
- Dyslipidemia, No HTN
- Actos

50 y/o WM
- T2DM dx’d 2 mo ago
- No HTN, Dyslipidemia
- Diet & Exercise

40 y/o BM
- T2DM dx’d 2 yrs ago
- No HTN, No Dyslipidemia
- Metformin
- Avandia
The Classification of Diabetes Mellitus: a Clinician’s Perspective

- Fam Hx of Diabetes:
  - Mother (+); Father (-)
  - Maternal GM (+)
  - 2 siblings (-); 3 children (-)
- Wt 195; Ht 5’9”
- BP 100/70
- LDL 196; HDL 56; Trig 223
- Glucose 344 mg/dl
- C-Peptide 1.6 ng/ml
- Anti-GAD (-); Anti-IA2 (-); Anti ICA (-)
- MODY 3 mutation TCF-1 gene

The Classification of Diabetes Mellitus: a Clinician’s Perspective

- 63 y/o BF
- T2DM dx’d 14 yrs ago
- HTN, Dyslipidemia
- Psych Disorder
- Insulin 90 units/day
- Trifluoperazine

The Classification of Diabetes Mellitus: a Clinician’s Perspective

- Fam Hx of Diabetes:
  - Father (+); Mother (-); GPs (-)
  - 2 siblings (-)
- Wt 223 lbs; Ht 5’3”
- BP 160/80
- LDL 118; HDL 68; Trig 22
- Glucose 148 mg/dl
- C-Peptide: <0.5 ng/ml
- Anti-GAD (-); Anti IA2 (-); Anti ICA (+)

The Classification of Diabetes Mellitus: a Clinician’s Perspective

- 37 y/o BF
- T2DM dx’d 8 yrs ago
- Dyslipidemia, HTN
- Insulin 100 units/day

The Classification of Diabetes Mellitus: a Clinician’s Perspective

- Fam Hx of Diabetes:
  - Mother (-); Father (-); GPs (-); 1 of 1 Sister (+); 1 Cousin (+) @ age 10
- Wt 162; Ht 5’4”; BP 120/86
- LDL 79; HDL 59; Trig 27
- Glucose 146 mg/dl; C-Peptide <0.5 ng/ml
- Anti-GAD (+); Anti-IA2 (+)

Heterogeneity of Diabetes in Alabama

- n = 1257
- Aam 1%
- Hispanic 2%
- White 68%
- Black 29%
- Females 56%
### Heterogeneity of Diabetes in Alabama

<table>
<thead>
<tr>
<th>All patients (n = 1257)</th>
<th>Age</th>
<th>Duration of Diabetes (Mean)</th>
<th>Age at Diagnosis (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50</td>
<td>11</td>
<td>39</td>
</tr>
<tr>
<td>Mean</td>
<td>50</td>
<td>9</td>
<td>40</td>
</tr>
<tr>
<td>Median</td>
<td>15.7</td>
<td>10.7</td>
<td>17.7</td>
</tr>
<tr>
<td>Std Dev</td>
<td>0.44</td>
<td>0.30</td>
<td>0.50</td>
</tr>
<tr>
<td>Range</td>
<td>17 - 88</td>
<td>0 - 66</td>
<td>0 - 82</td>
</tr>
</tbody>
</table>

### Heterogeneity of Diabetes in Alabama: Referring Diagnosis

#### Heterogeneity of Diabetes in Alabama: Auto-Antibodies in T2DM

- T2DMAA+: 17%
- T2DMAA: 83%

#### Relationship between islet autoimmunity and systemic inflammation in adult patients with diabetes.


#### The Spectrum of Diabetes in Alabama

- LADA: 12%
- T2DM: 33%
- T2DM: 34%
- Secondary DM: 3%
- MODY: 2%
- ACDM / KPT2DM: 2%
The Spectrum of Diabets in Scandinavia


Glycemic Control and Weight Reductions with 82 Weeks of Exenatide Treatment

Diabetes, Obesity and Metabolism, 8, 2006, 436-447

Glycemic Control and Weight Reductions with 82 Weeks of Exenatide Treatment

Diabetes, Obesity and Metabolism, 8, 2006, 436-447

The Spectrum of Diabetes in Alabama

n=1257
Summary

• Diabetes is an increasingly prevalent and heterogeneous group of diseases.

• Non-Traditional / Atypical forms of diabetes are rather common and may be becoming increasingly common

• The response to therapy in diabetes is also heterogeneous

• A thorough history is the most important factor in recognizing atypical diabetes, followed by exam and laboratory data

• Further insight into these subgroups should not only help elucidate the pathogenesis of T2DM but also facilitate more individualized treatment to improve glycemic control, thus maximizing individual benefit, minimizing risk, and providing reductions in global health cost.
THANK YOU