Diabetes overview and classification

Polly Bingley
Why classify diabetes?

- Guide immediate management
- Inform prognosis
- Reduce risk of diabetic emergencies
- Ensure curable causes are not missed
Summary
ADA/WHO Classification of diabetes

• **Type 1** (beta-cell destruction, usually leading to absolute insulin deficiency)

• **Type 2** (mixture of insulin resistance and insulin deficiency)

• **Other specific types** *(less than 10% of cases but may be potentially curable)*
  - Disease of the exocrine pancreas
  - Endocrinopathies
  - Drugs or chemical induced
  - Genetic defects, syndromes Etc. Etc.

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Outline

• The diabetes spectrum
• Aetiology and pathogenesis
• Clinical course
• How do you classify the patient sitting in front of you?
• age 9
• irritable for four weeks
• thirsty+++ for 2 weeks
• weight loss

• age 62
• diagnosed at insurance medical
• slightly thirsty and tired for 12 months
• No weight loss

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What makes their diabetes so different?
• Both have lost beta cells
  **BUT**
• for different reasons
• at different rates
• with different results

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AND

Different degrees of insulin resistance

Diabetes occurs when β-cell secretion doesn't match insulin resistance
- Insulin deficiency +++
  - Insulin resistance +++
  - Insulin deficiency +

**Type 1 diabetes**

**Type 2 diabetes**

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The hierarchy of insulin action

- **None**
  - ↑ glucose
- **Fat breakdown**
  - ↑ glucose
- **Weight loss**
  - Ketosis

Gluc. requires lower insulin concentrations
At diagnosis
Treatment needed?
Insulin

One month later

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The hierarchy of insulin action

None

↑ glucose

Some

↑↑↑ glucose

Fat breakdown

Weight loss

Ketosis

Gluc.

FFA

requires lower insulin concentrations
Clinical spectrum

Type 1 (~15%)
- Short duration of symptoms
- Weight loss
- Ketoacidosis
- Younger, lean

Type 2 (~85%)
- Osmotic symptoms or none
- Insidious onset
- May present with complications
- Hyperosmolar non-ketotic state
- Older, overweight

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Epidemiology of type 1 diabetes

• Peak onset in puberty but can occur at any age
• At least 50% of cases diagnosed after age 20
• More common in Europid populations
• Male >> female after puberty
• Marked geographical variation

(Laakso and Pyorala 1985)
Epidemiology of type 2 diabetes

- Peak onset in late middle-age but changing
- More common in non-Europid populations
- No gender difference
- Increasing rapidly
- 2.5 million people diagnosed in the UK (~4%), >4M expected by 2025
- ≥ 0.5M with undiagnosed diabetes

(US Centers for Disease Control and Prevention 2006)
Clinical characteristics of type 2 diabetes

• Other features of the metabolic syndrome
  - central obesity
  - hypertension
  - hyperlipidaemia
    • ↑ LDL, ↓ HDL, ↑ triglycerides
• Cardiovascular disease
Genetic characteristics

Type 1
- 30-50% concordance in MZ twins
- Sibling risk ~10%
- HLA associated
- polygenic

Type 2
- ~100% concordance in MZ twins
- Sibling risk ~25-50%
- Not HLA associated
- polygenic

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Aetiology and pathogenesis

**Type 1**
- Insulin deficient (~10% of \( \beta \) cells at diagnosis)
- Insulin sensitive
- Immune mediated

**Type 2**
- Partial insulin deficiency (50% \( \beta \) cells)
- Insulin insensitive
- Not immune mediated
Type 1 (autoimmune) diabetes

Insulitis: lymphocytic infiltration of islets at diagnosis

Circulating antibodies to β cell autoantigens indicate an ongoing autoimmune process many years before clinical onset

CD3 (T cells)

T cells are responsible for β cell destruction

Immunotherapy at diagnosis can prolong residual insulin secretion

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The major type 1 diabetes genes are related to the immune response

antigen presentation to CD4 T cells by HLA molecules on the antigen presenting cell

HLA 50% (both ↑ and ↓ susceptibility)
Gradient of HLA-determined risk
(short arm of chromosome 6)

Age of diagnosis

relative risk

~20

~0.1

DR3-DQ2/
DR4-DQ8

DR2-DQ6

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Overlap of HLA susceptibility explains why type 1 diabetes is associated with other autoimmune disease

- Thyroid
  - Hashimoto’s
  - Graves’ disease
- Coeliac disease
- Pernicious anaemia
- Addison’s disease
Initiation of the autoimmune response

- Occurs in infancy
- Genetic and environmental determinants
  - More common in relatives
  - Only 30% concordance in monozygotic twins
  - Rapid increase in incidence
  - Migrant studies
- What environmental factors?
  - New exposure? e.g. diet, virus
  - Removal of previous protection? e.g. ‘hygiene’
The pathogenesis of type 1 diabetes

- Islet autoantibodies
- Metabolic abnormalities

- Genetic predisposition
- Insulitis β cell injury

Clinical onset of diabetes (~90% β cells destroyed)
Clinical spectrum of type 1 diabetes

'Classical'

'Adult onset'

'Latent'

Clinical presentation and progression
Genetic susceptibility
Immune changes
Type 1 diabetes in adults

- Often less acute presentation than in children
- Longer duration of symptoms
- Can be indistinguishable from type 2 diabetes at diagnosis
Aetiology and pathogenesis

Type 2
- Partial insulin deficient
- Insulin insensitive
- Older, overweight
- Metabolic syndrome

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Type 2 diabetes

↓ β cell function/insulin secretory capacity

↑ blood glucose
β cell function genetics

- Most of the currently identified genes encode or proteins involved in insulin synthesis or secretion

Genes affecting insulin secretion

Genome wide association studies of type 2 diabetes 2007

Frayling TM Nature Reviews Genetics 2007
**β cell function**

environmental influences

- β cell growth in the fetus is controlled by availability of amino acids
- Insulin is an important regulator of fetal growth
- Fetal malnutrition causes irreversible defects in beta cell growth and function

(Hales and Barker 1992)
Type 2 diabetes

↓ β cell function/insulin secretory capacity

insulin resistance

↑ blood glucose

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Insulin resistance/insensitivity

“Inability of insulin to produce its usual biological actions at circulating concentrations that are effective in normal subjects”

↓ suppression of endogenous glucose production

↓ insulin-stimulated peripheral glucose uptake

↓ suppression of VLDL production and lipolysis

↑ serum triglycerides

↑ flux of NEFAs to liver and skeletal muscle
Causes of insulin resistance
environmental

- Obesity
- Lack of physical exercise
- Age
- Endocrine diseases
- Pregnancy
- Drugs
- Hyperglycaemia (glucose toxicity)
  - a vicious circle
Obesity is the major risk factor

Particularly truncal obesity

Relative risk of diabetes
US nurses’ health study

From Wellcome Trust Library

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Causes of insulin resistance

genetic

• Associated with fat mass and obesity in the general population
• People with two copies of the diabetes-risk allele had BMI 1.0 Kg/m^2 higher or were 2.3 kg heavier
• FTO is associated with diabetes through its effect on body mass index and insulin resistance

(Frayling TM Nature Reviews Genetics 2007)
Differences among people with type 2 diabetes
Type 2 diabetes

↓ β cell function/insulin secretory capacity

insulin resistance

↑ blood glucose

may range from predominantly insulin resistance with relative insulin deficiency to predominantly secretory defect with insulin resistance

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Type 2 diabetes

If mild insulin deficiency

If more marked insulin deficiency

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Type 2 diabetes: initial treatment

At diagnosis
Treatment needed?

Lifestyle modification
to reduce insulin resistance

Control of cardiovascular risk factors

At diagnosis
Treatment needed?

Lifestyle modification but
likely soon to need sulphonylurea to increase insulin secretion

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Clinical course
Diabetes is associated with **progressive** loss of beta cell function
Type 2 diabetes
Natural history

• β cells respond to insulin resistance by hypersecreting in the early stages, but fail progressively in later stages.
• Sometimes called the “Starling curve of the pancreas”.

Clinical importance:
- β cell failure is progressive
- Patients need progressively more treatment over time
Clinical course

- transient fall in insulin requirement during ‘honeymoon’ phase
- lifelong insulin

- lifestyle modification
  - + metformin to ↑ insulin sensitivity
  - + sulphonylurea ↑ insulin secretion
  - + injected insulin

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Classifying diabetes in practice
Initial assessment and classification

1) Does this person require admission?
   • acutely ill
   • vomiting
   • blood glucose >30 mmol/l
     and/or severely symptomatic

2) Is this type 1 (insulin-dependent) diabetes?
   • does this person need insulin now to prevent ketosis and death?
   • is this person likely to need insulin in the near future to prevent ketosis and death?
Any chance it is not primary diabetes?

• Could it be secondary diabetes (<10%)?
  - Disease of the exocrine pancreas
    • Chronic pancreatitis, pancreatic carcinoma, cystic fibrosis
  - Endocrinopathies
    • Acromegaly, Cushing's syndrome etc
  - Drugs or chemical induced
    • Corticosteroids etc.
  - Genetic defects, syndromes Etc. Etc.

• Could it be monogenic diabetes e.g. MODY (1-2%)?
  - Family history
  - Atypical history or clinical course
What type of diabetes?
Is it type 1 or type 2?

First presentation in diabetic ketoacidosis aged 75

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Epidemiological features of type 1 diabetes

- Peak onset in puberty but can occur at any age
- At least 50% of cases diagnosed after age 20

(Laakso and Pyorala 1985)
Changing patterns of type 1 and type 2 diabetes
Is it type 1 or type 2?

Age 23

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Initial assessment and classification

Type 1 or Type 2 diabetes?
The following features suggest type 1 diabetes (predominant insulin deficiency) and need for early insulin treatment:

*(ignore age and glucose level)*

- non-fasting ketonuria *(test everyone)*
- short history and/or severe symptoms
- marked weight loss (> 10% within 3 mth. from any weight)
- evidence of probable genetic susceptibility i.e.
- family history of type 1 diabetes
- personal or family history of autoimmune disease*

*Thyroid/coeliac/pernicious anaemia/vitiligo/Addison's etc*
Is it type 1 or type 2?

It may not be immediately apparent

August 2005
Blood glucose 27 mmol/l
Is it type 1 or type 2?

August 2005
Blood glucose 27 mmol/l

October 2005
Two stone weight loss
Flags suggesting your patient doesn’t really have type 2 diabetes

• Weight loss
• Atypical course
  – Blood glucose does not improve with diet and tablets
  – Rapid increase in treatment requirement
• Appearance of urinary ketones e.g during intercurrent illness
Diagnosis and Classification
Conclusions

• Diagnosing diabetes is really easy but
• Classifying it can be hard!
• If you are uncertain, seek help from the specialist team
• If in doubt, treat as type 1; the evidence can then be reviewed at leisure.
• The situation may change
• The initial clinical classification may be incorrect – whoever made it