Classifying Diabetes

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Outline

01 The challenge of classification
02 Some example cases
03 Using C-peptide and antibodies
What type of diabetes?

24 year old
Feeling tired, thirsty
BMI 26 kg/m²
Random glucose 22 mmol/L

★ SLIDO QUESTION 1: What type of diabetes is this?
24 year old
Feeling tired, thirsty
BMI 26 kg/m²
Random glucose 22 mmol/L

24 year old
Feeling tired, thirsty
BMI 36 kg/m²
Random glucose 22 mmol/L

🌟 SLIDO QUESTION 2: What type of diabetes is this?
What type of diabetes?

24 year old
Feeling tired, thirsty
BMI 26 kg/m²
Random glucose 22 mmol/L

24 year old
Feeling tired, thirsty
BMI 36 kg/m²
Random glucose 22 mmol/L

54 year old
Feeling tired, thirsty
BMI 26 kg/m²
Random glucose 22 mmol/L

🌟 SLIDO QUESTION 3:
What type of diabetes is this?
How might ethnicity impact your choices?

24 year old, south Asian
Feeling tired, thirsty
BMI 26 kg/m²
Random glucose 22 mmol/L

24 year old, African-Caribbean
Feeling tired, thirsty
BMI 36 kg/m²
Random glucose 22 mmol/L

54 year old, Middle Eastern
Feeling tired, thirsty
BMI 26 kg/m²
Random glucose 22 mmol/L
How does ethnicity impact diabetes?

- Risk of diabetes
- Mechanism of diabetes
- Phenotype of diabetes
- Progression of diabetes
- Stratified diabetes care
- Classification
- Treatment of diabetes
- Risk of complications
Diabetes subtype matters

28 year old man
Glucose 22 mmol/L
Thirsty ++

Type 1 diabetes
- Insulin injections / pump
- Self-monitoring blood glucose
- Type 1 diabetes education
- Ketoacidosis prevention
- Structured education
- Driving guidance & Employment

Type 2 diabetes
- Metformin / Sulphonylureas
- SGLT-2 inhibitors/ DPP4 inhibitors
- Injectables
- Different insulin regimes
- No routine glucose testing
- Type 2 specific education

Another type?
- Insulin
- Tablets
- Nothing
Consequences of misclassification

- Someone with type 2 diabetes needlessly receives insulin injections
- Someone with type 1 diabetes doesn’t receive insulin: life-threatening
- Someone with a different type of diabetes may not be on optimal treatment
- Impacts education, location of management, access to support, employment etc
- Impact on well-being, frustration, upset
Phenotypes that challenge classification

- Young-onset type 2 diabetes
- Lean type 2 diabetes
- Ketosis-prone type 2 diabetes
- Late onset type 1 diabetes
- Type 1 diabetes in overweight
- Type 1 diabetes in non-white ethnic groups
- Pancreatogenic diabetes
- Maturity onset diabetes of the young (MODY)
Phenotypes that challenge classification

- Increasing Age
- Type 2 diabetes
- Type 1 diabetes
- Young onset type 2
- Type 2 in lean people
- Ethnicity
- Increasing BMI
- Type 1 diabetes
- Type 2 diabetes
How big of a problem is this?

CHALLENGING TO ASCERTAIN

NO GOLD STANDARD DEFINITION FOR TYPE 1 OR TYPE 2 DIABETES

RECLASSIFICATION CAN OCCUR AT ANY TIMEPOINT AFTER DIAGNOSIS

We are all seeing more grey cases
SLIDO QUESTION 4: What helps you decide type of diabetes?
How do we decide?

- Age and body mass index (BMI) are the two factors most likely to influence type of diabetes

- Age and BMI are increasingly poor at discriminating diabetes subtype

- There is no test that 100% accurately diagnoses diabetes subtype
Clinical features
Overlap considerably

Pancreatic auto-antibodies
Low negative predictive value

C-peptide
How do we interpret it at diagnosis?
No cut-offs are wholly accurate

Strategies to improve classification

Time & Reflection
Diagnose type 1 diabetes on clinical grounds:

- ketosis
- rapid weight loss
- Aged <50 years
- BMI <25 kg/m²
- history of autoimmune disease

Do not discount a diagnosis of type 1 diabetes if:

- BMI >25 kg/m²
- Aged > 50 years

NICE guidelines [NG17]
C-peptide & Pancreatic Antibodies

Atypical features

Suspected maturity onset diabetes of the young

Confirmation of type 1 diabetes may impact access to certain treatments

Unless...

1.1.3 Do not measure C-peptide and/or diabetes-specific autoantibody titres routinely to confirm type 1 diabetes in adults. [new 2015]

If type 1 diabetes suspected, DO NOT delay starting insulin
SLIDO QUESTION 5:
Is C-peptide a good indicator of the need for insulin treatment?

SLIDO QUESTION 6:
Does negativity to pancreatic auto-antibodies (at diagnosis) exclude type 1 diabetes?
What are atypical features?

1.1.3 Do not measure C-peptide and/or diabetes-specific autoantibody titres routinely to confirm type 1 diabetes in adults. [new 2015]

Unless...

Atypical features

Suspected maturity onset diabetes of the young

Confirmation of type 1 diabetes may impact access to certain treatments

What are atypical features?
Lessons from the ADDRESS-2 study

Clinician-assigned diagnosis of Type 1
< 6 months from diagnosis
Age 5 years or older (children and adults)
GAD, IA-2 & ZnT8 antibodies

• Network of >150 sites in NHS Trusts and Welsh Health Boards
• Support of NIHR CRN
• Overall 40% overweight or obese
• Change from the classical description
• Not an atypical feature

**Adults**

- Obese: 10%
- Underweight: 4%
- Overweight: 30%
- Normal weight: 56%

< 28 days diagnosis. n=554, p=0.009
Walkey et al, BMJ open, 2017

Sattar et al, Lancet, 2016
Age at diagnosis in type 1 diabetes

ADDRESS-2 study
Walkey et al, BMJ open, 2017

1 in 10 diagnosed with type 1 aged >40 years

UK Biobank
Thomas et al, Lancet D&E, 2018

42% of type 1 diabetes >30 years
What are atypical features?

1.1.3 Do not measure C-peptide and/or diabetes-specific autoantibody titres routinely to confirm type 1 diabetes in adults. [new 2015]

Unless...

Atypical features

Suspected maturity onset diabetes of the young

Confirmation of type 1 diabetes may impact access to certain treatments

What are atypical features?

The typical features are changing
• 27 year old, Eritrean
• BMI 27.5 kg/m²

• Admitted, unwell 1 week
  • Glucose 28 mmol/L
  • Ketoacidosis (ketones 6 mmol/L)
  • Treated as DKA
  • Started on insulin
  • HbA1c 115 mmol/mol

• Type 2 diabetes 18 months
  • metformin,
  • last HbA1c 52 mmol/mol
What type of diabetes?

- Discharged with basal bolus insulin – labelled as type 1 diabetes

- Follow-up 2 months
  - Pancreatic antibodies negative
  - Euglycaemic on minimal doses

🌟 SLIDO QUESTION 7: What would you do next?
- Continue on insulin
- Stop insulin
- Stop insulin and start orals
- Stop insulin and lifestyle advice
What type of diabetes?

- Acute treatment = insulin
- Discharge treatment = insulin
- Diagnosis is important for follow-up and subsequent management

Type 2 Diabetes:
- Ketosis-prone type 2 diabetes

Type 1 Diabetes
Ketoacidosis – who is at risk?

Type of diabetes
- Type 1 Diabetes
- Type 2 Diabetes
- Ketosis-prone type 2 diabetes (KPDM)
- Other insulin deficient states

Individual factors
- SGLT-2 Inhibition
- Unwell / catabolic
- Ketogenic diet
- Prolonged fasting or starvation

All people with diabetes can develop ketoacidosis
Ketosis-prone type 2 diabetes

‘FLATBUSH’ DIABETES

PREDOMINATES IN AFRICAN-CARIBBEAN & HISPANIC, DESCRIBED IN EVERY ETHNIC GROUP

MARKED BETA-CELL DYSFUNCTION AT PRESENTATION

AFTER INSULIN THERAPY BETA-CELL, FUNCTION IS RESTORED

EUGLYCAEMIC REMISSION

AT RISK OF RECURRENT DKA
Ketosis-prone type 2 diabetes

- DKA at presentation
- Initiated on insulin
- Euglycaemic remission by 12 months
- Insulin stopped
- Recovery of C-peptide over months

- Usually no precipitant
- 50% first presentation of diabetes
- Short duration of symptoms
- BMI: overweight or lean?

Negative pancreatic auto-antibodies
Key points

- Must be treated with insulin – assume type 1 diabetes
- Subsequently can maintain euglycaemia off insulin
- Pancreatic autoantibodies are negative
- Retrospective diagnosis
- All ethnic groups
Case 2

- 41 year old
- 2015 – incidental pick up, HbA1c 83 mmol/mol
- Weight 89kg, BMI 26 kg/m²
- Started on metformin and HbA1c reduced to 54 mmol/mol

- Seen in community diabetes clinic
  - Mother type 2 diabetes in her 50’s
  - C-peptide 363 pmol/L, GAD-65 antibodies negative
  - Referred to diabetes clinic ?type
- Seen in Non-classical diabetes clinic at ICHT
- HbA1c 48 mmol/mol
- C-peptide 487 pmol/L
- GAD-65, IA-2 and ZnT8 antibodies negative
- Pancreatic imaging normal
- Extended MODY testing – no mutation

• Atypical type 2 or slow-burning type 1?
Case 2 continued

- Seen in Non-classical diabetes clinic at ICHT
- HbA1c 48 mmol/mol
- C-peptide 487 pmol/L
- GAD-65, IA-2 and ZnT8 antibodies negative
- Pancreatic imaging normal
- Extended MODY testing – no mutation

- Atypical type 2 or slow-burning type 1?
Case 2 continued

- Weight: 89 kg to 91 kg
- C-peptide: 412 pmol/L to 712 pmol/L
- Glucose: 5.7 mmol/L to 11 mmol/L to 18.2 mmol/L

Graph showing HbA1c mmol/mol over years post-diagnosis.
Are we certain this is type 1 diabetes?
Pancreatic auto-antibodies

Glutamate decarboxylase (GAD-65)

Islet antigen 2 (IA-2)

Zinc transporter 8 (ZnT8)

Insulin

Tetraspanin 7

• Primarily studied in a research setting to predict onset of type 1 diabetes

• Role in classification of diabetes is unclear
Caveats when interpreting antibodies

1. Antibody negativity does not exclude type 1 diabetes
2. Less than complete testing
3. People from some ethnic groups may have low rates of positivity
4. Titres diminish with duration
Antibodies in ADDRESS-2

<table>
<thead>
<tr>
<th>Autoantibody positive (n=1,778)</th>
<th>All</th>
<th>Children</th>
<th>Adults</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>85%</td>
<td>90%</td>
<td>82%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Other studies: detectable at onset in 80-90% Type 1
Diabetes duration and antibody positivity

Caution when measuring antibodies beyond diagnosis
Best practice for testing antibodies

**WHAT’S THE CLINICAL QUESTION?**

- Clinical suspicion high
- Clinical suspicion low
- Clinical suspicion intermediate and antibodies positive

**ANTIBODIES SHOULD ONLY BE MEASURED TO SUPPORT A DIAGNOSIS OF TYPE 1 DIABETES**

- Do not defer insulin
- Why measuring? Clear clinical question in mind
- Supportive of type 1 diabetes

**TYPE 1 DIABETES IS NOT EXCLUDED IF ANTIBODIES ARE NEGATIVE**
C-peptide

- Cleavage product of pro-insulin
- Compared with insulin
  - Longer half-life
  - More stable than insulin
  - No first pass metabolism
- Established marker of beta-cell function
C-peptide doesn’t just indicate beta-cell function.

Increasing insulin production

Glucose Level
Insulin sensitivity
C-peptide Level

Not as straightforward as other endocrine axes

Increasing insulin sensitivity

diabetes
What is a normal C-peptide?

- NO ‘NORMAL RANGES’ DEFINED
- NO ROBUSTLY EVALUATED CUT-OFF THAT DELINEATES ONE TYPE FROM ANOTHER
- NOT INTERPRETABLE AT DIAGNOSIS
What is the clinical question?

• Need to know the contemporaneous glucose level
• And the clinical context
  • shouldn’t be asking, does this patient need insulin?
  • could it be something other than type 1 diabetes

• Low (<400 pmol/L) or undetectable
  Assuming glucose >8mM

• Above 400 pmol/L
  • Context and question
C-peptide variability

African-Caribbean man in 50’s
Referred as likely type 1

Glucose 2.6 mmol/L
Does this patient need insulin is not the right question

- C-peptide 250 pmol/L + glucose 29 mmol/L

- C-peptide 1250 pmol/L + glucose 29 mmol/L
Insulin secretion in type 1 diabetes

A:
‘C-peptide is not low, so patient doesn’t need insulin’
‘Pancreatic antibodies were negative, so not type 1 diabetes’
‘Asian person so probably type 2 diabetes’

‘I checked the C-peptide and it wasn’t as low as expected for someone with type 1, should we consider MODY?’

‘This is an Asian person, so likely type 2, but should I be considering type 1 given young age and lean BMI?’
Case 3

- 56 year old Asian woman, lean
- 31 years duration of type 1 diabetes
- Clinical flag
  - HbA1c 52 mmol/mol on once daily basal insulin
  - No microvascular complications
- C-peptide 350 pmol/L
- Pancreatic auto-antibodies negative
• Maturity onset diabetes of the young
• Single gene defect causing diabetes
• Treatment differs to type 1 and type 2 diabetes
  • depends on gene affected

• Frequently misdiagnosed
  • Young age at onset
  • Non-insulin requiring
  • Generational history
Monogenic diabetes

- >10 genes implicated in MODY
- Glucokinase: No treatment needed
- HNF1A / HNF4A: Sulphonylureas
- Other genes: Tablets or insulin
Case 3

Genetic testing

- HNF4-Alpha mutation
- Patient offered trial switch to gliclazide
- Declined, happy on insulin
- Cascade testing of family members
- HNF1A/HN4A: longer duration before switch = less likely to switch
MODY is being missed

- Diagnosed any diabetes <30 years
  - Antibody negative
  - Urine C-peptide: creatinine >0.2 nmol/mmol
- 2.5% MODY

Chances of finding a MODY mutation in people referred to Exeter molecular genetics lab for genetic testing

<table>
<thead>
<tr>
<th></th>
<th>White pick-up rate</th>
<th>South Asian pick-up rate</th>
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<tbody>
<tr>
<td></td>
<td>29%</td>
<td>12%</td>
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</table>

p<0.001

Shepherd et al 2016, 2017 & 2018

Misra et al Diabetologia 2016
Suspected MODY

- Refer to local MODY clinic / genetic diabetes nurse
  - Stratify

- Centralised testing portal from NHS England coming soon
Biggest barrier to correctly classifying diabetes?
- Us!
- Ask, could this be a different type of diabetes?
- Red flags in the history or presentation?

If you suspect type 1 diabetes
- Do not delay starting insulin and referring to specialist care

If type of diabetes unclear
- Consider referral to a specialist clinic
- NW London (Non-classical diabetes clinic at Imperial)
<table>
<thead>
<tr>
<th>C-peptide &amp; antibodies</th>
<th>Genetic testing for MODY</th>
<th>Ethnic groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Challenging to interpret</td>
<td>• MODY clinics around the country can stratify cases arrange testing</td>
<td>• May present differently with any types of diabetes</td>
</tr>
<tr>
<td>• Have a clear clinical question in mind before requesting</td>
<td>• Cascade testing</td>
<td>• Avoid using ethnicity to influence decision making around type of diabetes, especially in young adults</td>
</tr>
<tr>
<td>• Are not diagnostic</td>
<td>• Imperial: north London</td>
<td></td>
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<tr>
<td>• Best undertaken in a specialist clinic or with specialist input?</td>
<td>• Guys: south London</td>
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**Practice Pointers (2)**