Time to measure Insulin!
Endogenous insulin secretion as a guide to therapeutic decisions

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www.diabetesgenes.org

Is Diabetes really Endocrinology?

	Endocrinology	Diabetes
Diagnosis	+++	-
Treatment	+	+++
Patient centered	?	+++
MDT	?	+++
Science based	+++	+
Trial based	+	+++
Needs clever Drs!	+++	?
Measure hormone	+++	-

Mr 33

33 yr UK Caucasian Factory Worker

Thirsty drinking Coca Cola

Slightly dehydrated

BMI 33 kg/m^2

Glucose 33 mmol/l

Ketones +

Treated with 33U Mixtard bd

1 year latter HbA1c 9.2%

Diagnosis? Treatment?

Is Classification important in diabetes?

NICE

Clear guidelines for treating type 1 diabetes

Clear guidelines for treating type 2 diabetes

No criteria on diagnosis of Type 1 / Type 2
No mention of other subtypes of diabetes

What happens if you have the classification wrong?

Protocol led care
Target led care

Both protocols and the targets are good but not for everyone….

Especially if have wrong protocol!

Classification matters because it impacts on treatment

Mr 33 Uno

33 yr UK Caucasian Factory Worker

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BMI 33 kg/m^2

Glucose 33 mmol/l

Ketones +

Treated with 33U Mixtard bd

1 year latter HbA1c 9.2%

Diagnosis T1D

Treatment: Basal bolus Insulin
?Metformin?Insulin pump
DAFNE

Mr 33 Duo

33 yr UK Caucasian Factory Worker

Thirsty drinking Coca Cola

Slightly dehydrated

BMI 33 kg/m^2

Glucose 33 mmol/l

Ketones +

Treated with 33U Mixtard bd

1 year latter HbA1c 9.2%

Diagnosis T2D

Treatment: Diet. Metformin
? Intermediate insulin
? GLP1 agonists ?Pio
Type 2 education

The Classification of diabetes is Aetiological

WHO & ADA in late 90's based classification on aetiology T1D v T2D replacing IDDM v NIDDM

Type 1 - destructive process of the beta-cell (usually autoimmune) leading to total insulin deficiency

Type 2 – is diabetes where there is no known aetiology

Other aetiological subtypes recognised

Genetic defects of beta-cell function
Genetic defects in insulin action
Disease of the Exocrine pancreas
Endocrinopathies
Drug- or chemical induced
Infective
Uncommon forms of autoimmune diabetes
Other genetic syndromes sometimes a/w diabetes

The Classification of diabetes is not based on defined Clinical Criteria

Broad guidance only

No guidelines on specific clinical criteria

Why are there are no Clinical Criteria for Classifying diabetes

Too easy: not needed

Too difficult: not possible

Not needed: make no difference

In the absence of criteria diagnosis is very variable

UK QUAF data 2008

Type 1: Prevalence 4 – 44% in GP practices
Suggests Type 1 often incorrectly diagnosed

Insulin Treated T2D often called "T1D"

Other subtypes: not recorded

Aren't there simple Clinical Criteria for Diagnosis?

- **Diabetes characteristics**
  age of diagnosis - young T1D
  diagnosis: DKA, T1D....

- **Non-pancreatic manifestations**
  obesity T2D

- **Family History**
  who is affected, their diabetes, other features

- **Yes but**
  T2D < 18yr
  50% DKA T2D

T1D 15% obese

families mixed T1 & T2

RCGP Diagnostic Guidelines

Needs to include all diagnostic categories but be simple

Broad categories and include unknown/ uncertain .

Diagnosis by probability

Like evidence based treatment it will be correct in a majority but not all cases. Should be guide not absolute.

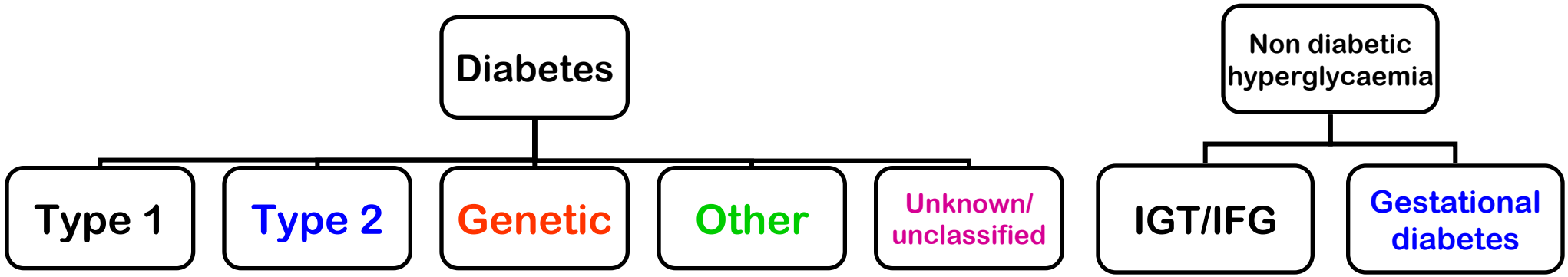
Limited to available data

Autoantibodies, C peptide, not routinely available
Other data not recorded on database – family history
Which data is easily available?
Age diagnosis, treatment and expert opinion
- should these be modified by BMI and ethnic origin?

Use Treatment in Algorithm?

Advantage: reflects clinical decision
Disadvantage: that decision may be wrong

Draft RCGP practical diagnostic guidelines



Diag. < 35 yr
AND
Continual insulin treatment. within 6/12 diagnosis

OR

Diag ≥35 yr
AND
Continual insulin from diag

Diag <35 yr
AND
not on continual insulin before 6/12 from diagnosis

OR

Diag ≥35 yr and not on continual insulin from diag

Diagnosed < 6/12
OR
Specific genetic or clinical diagnosis (MODY. Neonatal diabetes)

Specific Primary diagnosis e.g
pancreatitis
pancreatectomy
haemochromatosis
cystic fibrosis
Cushing's
Acromegaly

To early in clinical course to make diagnosis

OR

Uncertainty if specific diagnosis

Biochemical diagnosis
IGT
IFG

Not known diabetes prior to pregnancy

AND

Diabetes/IGT during pregnancy

AND

Not diabetes after pregnancy

What investigations are there?

Auto-antibodies: especially at diagnosis

C peptide: latter > honeymoon –

Other tests: lipids,
specific aetiological genetic tests
specific tests secondary diabetes

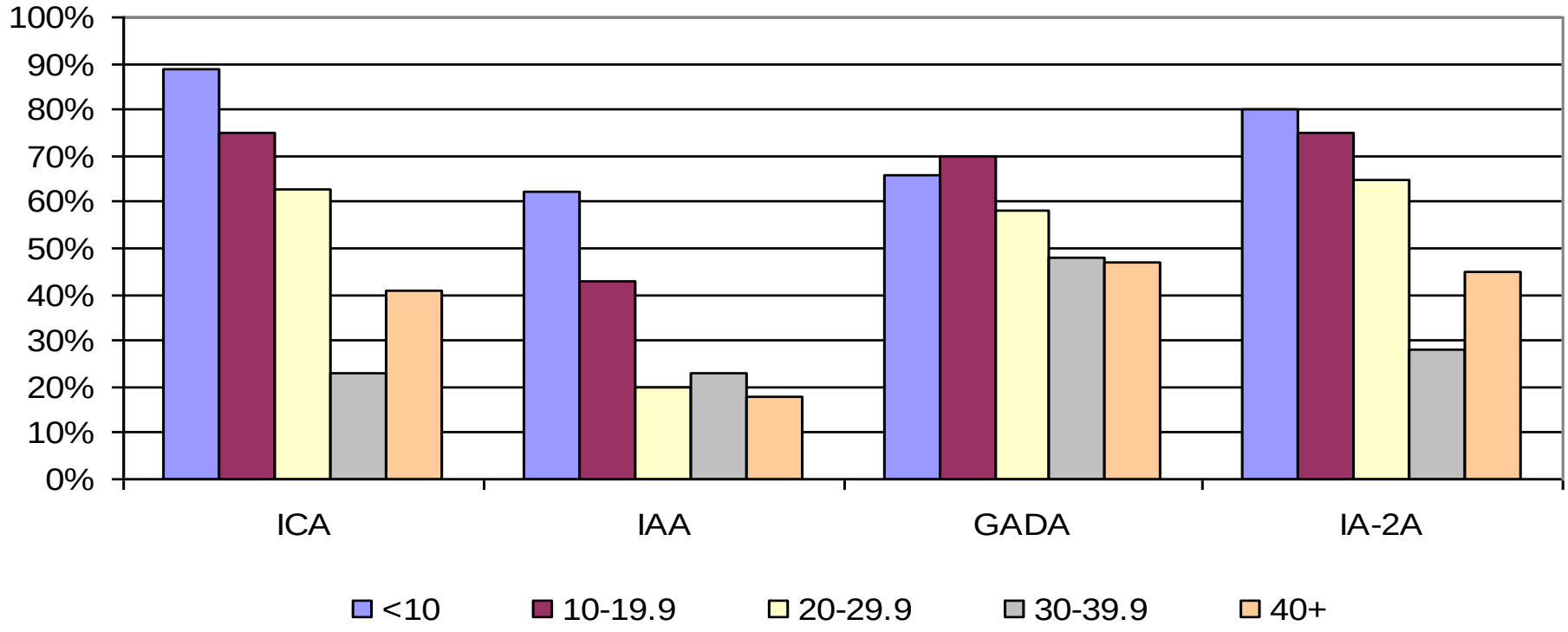
Beta-cell auto-antibodies

Which ones?

When?

What mean?

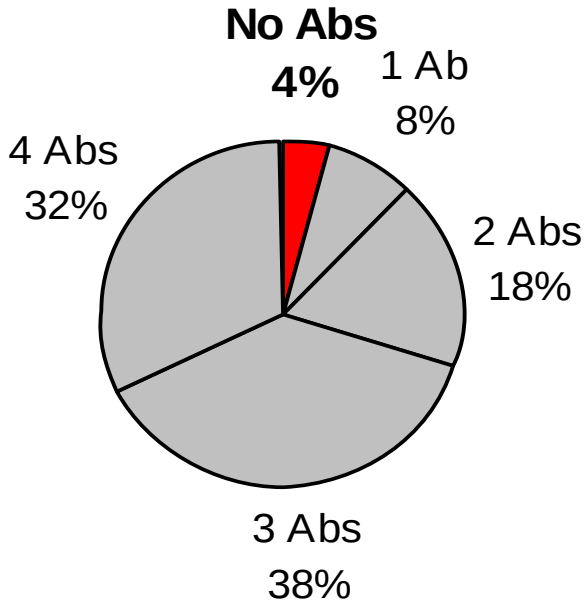
Autoantibodies at diagnosis
Less common in adults



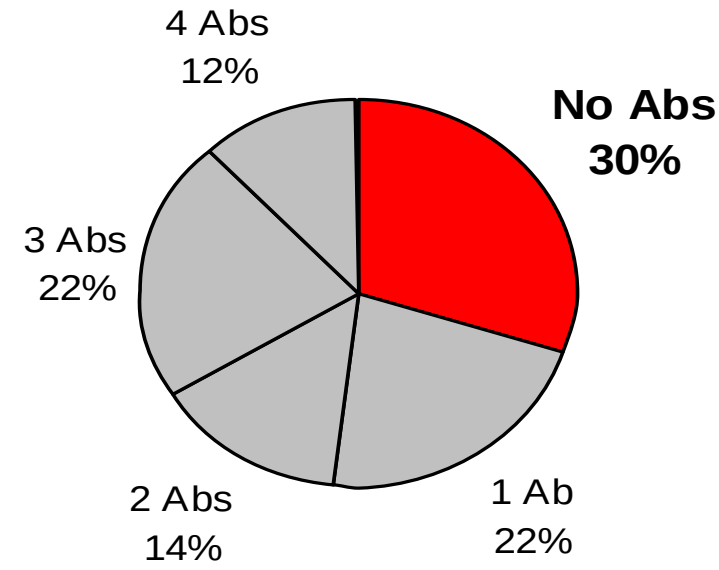
Sabbah et al Diabetes Care 2000;23:1326-1332

Majority with T1 DM are Ab + at diagnosis most likely to detect if multiple antibodies tested

Children and adolescents (n=252)



Adults (n=100)



Sabbah et al Diabetes Care 2000;23:1326-1332

Beta-cell auto-antibodies

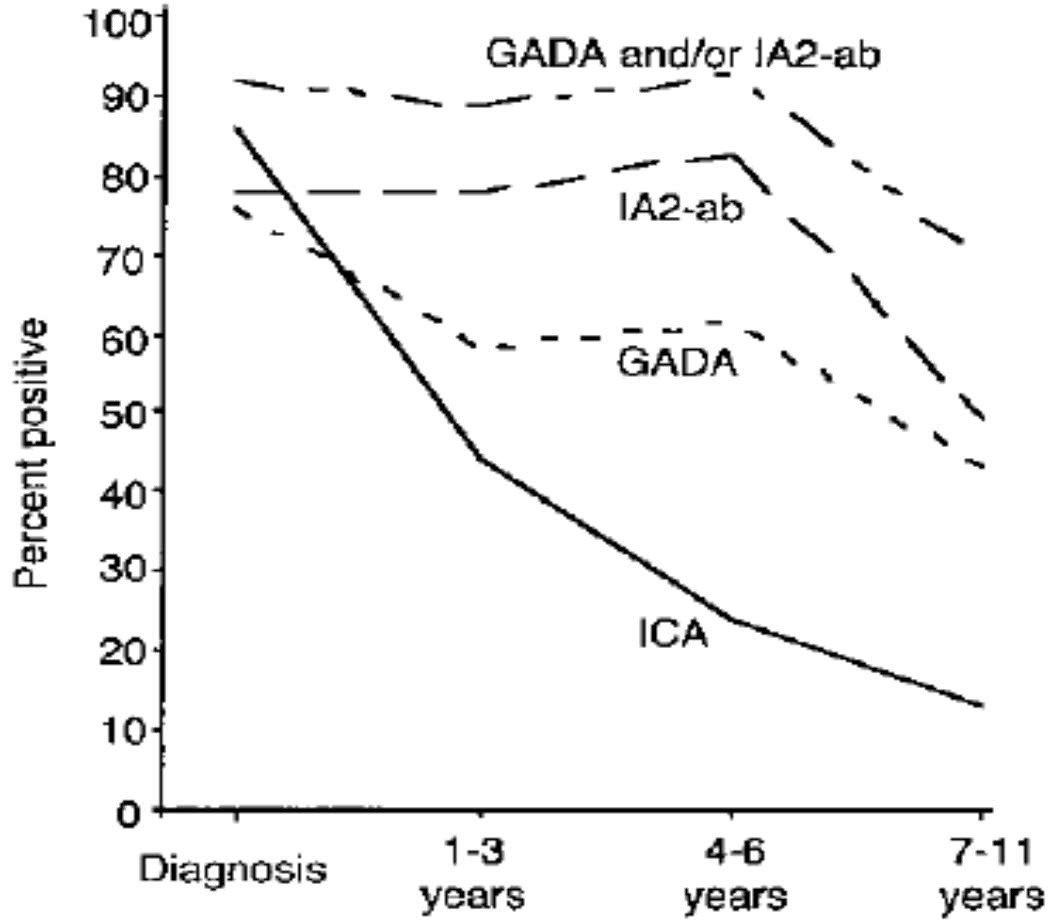
Which ones?

- ICA – rat bad, human better but not available
- GAD - titre matters
- IA2 , Insulin (pre- treat,) – difficult outside research
  IA2 Available in Exeter

When?

What mean?

ICA falls after diagnosis but GADA/IA2 persist



Borg et al Acta Paediatr 2000;89:46-51

Beta-cell auto-antibodies

Which ones?

- ICA – rat bad, human better but not available
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- IA2 , Insulin (pre- treat,) – difficult outside research
  IA2 Available in Exeter

When?

- At diagnosis best
- 5% AA -ve develop on retesting at 6/12
- GAD and IA2 most persistent

What mean?

What do Beta-cell auto-antibodies mean?

False positive rate – low if correct cutoff (1-2.5%)
False negative rate – 10-20% AA -ve (all tested at diagnosis)

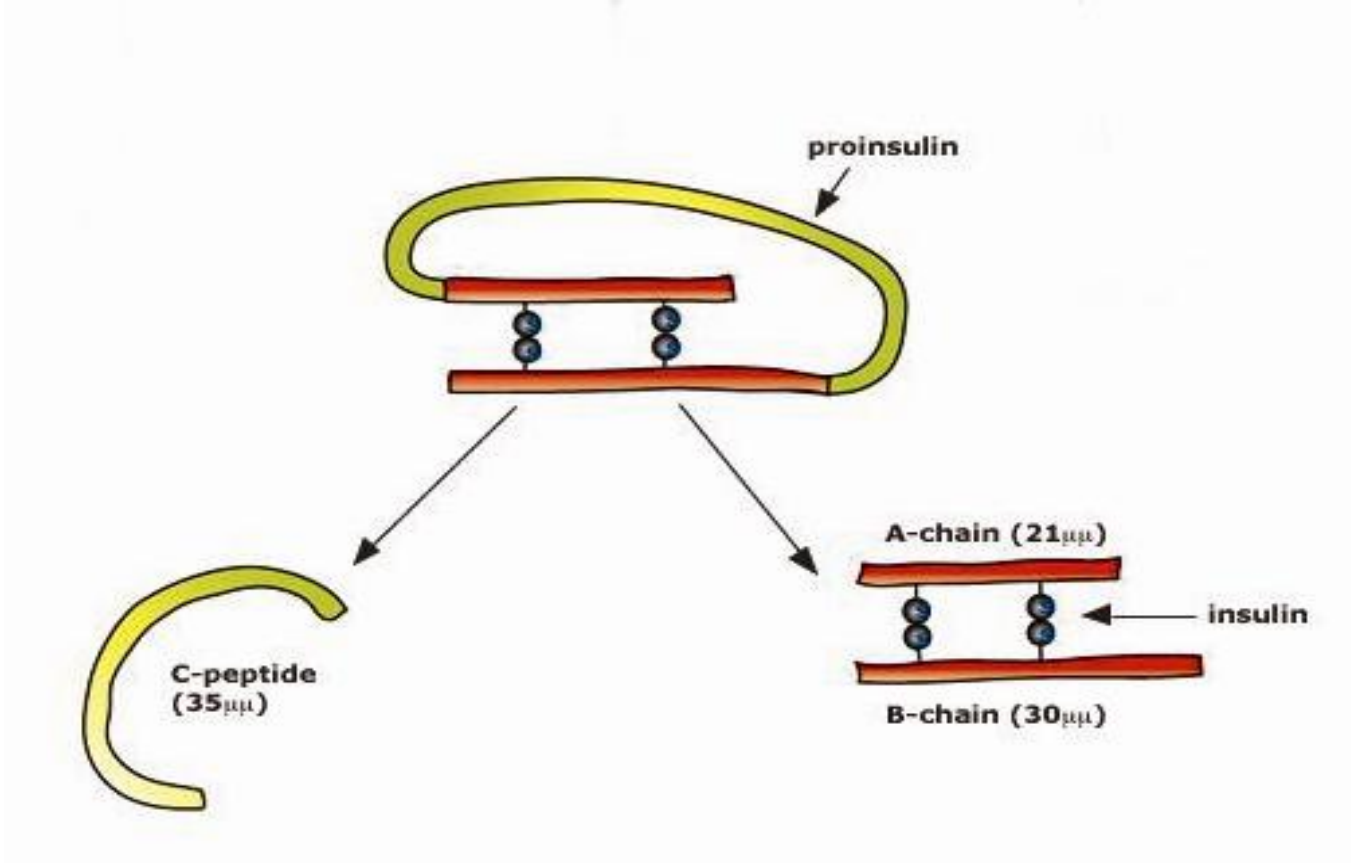
Can say aetiology if positive

Can not say aetiology if negative

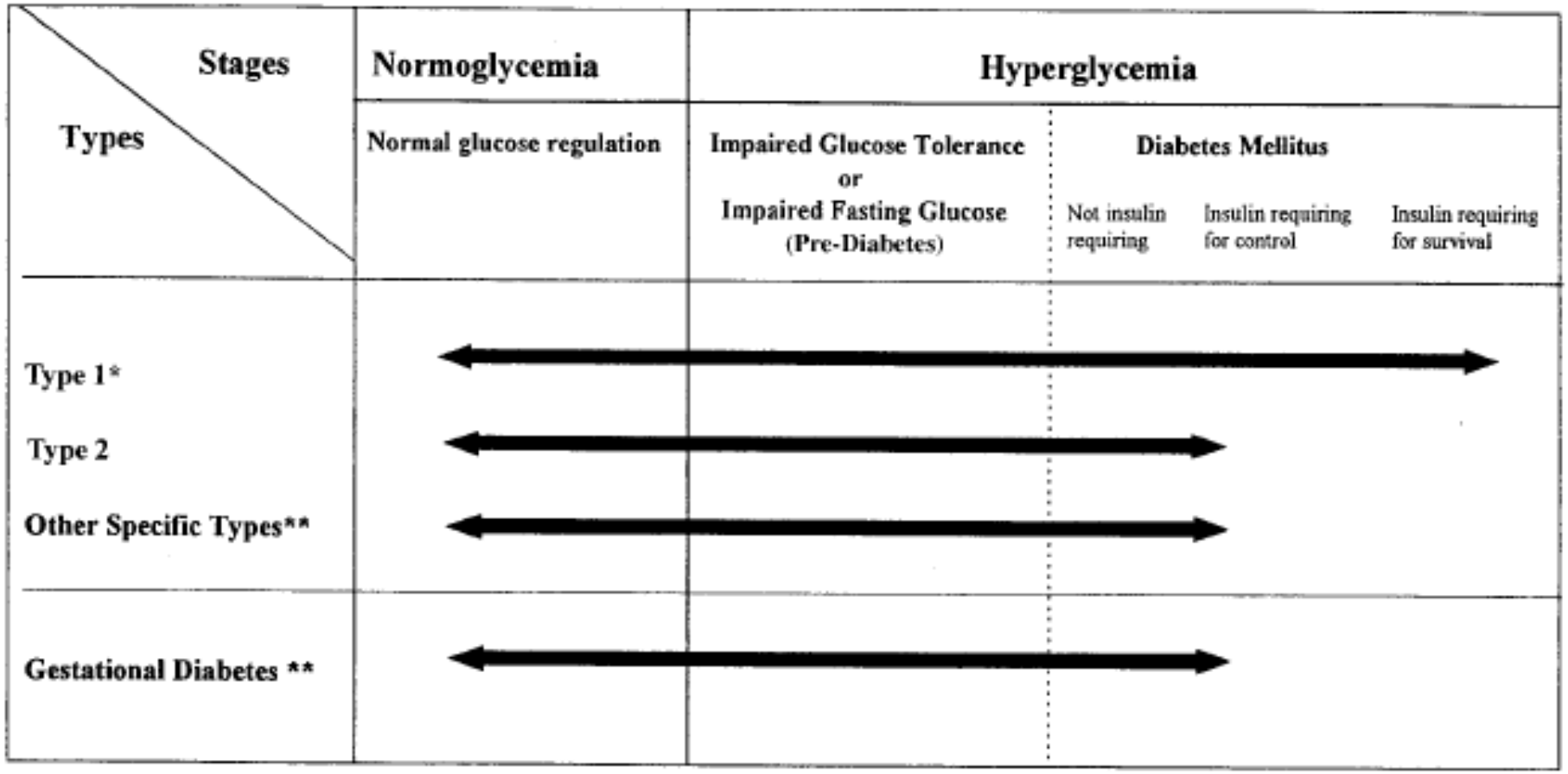
Can not use to guide treatment – does not say when insulin dependency will occur

Is it time for the Insulin Endocrinologists to measure their hormone?

C-peptide cleaved from proinsulin during insulin production



Insulin Dependent – absent C peptide = Type 1



ADA Guidelines Diabetes Care, 2011

How can we measure endogenous beta-cell function in people on insulin?

C peptide the only way

Measurement is critical for classification and more importantly for best treatment

Measurement of C peptide in insulin treated patients

Conventional tests measure plasma C peptide

Advice to separate immediately and freeze as unstable.
Makes inconvenient clinically and not possible in general practice

Most tests stimulate endogenous insulin secretion

Gold standard – max concentration post mixed meal (BOOST) or post glucagon after missing short acting insulin dose

C-peptide positive in T1D

Definition

Stimulated	>0.20nmol/l	200pmol/l
Fasting	>0.08nmol/l	80pmol/l

Derivation

DCCT 1991: 1,441 subjects, 1-15y duration

Stimulated C-peptide >0.2 nmol/l 'responders'

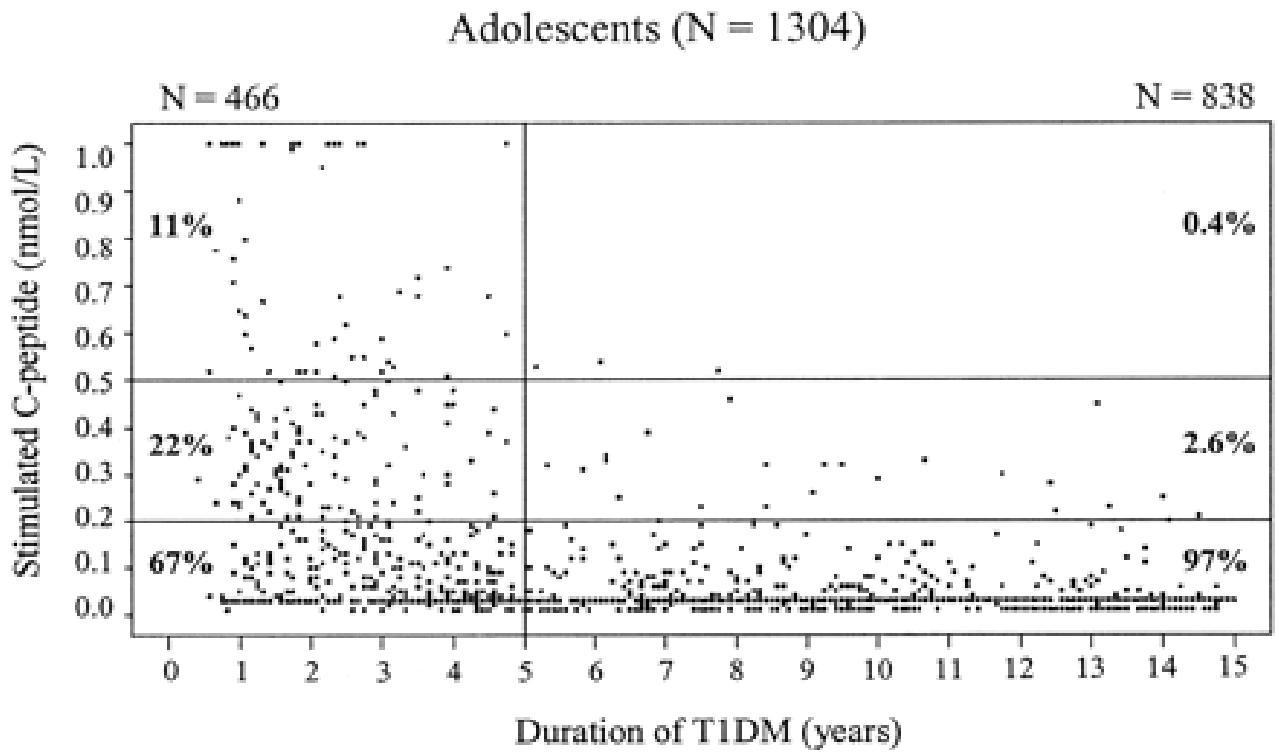
- lower fasting glucose (9.8 v 12.3 mmol/l)
- lower HbA1c (8.4% v 9.2%)
- Less retinopathy and less microalbuminuria
- Less severe hypos

Natural decline in C-peptide in T1D

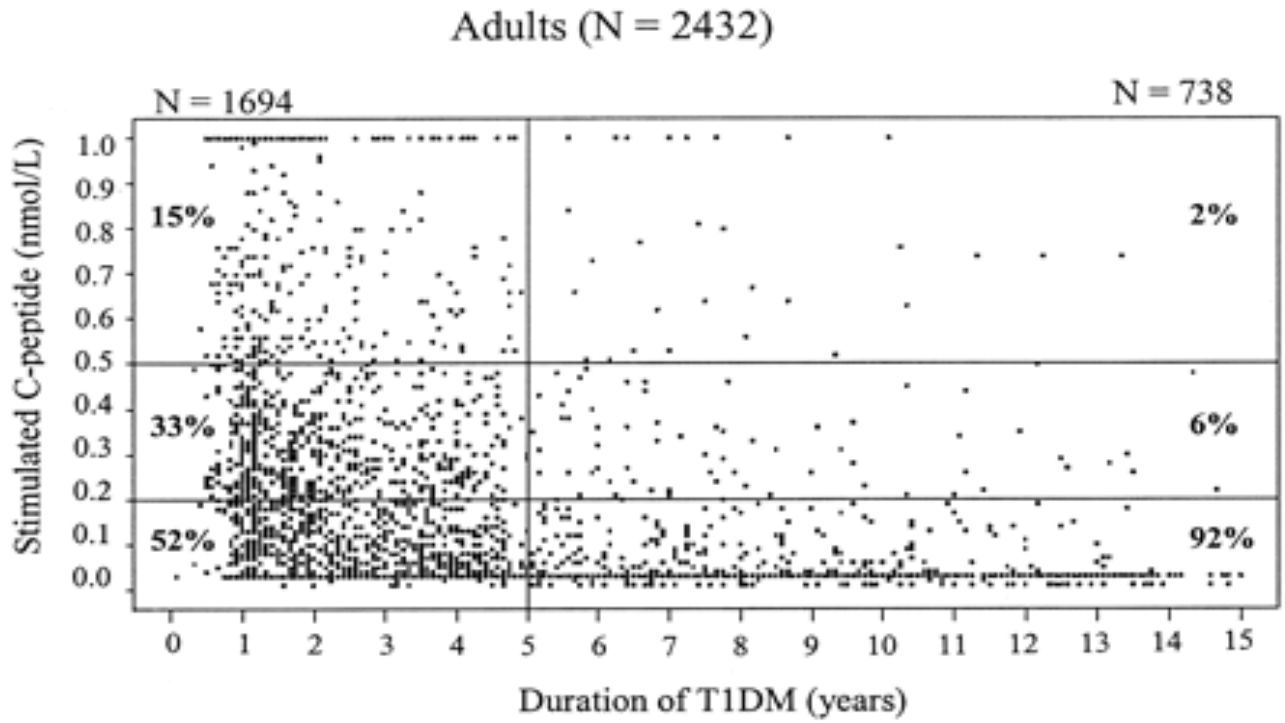
Depends on:

- **Correct diagnosis**
- **Time from diagnosis**
- **Age of diagnosis**
- **DKA at diagnosis**

T1D diagnosed <18y, 97% have stimulated C-peptide response <0.2nmol/l 5yr post diagnosis



T1D diagnosed >18y, 92% have stimulated C-peptide response <0.2nmol/l 5y post diagnosis



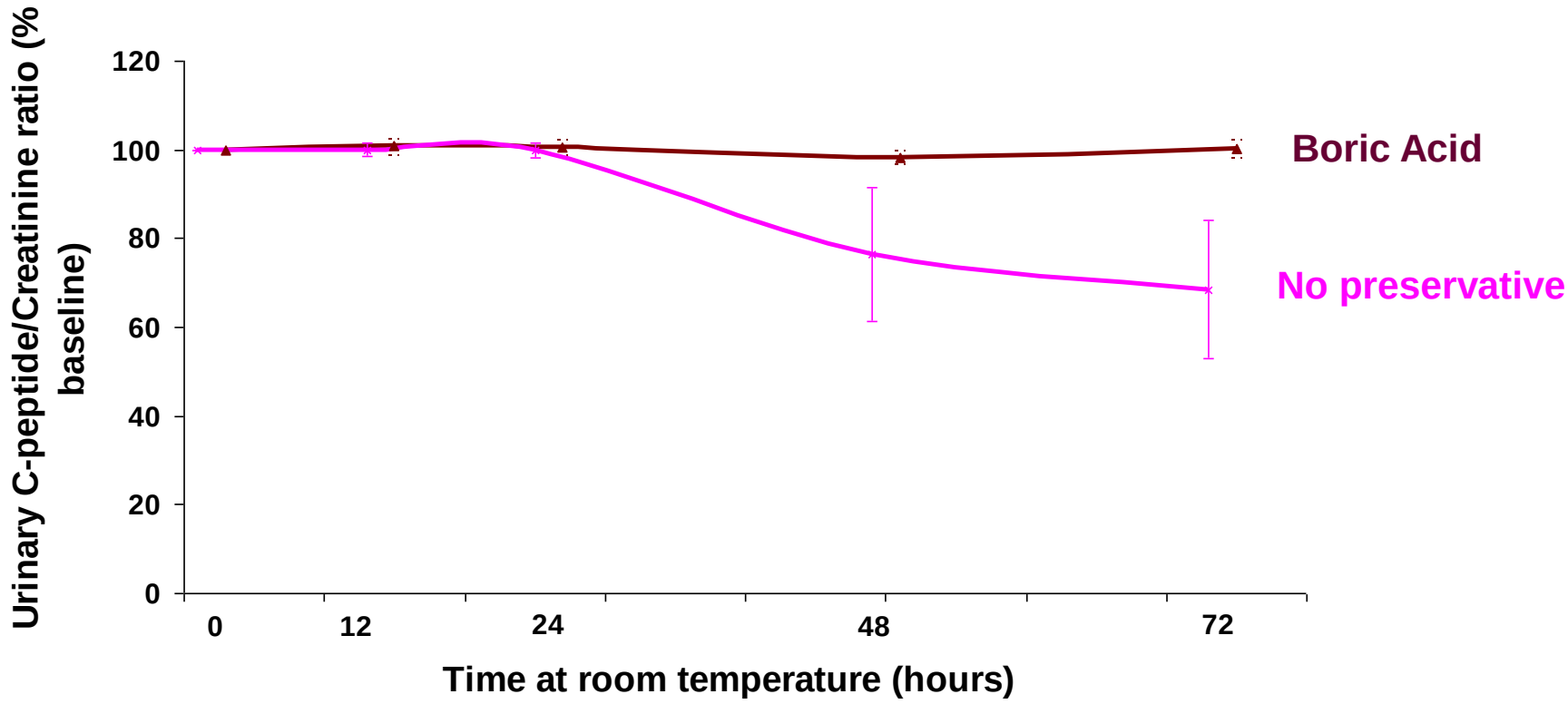
Making C-peptide measurement easier

Urinary C peptide Creatinine Ratio

- 10% C peptide excreted in Urine
- Urine measures practical and easy
- Stable at room temp for 72 hours
- Using creatinine ratio accounts for dilution
- Can be posted

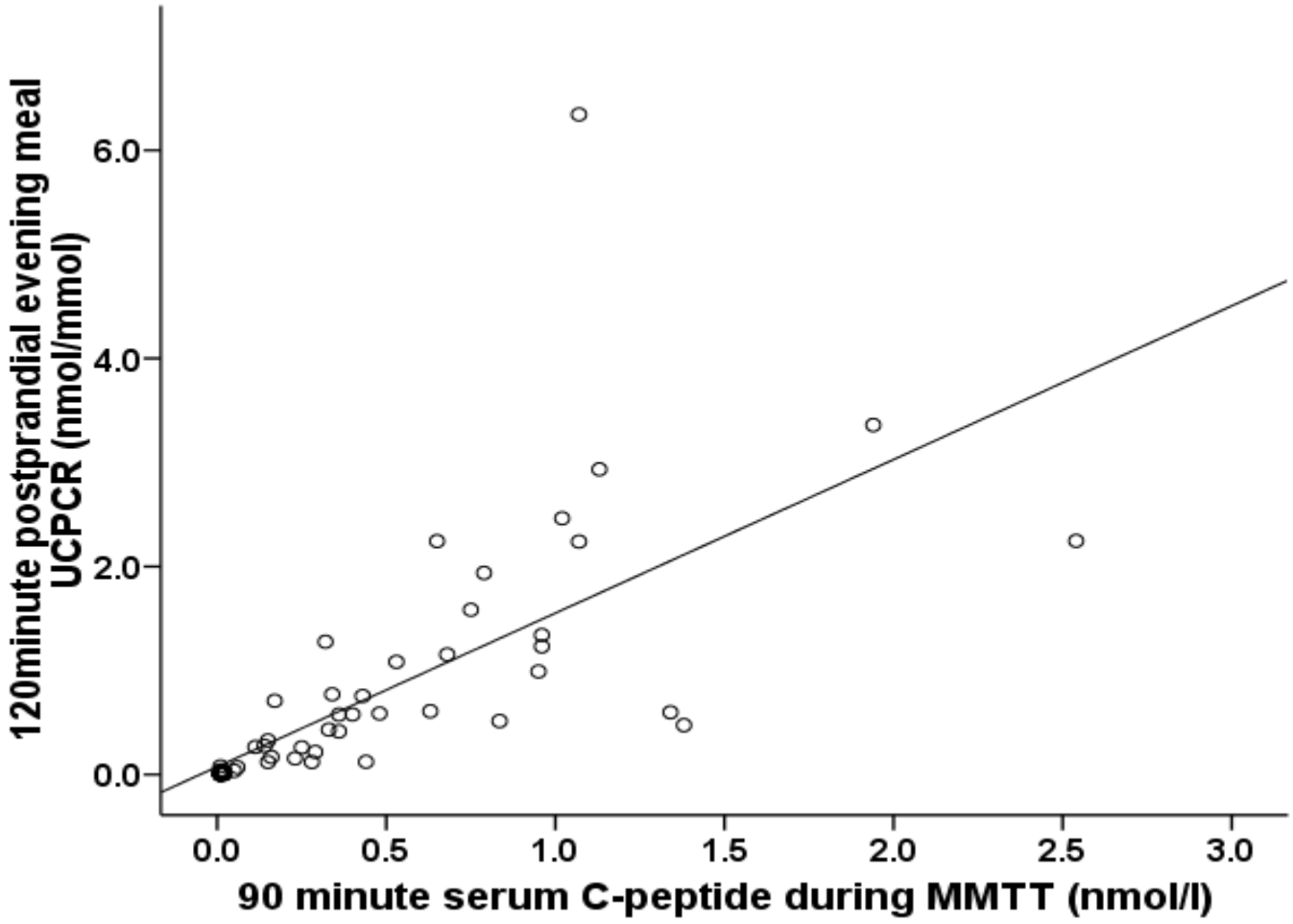
Urine C-peptide creatinine ratio (UCPCR) may be an alternative

- Stable at room temp in boric acid for 72 hours
- Stable no preservative 24 hours



McDonald Clin Chem 2009

A home postprandial UCPCR is a non-invasive alternative in routine practice

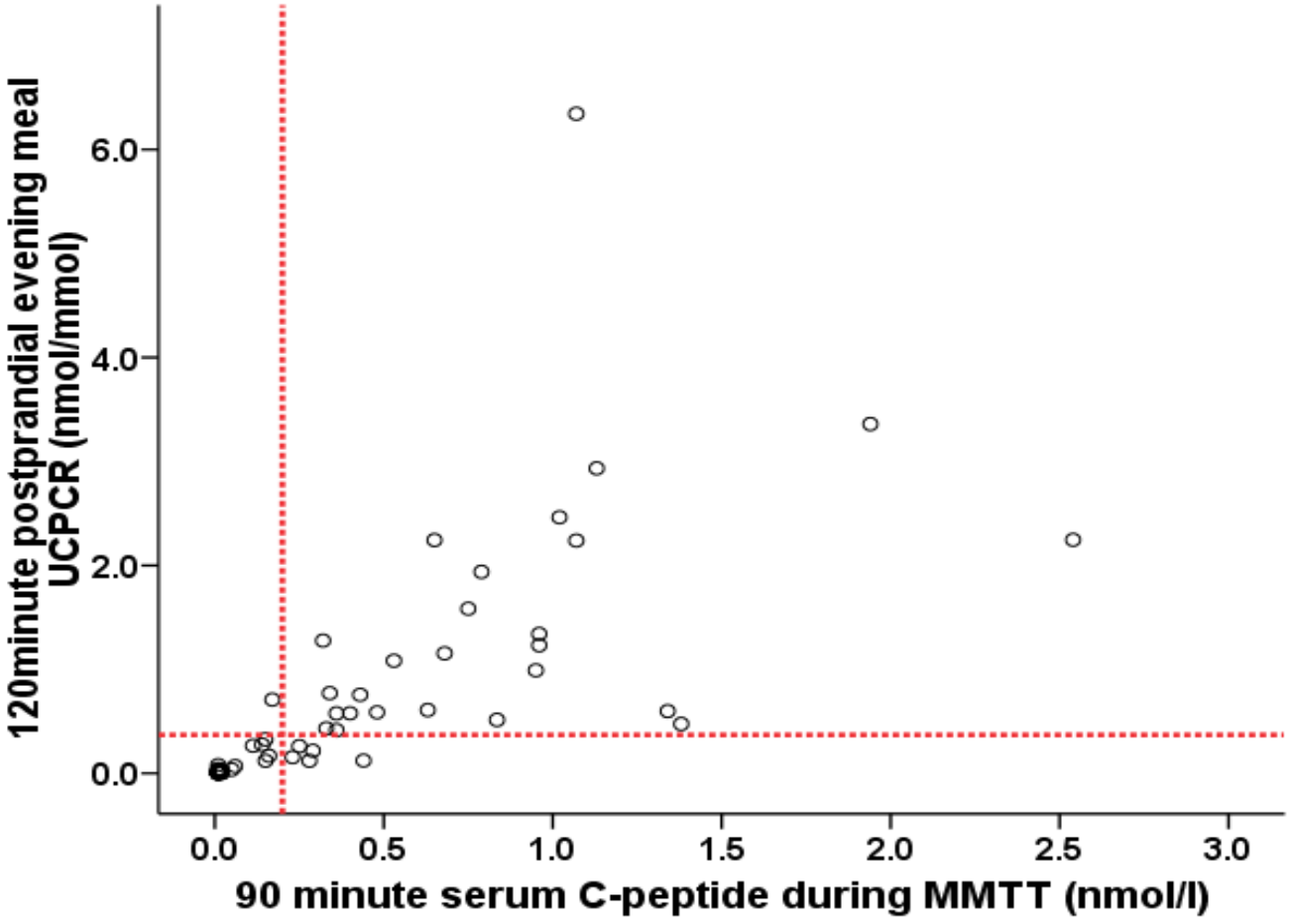


r= 0.91
p<0.0001

Besser et al Diabetes Care 2011

Can define Sensitive and Specific UCPCR equivalent of serum C pep 0.2 nmol/l

0.2



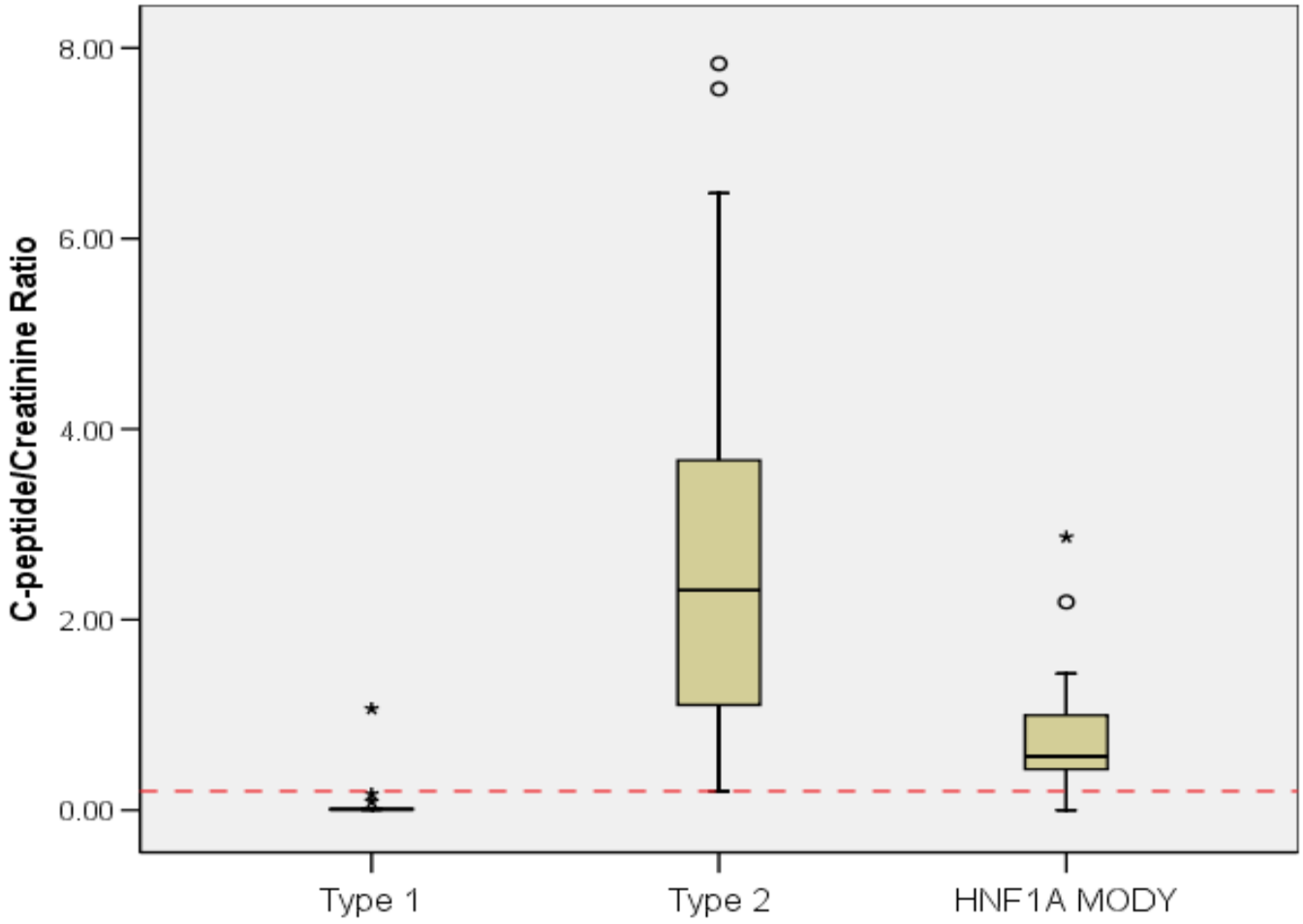
ROC curve
AUC 0.97

84% sensitive
97% specific

0.4

Besser et al Diabetes Care 2011

UCP/Cr ratio allows differentiation of Type 1 from other subgroups >5yrs post diagnosis



UCP/Cr < 0.2
Sensitivity: 98%
Specificity: 96%

Besser et al, Diabetes Care 2011

Urinary C peptide Creatinine Ratio

NHS test through Royal Devon and Exeter Biochemistry lab

£10 / test

Find using Assayfinder

www. diabetesgenes.org

Can be posted

Does measuring C peptide make any Difference to Treatment?

Miss D

Age diagnosis	50 yr
Present Age	69yr
BMI	26
Initial Treatment	OHA for 2 years then insulin
Present Treatment	Metformin 1g bd Insulatard 22/-/16/-
Clinical Problem	Variability in glucose – problem with hypos HbA1c 8.9%

Do Type 2 patients ever become C peptide negative?

174 insulin-treated subjects T2D on clinical criteria

- diagnosed ≥45 years (median 58yrs IQR 50-65)

- started insulin >12 m (median 72 m, IQR 36-123) post-diagnosis

Tested with UCPCR and then MMTT

5 (3%) C Peptide negative

2/5 Antibody (GAD positive)

Major problems: hypos and inappropriate treatment

Oakes, Hattersley et al unpublished

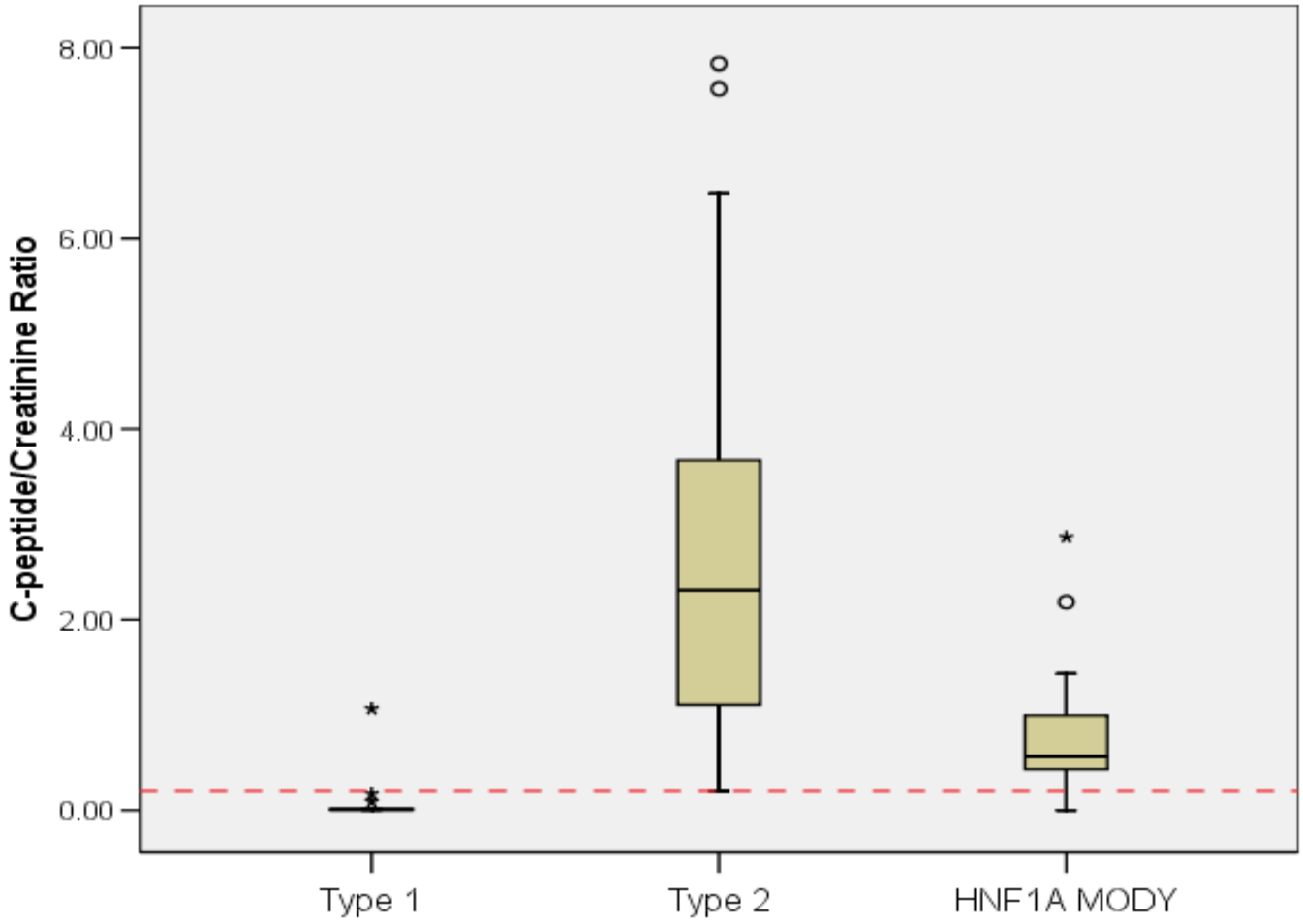
Miss D2

Age diagnosis	42
Present Age	46
BMI	34
Initial Glucose and Treatment	Glucose 24 ketones + Insulin
Present Treatment	Novomix 30 31/ - /20/-
Clinical Problem	Weight gain HbA1c 8.9%

Mrs M

Age diagnosis	24
Present Age	40
BMI	26
Initial Treatment	Insulin
Present Treatment	Novorapid 4/2/6/- Insulatard -/-/-/10
Clinical Problem	None HbA1c 6.8%

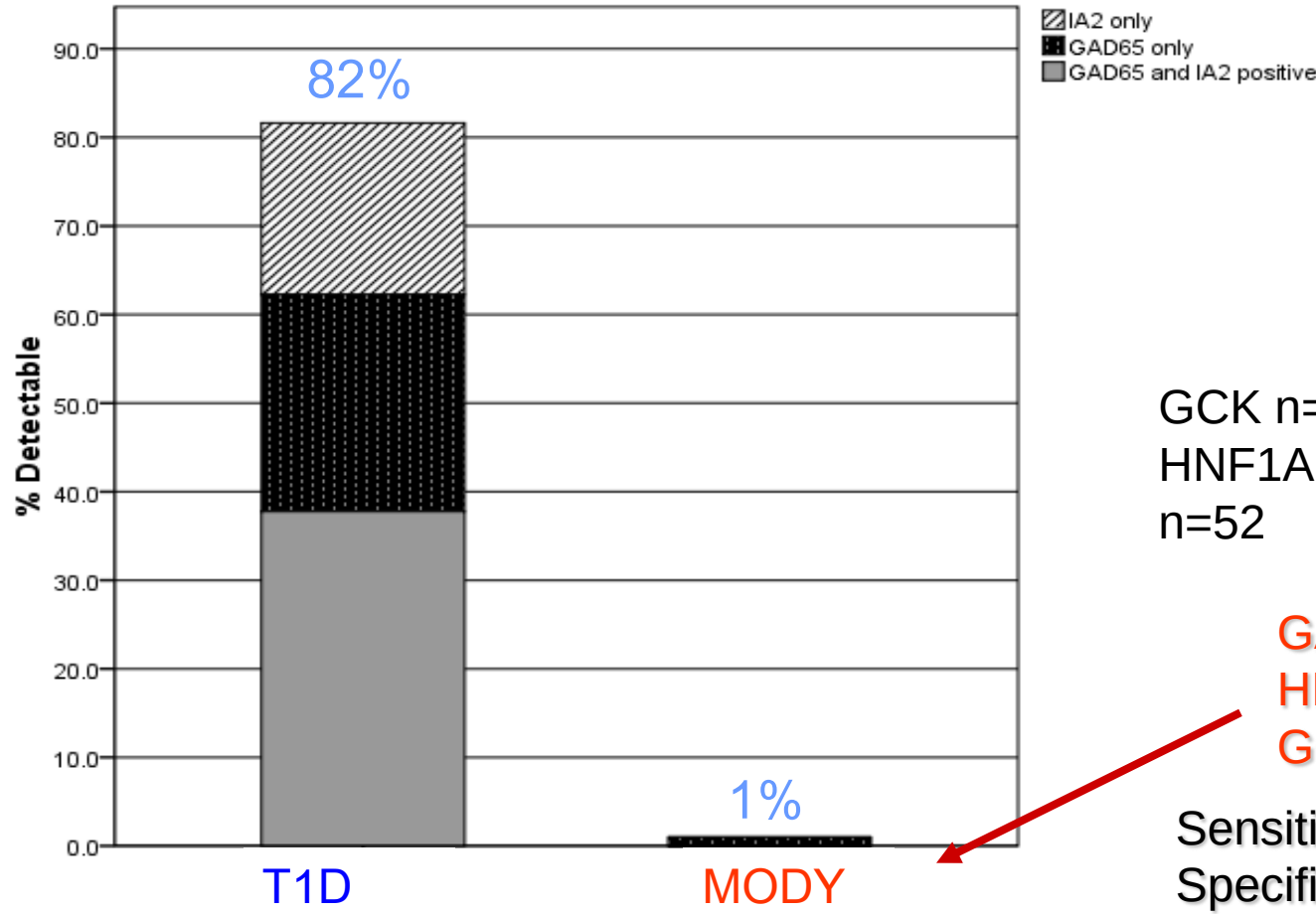
UCP/Cr ratio allows differentiation of Type 1 from other subgroups >5yrs post diagnosis



UCP/Cr < 0.2
Sensitivity: 98%
Specificity: 96%

Besser et al, Diabetes Care 2011

GAD65 and IA2 antibody prevalence in recently diag. T1D (n=99) & MODY (n=508)



GCK n=227
HNF1A n=229 HNF4A n=52

GAD +ve
HNF1A n=3
GCK n=2

Sensitivity 98%
Specificity 82%

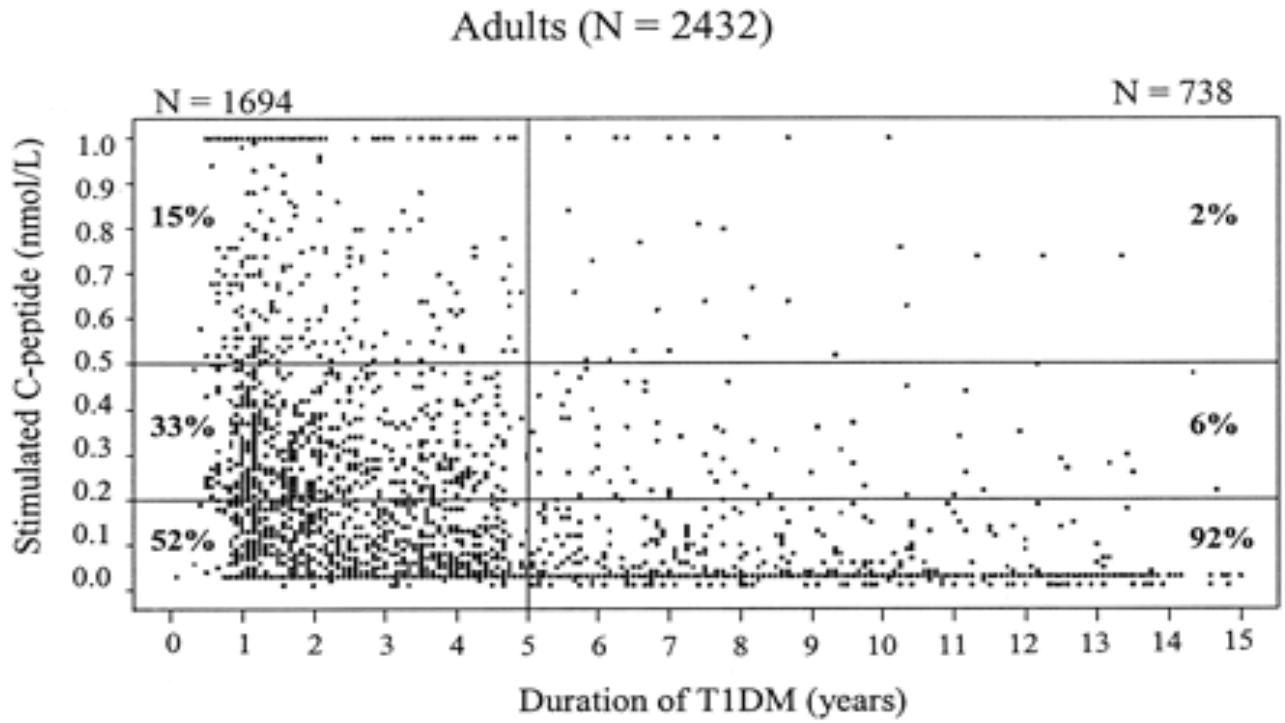
IA2 and/or GAD antibodies (99th cent > 50) make MODY very unlikely

McDonald et al, Diabetic Medicine 2011 in press

Mr H

Age diagnosis	19
Present Age	22
BMI	25
Initial Glucose and Treatment	Glucose 21 Basal bolus insulin
Present Treatment	Novorapid 4/4/4/- Glargine -/-/-/20
Clinical Problem	HbA1c 6.9% No hypos Occasional monitoring

T1D diagnosed >18y, 92% have stimulated C-peptide response <0.2nmol/l 5y post diagnosis



Mr G

Age diagnosis	52
Present Age	62
BMI	36
Initial Treatment	Diet
Present Treatment	Metformin 1g bd Gliclazide 160g bd Insulatard 20u bd
Clinical Problem	HbA1c 9.5% Poor control Next Step?

Can Endogenous Insulin Secretion Measurement predict treatment response to 3rd line agents in T2D

Prospective study of all 3rd line agents in SW (Angus Jones, Andrew Hattersley)

Prospective study of Liragulatide response in some ABCD Centres (Ken Thong, Bob Ryder)

Planned National Study of Super responders to all third line treatment (Jones, Hattersley)

When it helps to measure C-peptide?

1. To detect/confirm severe insulin resistance especially when non obese (typically fasting)
2. To assess if patient on insulin is making their own insulin

   - Assessment of T1D honeymoon
   - Diagnosis – Long duration type 1 – C-peptide low differentiate Type 2/MODY
   - Guidance on other therapy if high C-peptide insulin sensitisers have greater impact
3. To assess if type 2 with variable glucose values who has gone on insulin is still producing own insulin
4. ?Treatment response to third line agents in T2D

Interpretation of measurement of UCPCR is needed

Need to interpret results carefully
Glycaemia alters interpretation

UCPCR overlap between T1D and non diabetic controls

Needs Experts

If we measure our hormone Diabetes is Endocrinology?

	Endocrinology	Diabetes
Diagnosis	+++	+++
Treatment	+	+++
Patient centered	?	+++
MDT	?	+++
Science based	+++	++
Trial based	+	+++
Needs clever Drs!	+++	+++
Measure hormone	+++	++

Urinary C peptide Creatinine Ratio

NHS test through Royal Devon and Exeter Biochemistry lab

£10 / test

Find using Assayfinder

www. diabetesgenes.org

Can be posted