

# Time for diabetologists to measure their hormone: utility and interpretation of C peptide in Type 1 diabetes

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# Is Diabetes really Endocrinology?

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

## What does a consultant physician offer in diabetes above a specialist nurse or GP?

Following NICE guidance x

Unique treatment or investigation x

Treatment expertise ?

Diagnostic expertise ✓?

Interpretation of investigations ✓?

How good are your diabetes diagnostic/ investigation skills?

## 2 cases of ? Cushing's Endocrine v Diabetes



**Presentation- Hypertension**  
**Investigations- Endocrinology**  
24hr Urinary cortisol x3  
Dex suppression test  
9am cortisol/ ACTH  
Pituitary MRI  
Adrenal CT  
IPPS  
MRI Chest, Abdo, Pelvis  
Ostreoscan

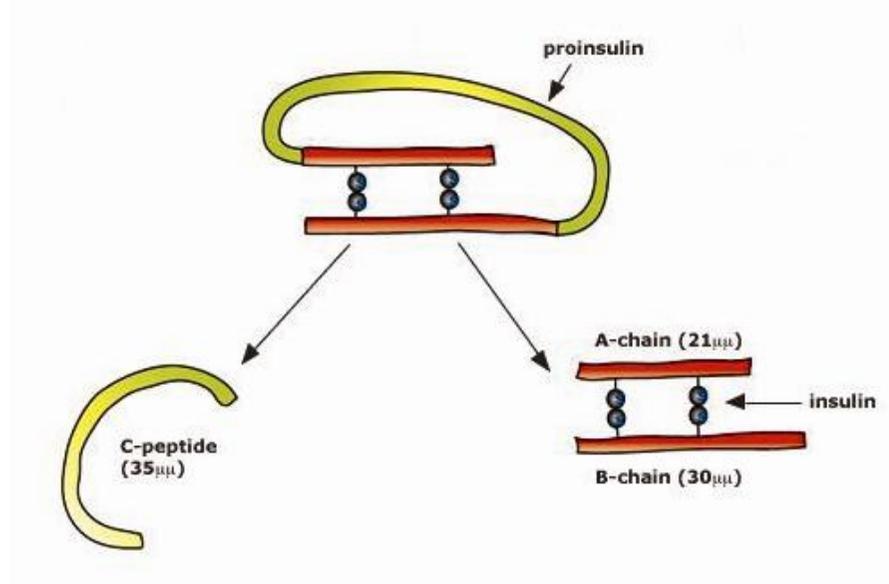


**Presentation- Diabetes**  
**Investigations- Diabetes**  
24hr Urinary cortisol x 1  
ICA/GAD negative



**Investigations- Diabetes**  
Fasting insulin /C peptide  
Fasting TG/HDL  
Adiponectin/Leptin  
Genetic tests:  
LaminAC, PPARG

C peptide can be used to measure endogenous insulin secretion in patients on insulin.



C-peptide cleaved from proinsulin during insulin production  
Equi-molar with insulin

C-peptide measures endogenous insulin secretion

# Why do Insulin Endocrinologists not measure their hormone?

Difficult to measure

Unstable

Need to stop insulin and perform a MMTT

Don't need to measure

Can use clinical features and antibodies

Won't alter treatment

# Making C-peptide measurement easier



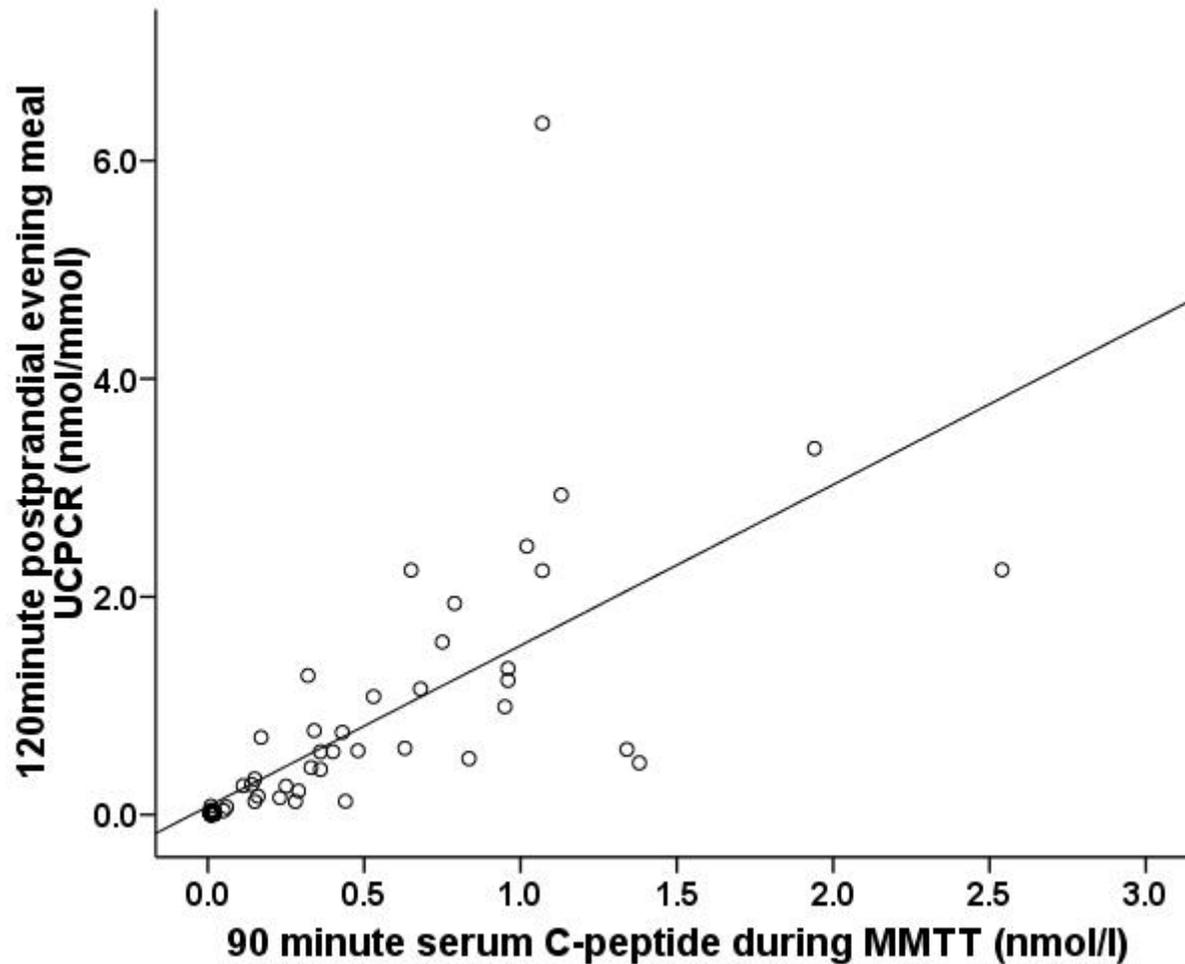
Tim McDonald

## Urinary C peptide Creatinine Ratio

- 10% C peptide excreted in Urine
- Urine measures practical and easy
- Stable at room temp for 72 hours in boric acid
- Using creatinine ratio accounts for dilution. Spot sample represents insulin secretion since last micturition
- Can be posted NHS cost £11 through biochemistry at Royal Devon and Exeter hospital, Exeter



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



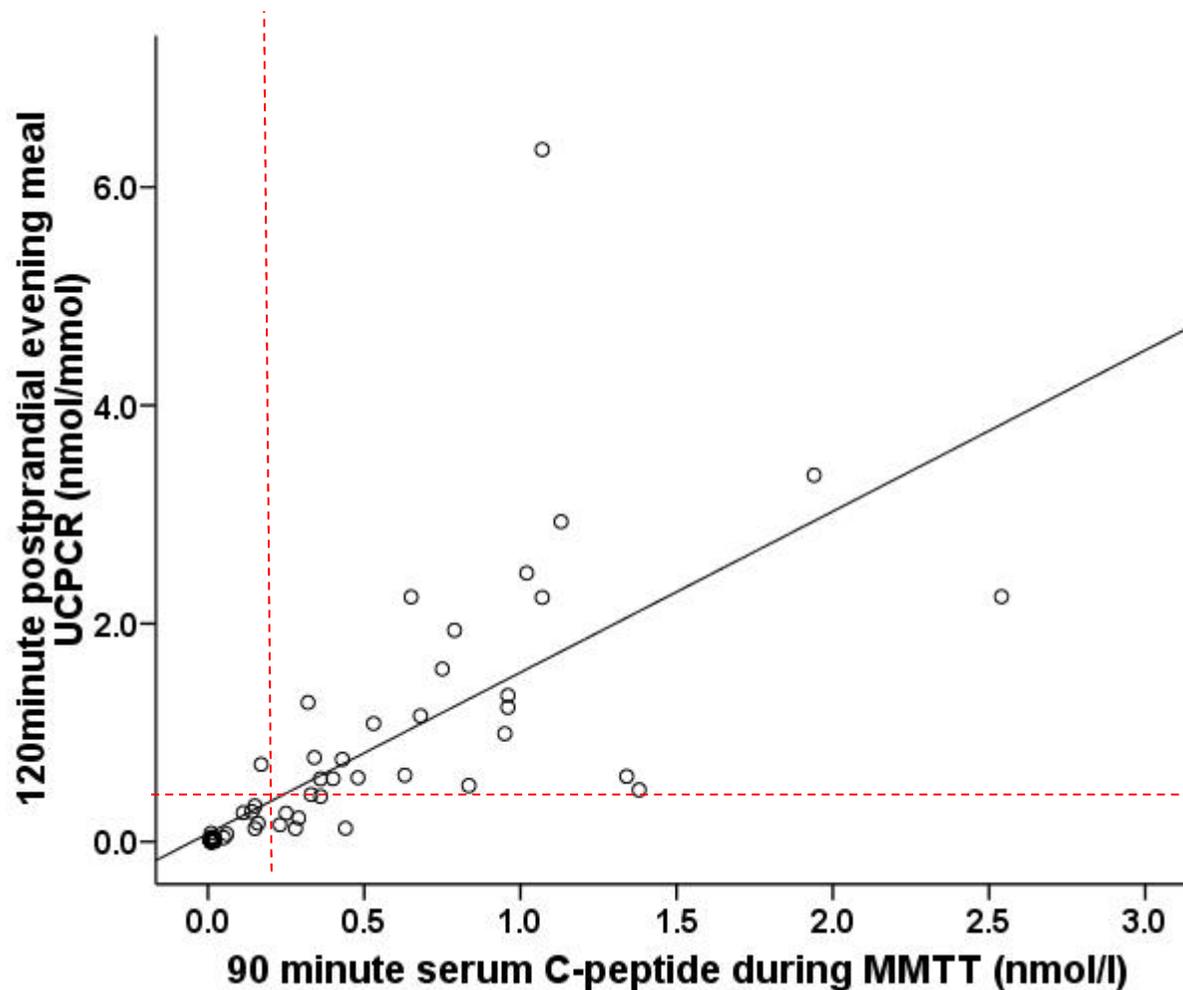
$r= 0.91$   
 $p<0.0001$



Rachel Besser

UCPCR < 0.2nmol/mol is sensitive & specific  
equivalent of serum C pep <0.2 nmol/l

0.2 nmol/l



ROC curve  
AUC 0.97

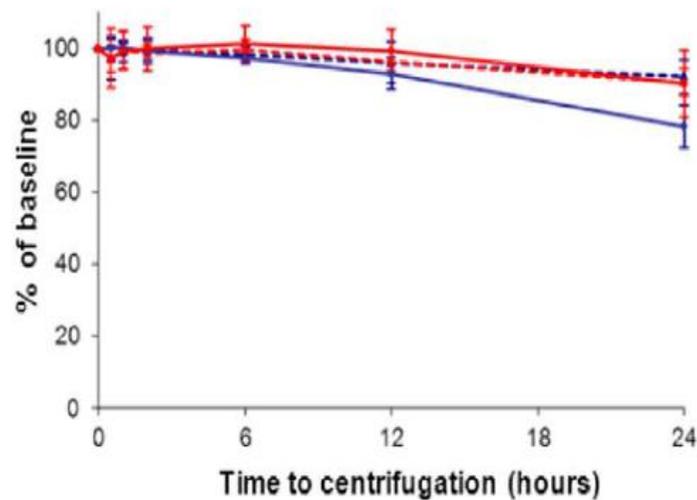
84% sensitive  
97% specific

0.2 nmol/mmol

# We can now measure C peptide easily

Blood C peptide *is* stable at room temperature

**B** C-peptide: Room Temperature



EDTA plasma stable 24 hours

Serum Gel stable 6-12 hours



Tim McDonald

Plasma C peptide -can be measured easily in all hospitals

Chemiluminescence assay

Sensitive and robust

Measurable on standard biochemistry platforms

# We can now measure C peptide easily

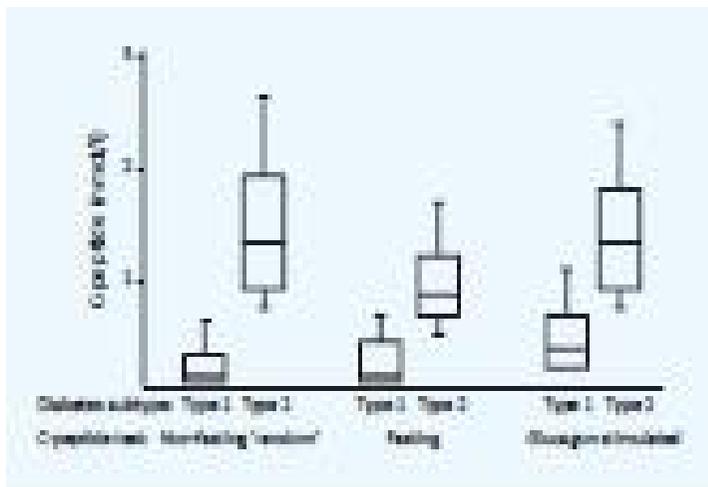
Do not need to stimulate endogenous insulin secretion as fasting well correlated with stimulated

Besser et al Diab Med 2012

Stopping fast acting insulin not needed

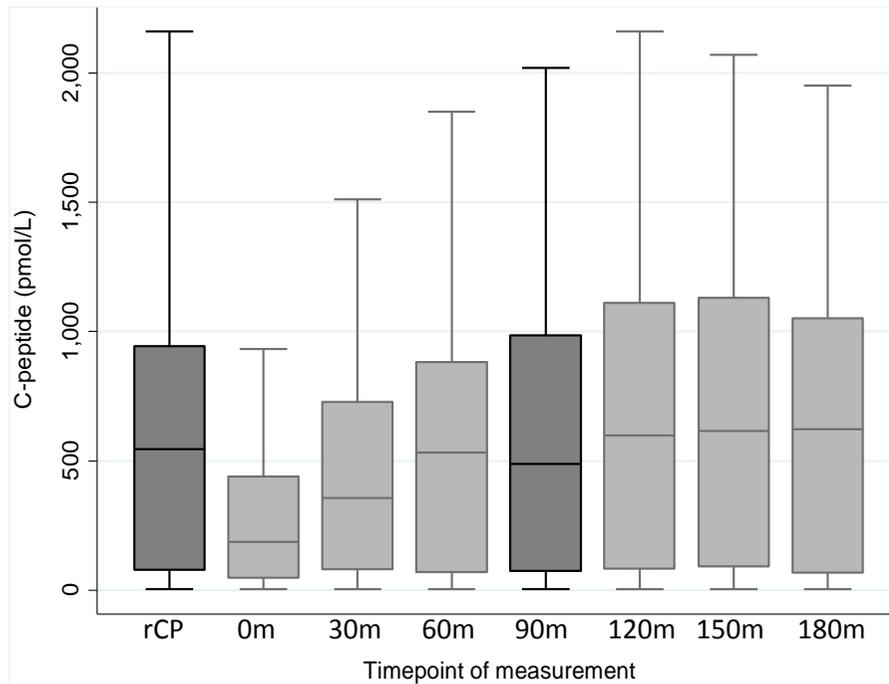
Besser et al Diab Med 2012

Non fasting random with glucose works well



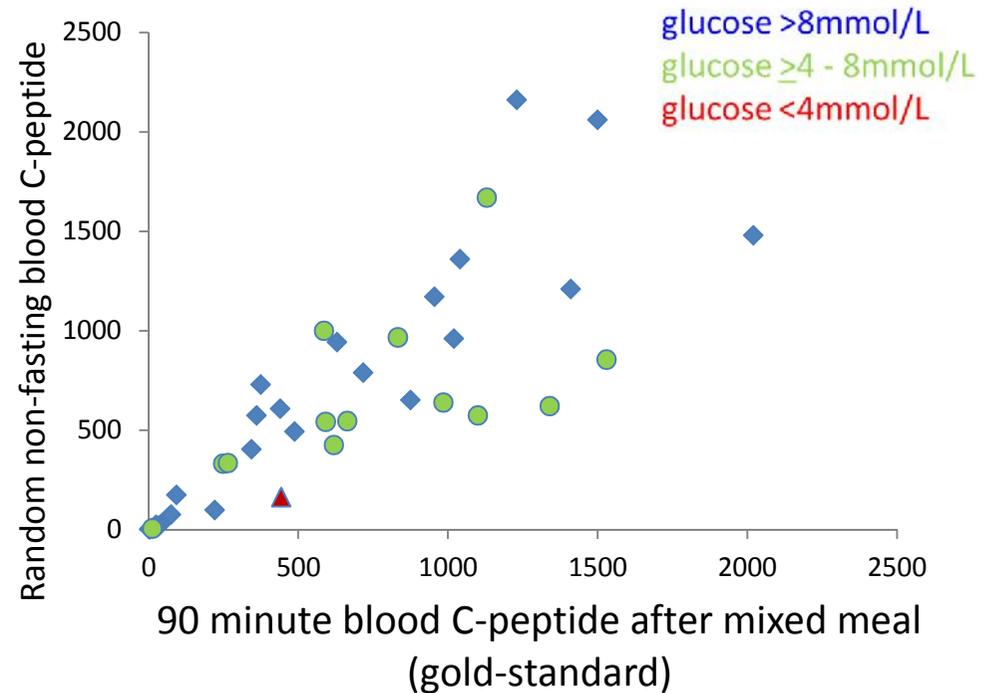
Berger et al Scan J Clin Invest 2000

# Non-fasting random blood C-peptide is both sensitive & specific



Random C peptide (rCP) and  
values taken during MMTT

Take >60min post meal  
Avoid hypoglycaemia (<4mmol/l)



$r=0.913$ ,  $p<0.0001$

Highly predictive of insulin deficiency  
(<200pmol/l)

# Using C-peptide to diagnose subtypes of diabetes

# Obese young diabetes



Mr 33

33 yr UK Caucasian Factory Worker

Thirsty drinking Coca Cola

Slightly dehydrated

BMI 33 kg/m<sup>2</sup>

Glucose 33 mmol/l

Ketones +

5 years later HbA1c 8.2%

Diagnosis? Treatment?

# Mr 33 Uno



33 yr UK Caucasian Factory Worker

Thirsty drinking Coca Cola

Slightly dehydrated

BMI 33 kg/m<sup>2</sup>

Glucose 33 mmol/l

Ketones +

Treated with 33U Mixtard bd

4 years later HbA1c 8.2%

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<sup>2</sup>

Glucose 33 mmol/l

Ketones +

Treated with 33U Mixtard bd

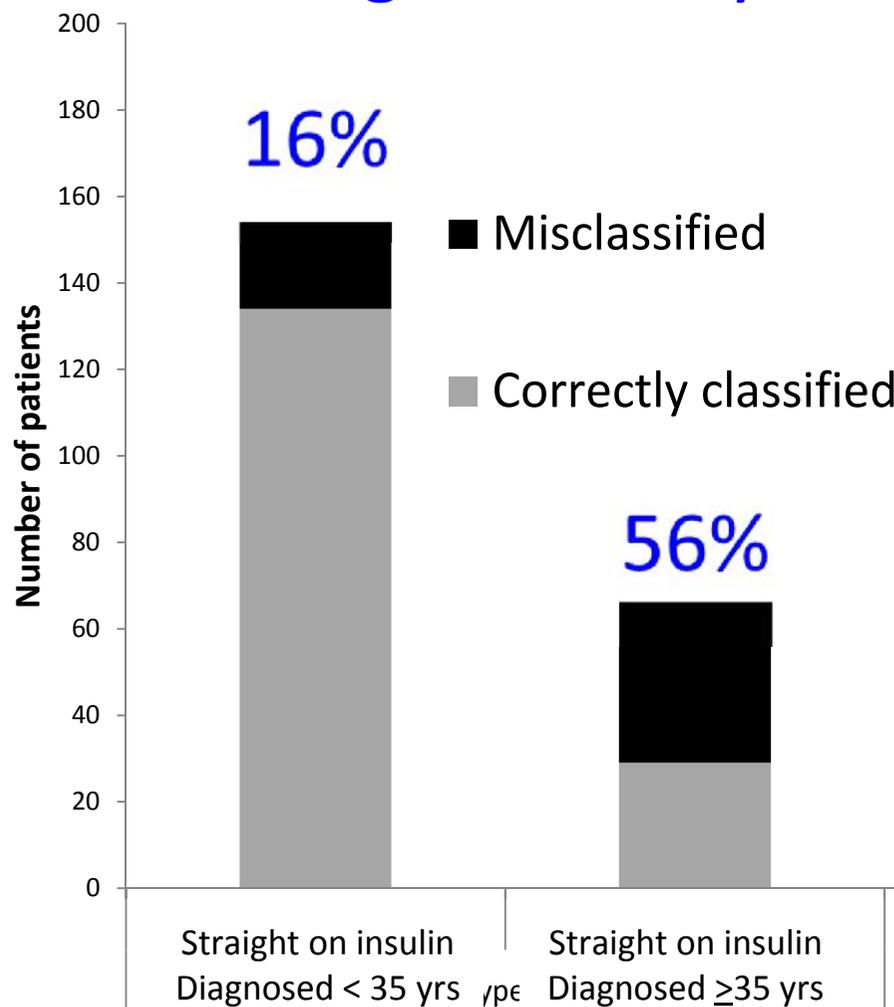
5 years later HbA1c 8.2%

Diagnosis T2D

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

# Diagnosing T1D in slim elderly patients

patients diag T1D > 35yr 56% misclassified



n

Hope et al 2015, BJGP  
n=601

# T1D – why do we get it wrong in adults?

## Usually use Clinical Criteria +/- autoantibodies

### Clinical Criteria

Broad imprecise guidance only (ADA,EASD,WHO)

T1D: diagnosed “young”, “slim”, “DKA presentation”

No cut offs define against future absolute insulin deficiency

Evidence base – weak

Systematic review: Only 10 studies clinical features v C peptide outcome

Favoured age of diagnosis (<35yr) over BMI ( Shields et al BMJ Open 2015)

### Autoantibodies

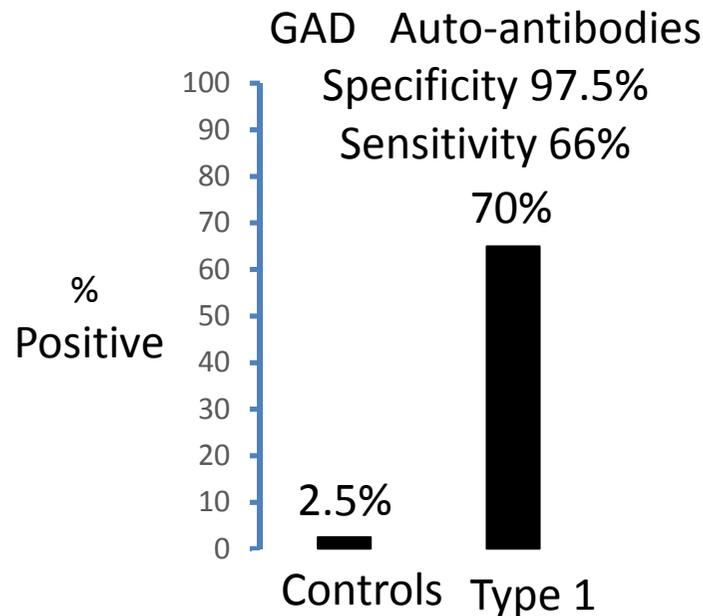
Assays not standardised > 50% UK labs measure rodent ICA!

Prospective studies almost entirely children

Not routinely measured in adults

# Recognising Type 1 diabetes in elderly population

## Why GAD antibodies are not ideal



Patients tested alters interpretation

< 20 years – 95% T1D

Positive predictive value 99.6%

Specific test – false positives rare (0.4%)

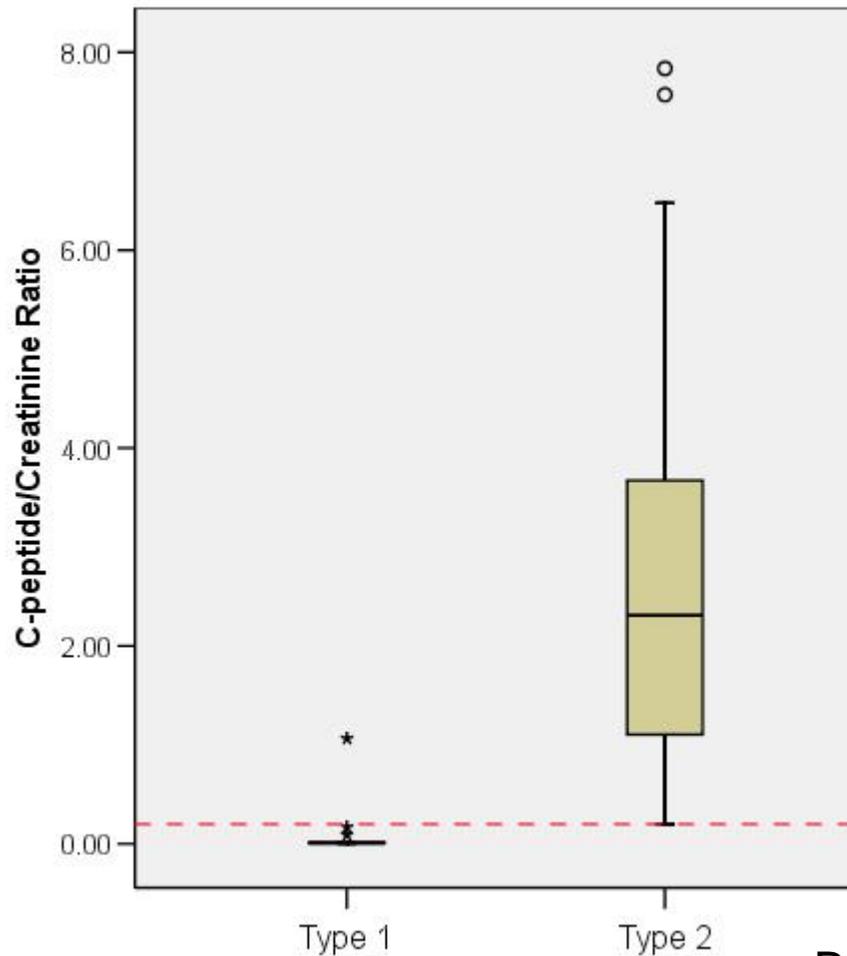
> 40 years - 5% T1D

Positive predictive value 60%

Non specific – false positives common (40%)

If you diagnose “T1D” in adults using GAD - 40% will have T2D  
Therefore LADA will be a mixture of Type 1 and Type 2

# UCP/Cr ratio allows differentiation of Type 1 from Type 2 if over 5 years duration



Rachel Besser

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

Besser et al, Diabetes Care 2011

# Mr 33



33 yr UK Caucasian Factory Worker

Thirsty drinking Coca Cola

Slightly dehydrated

BMI 33 kg/m<sup>2</sup>

Glucose 33 mmol/l

Ketones +

Treated with 33U Mixtard bd

4 years later HbA1c 8.2%

Diagnosis? Treatment?

UCPCR 0.17 nmol/mmol Type 1

# Mr 33



33 yr UK Caucasian Factory Worker

Thirsty drinking Coca Cola

Slightly dehydrated

BMI 33 kg/m<sup>2</sup>

Glucose 33 mmol/l

Ketones +

Treated with 33U Mixtard bd

4 years later HbA1c 8.2%

Diagnosis? Treatment?

UCPCR 1.7 nmol/mmol Type 2

# Dorothy



Age diagnosis	51 yr
Present Age	69yr
BMI	27
Initial Treatment	OHA for 4 years then insulin
Present Treatment	Metformin 1g bd Insulatard 22/-/16/-
Clinical Problem	Variability in glucose – severe problem with hypos HbA1c 8.9%

UCPCR 0.1 nmol/mmol

# Type 2 patients can become C peptide negative



Suzy Hope

- 174 insulin-treated subjects T2D on clinical criteria
  - diagnosed  $\geq 45$  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 (stimulated  $<200$ pmol)  
2/5 Antibody (GAD positive)

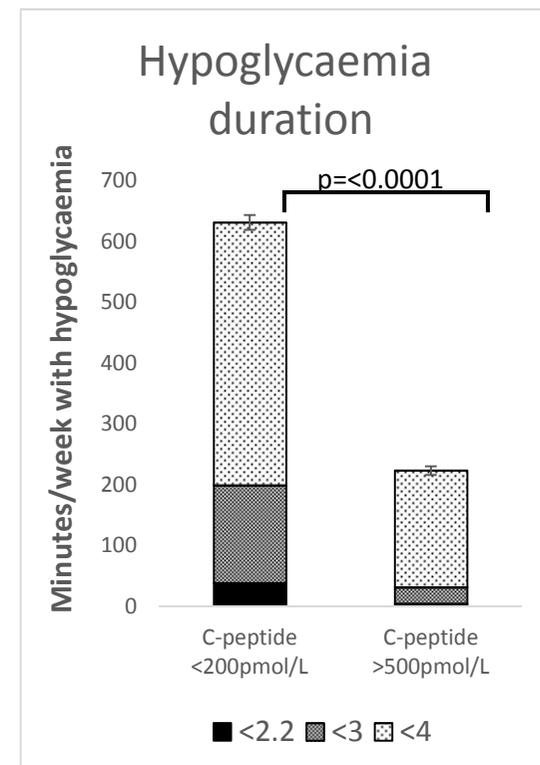
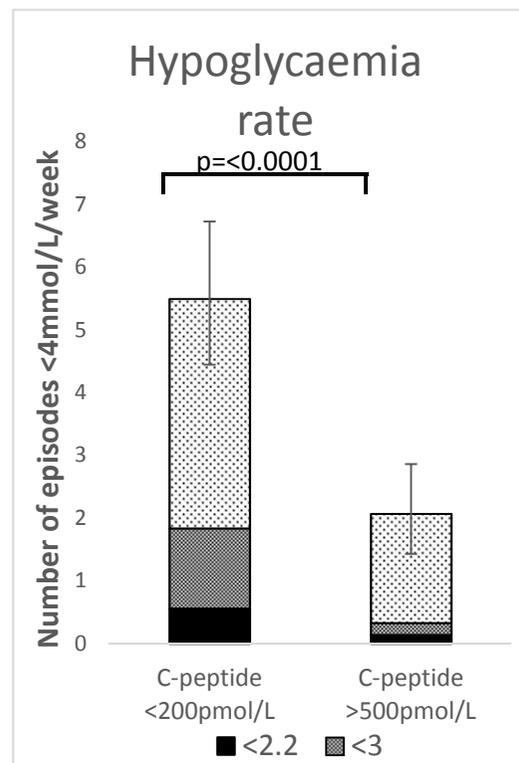
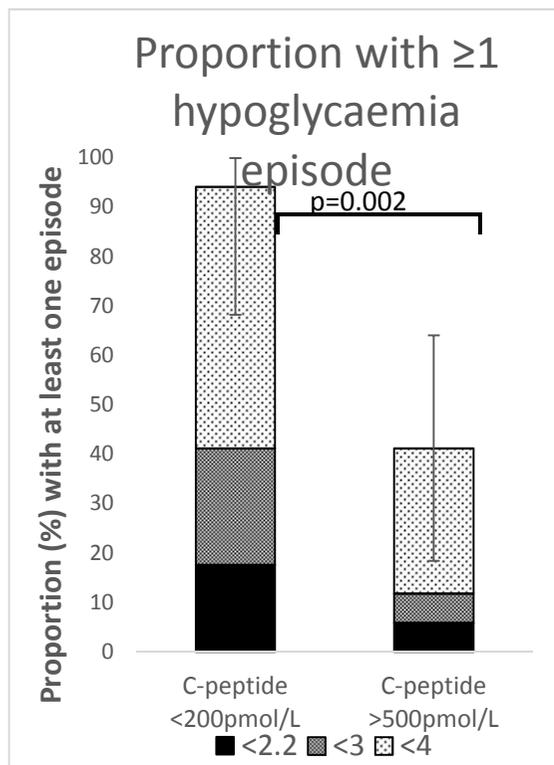
Major problems: hypos and inappropriate treatment

Need Type 1 education and treatment

Oakes, Shepherd, Hattersley et al Diabetic Medicine 2013

# Endogenous insulin secretion, not clinical diagnosis determines risk of hypoglycaemia

- Comparison of CGM assessed hypoglycaemia in 17 matched pairs
- Insulin treated Type 2 diabetes, onset age >35, >2 years to insulin
- Low/high C-peptide groups not distinguishable by clinical characteristics



S Hope & A Jones

Peter



15 yr diagnosed 14 yr  
glucose 19 mmol/l  
Treated basal bolus insulin 0.5U/kg  
HbA1c 8.2%

His family



“Type 1 and Type 2”

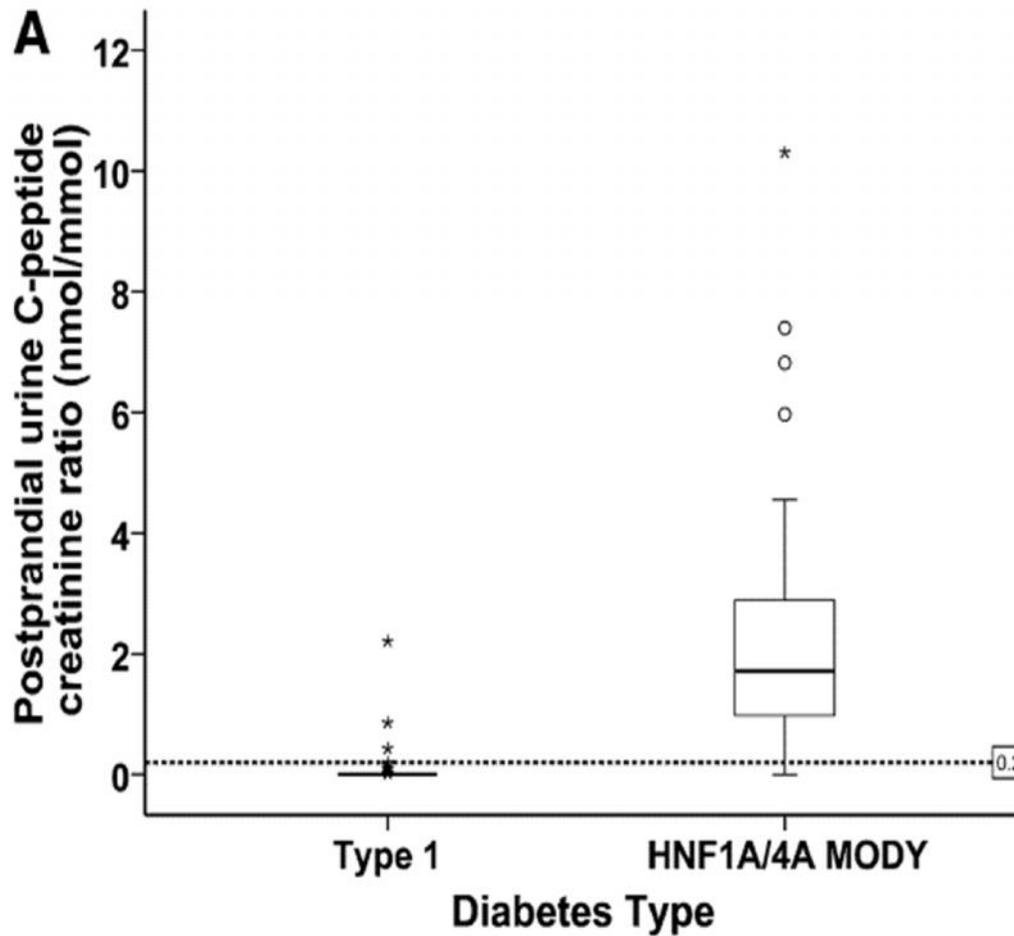
UCPCR 1.3 nmol/mmol

Father insulin for 18 years

UCPCR 0.7 nmol/mmol

Autosomal dominant, non insulin dependent

## UCP/Cr ratio allows differentiation of Type 1 from MODY >5yrs post diagnosis



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

## Large impact on treatment

HNF-1A MODY diagnosed on molecular genetic testing



Stopped insulin  
Started a single half tablet of gliclazide  
Control improved  
HbA1c 8.2% to 6.5%

All “Type 1” stopped insulin and went on sulphonylurea tablets with better control.

All “Type 2” stopped treatment and went on sulphonylurea tablets with better control.

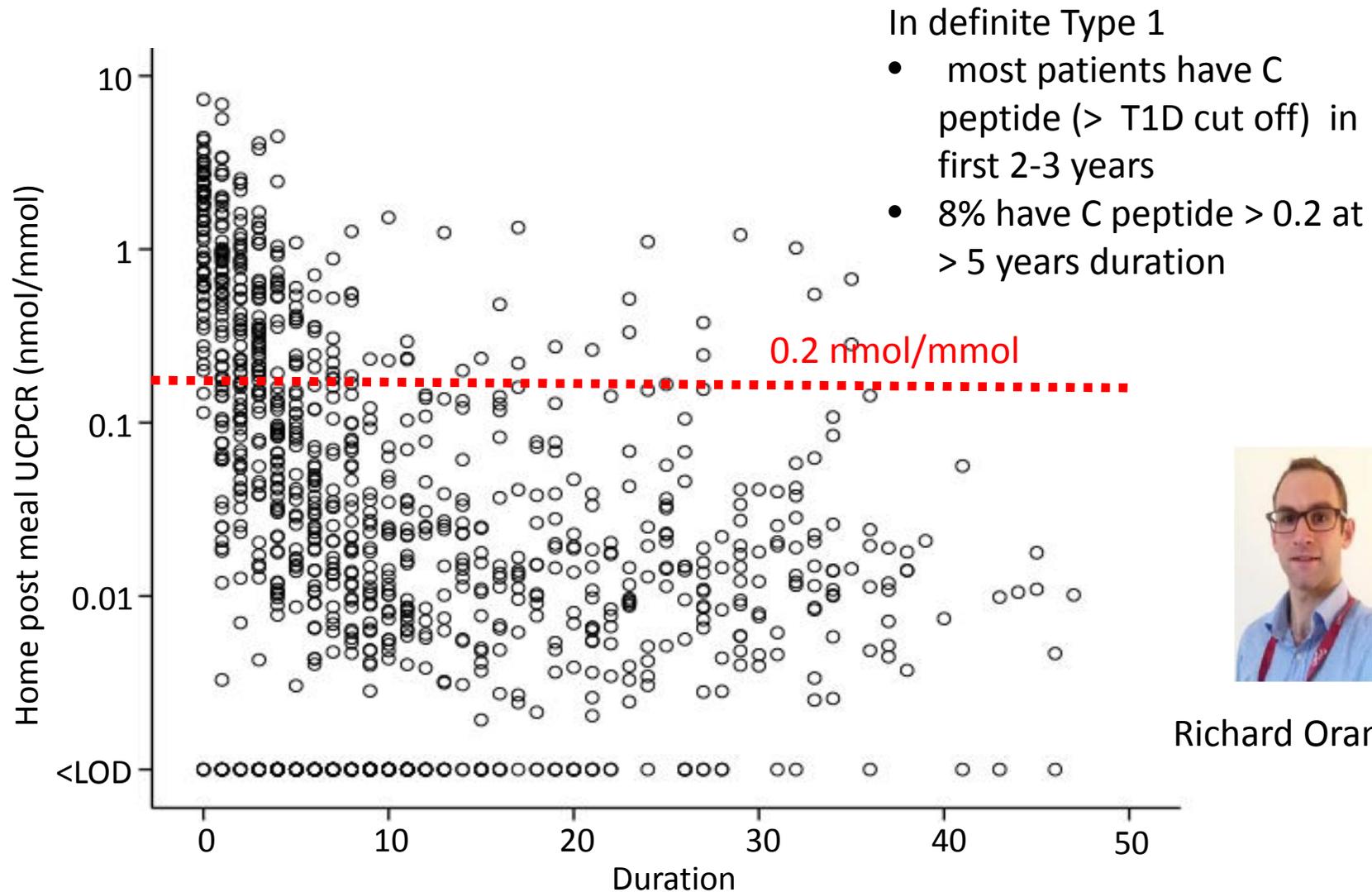
Shepherd Diab Med 2009

# Clare



Age diagnosis	20
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

# C peptide continues well after diagnosis in Type 1 diabetes



Richard Oram

Can UCPCR aid management of paediatric patients with Type 1 diabetes?

## UCPCR positive Type 1 (AB+) patients: older at diagnosis and had a shorter duration

	UCPCR <0.2nmol/mmol 'negative' n=549 Median (IQR)	UCPCR ≥0.2nmol/mmol 'positive' n=185 Median (IQR)	p value
Age at Diagnosis (Years)	6 (3,9)	11 (8,13)	<b>&lt;0.0001</b>
Duration (Months)	74 (44,112)	15 (4,31)	<b>&lt;0.0001</b>

## UCPCR positive Type 1 (AB+) patients were on less insulin but had same level of HbA1c

	UCPCR <0.2nmol/mmol 'negative' n=549 Median (IQR)	UCPCR ≥0.2nmol/mmol 'positive' n=185 Median (IQR)	P value
Insulin Dose (u/kg/day)	0.93 (0.76, 1.14)	0.68 (0.5, 0.97)	<b>&lt;0.0001</b>
HbA1c (mmol/mol)	70.5 (62, 81)	70 (61, 84)	0.75

UCPCR positive patients could increase insulin to achieve better control

More aggressive treatment protective against complications and beneficial when UCPCR reduces over time

## When it helps to measure C-peptide in Type 1?

1. To assess if patient on insulin is making their own insulin
  - Assessment of T1D honeymoon
  - Diagnosis –type 1 vType 2/MODY
  - Guidance on other therapy
2. To assess if type 2 with variable glucose values who has gone on insulin is still producing own insulin
3. To detect/confirm severe insulin resistance
4. ? Stratify for treatment response to third line agents in T2D

# Interpretation of measurement of C-Peptide 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	+++	++