C-Peptide and Exercise in people with Type 1 Diabetes

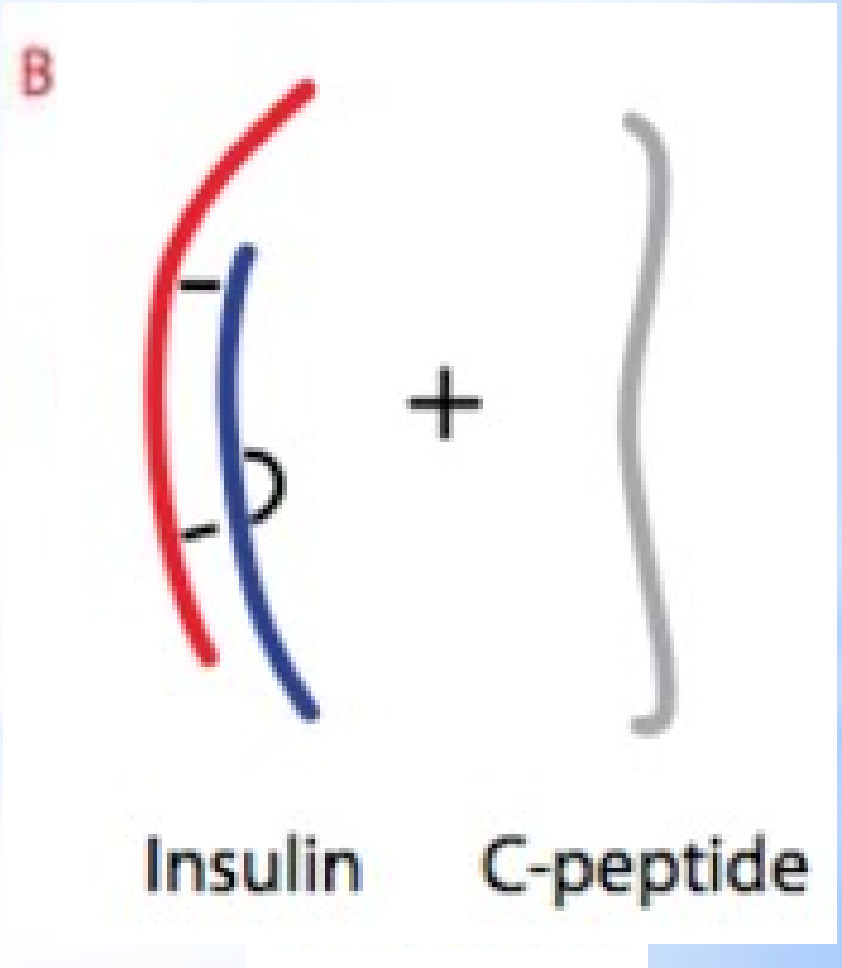
Guy Taylor

Newcastle University

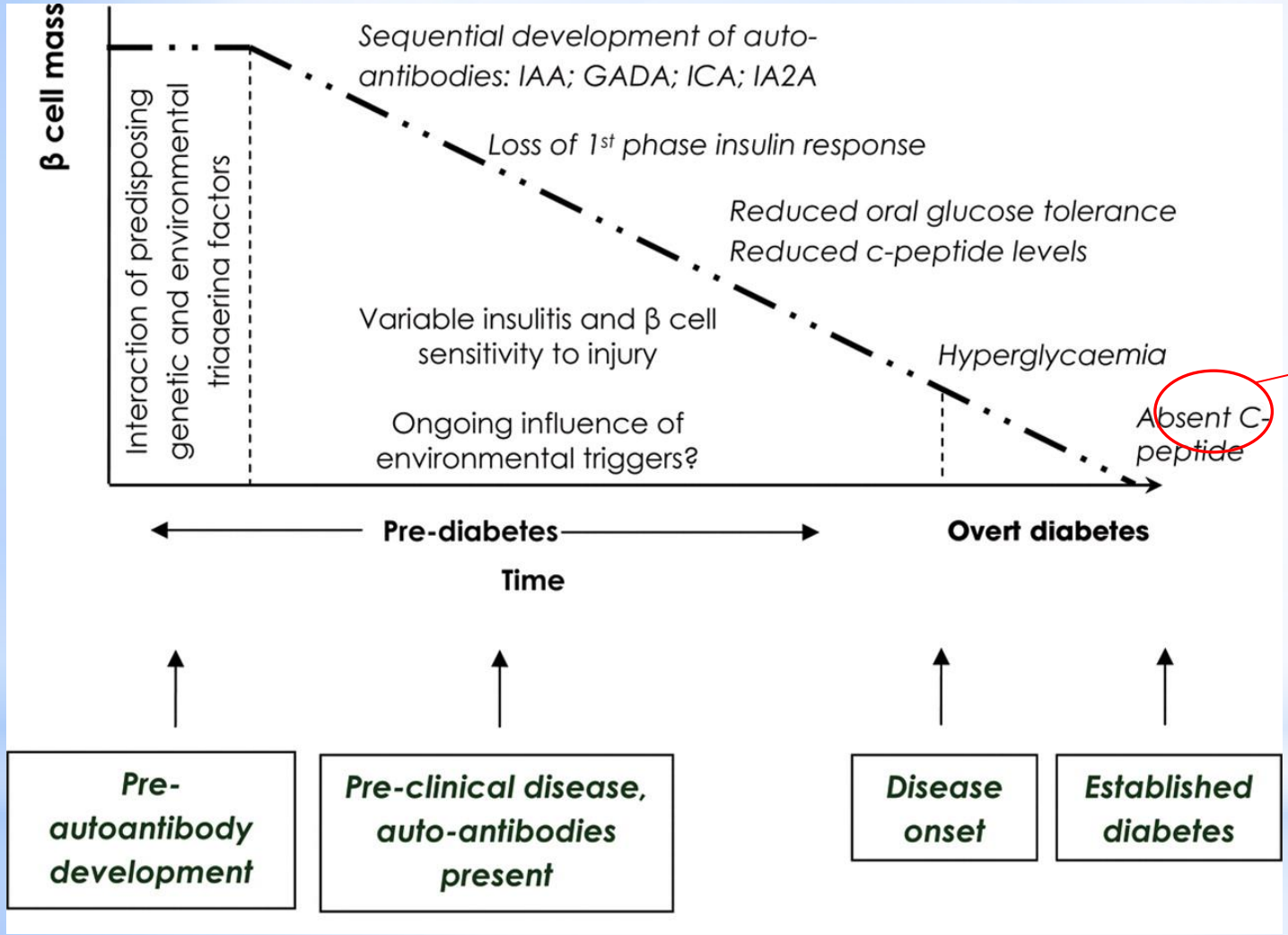
Move Lab
Physical Activity & Exercise Research

C-Peptide

- Produced in equal amounts to insulin
- Used to assess endogenous insulin secretion – not injected with exogenous insulin

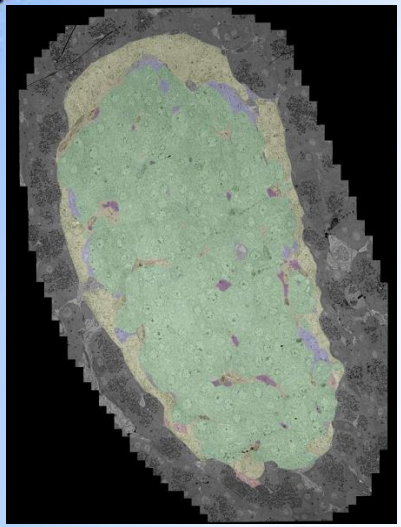
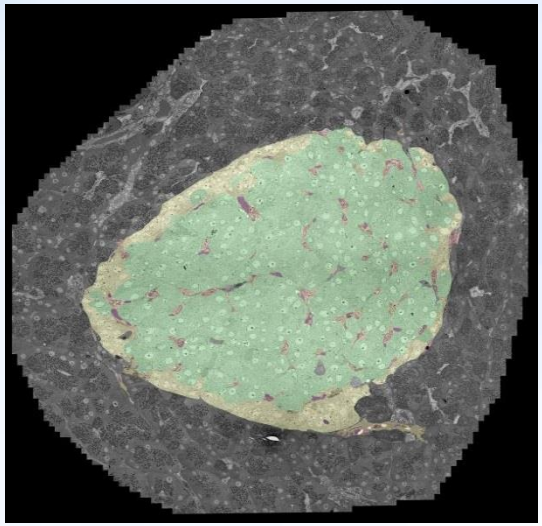
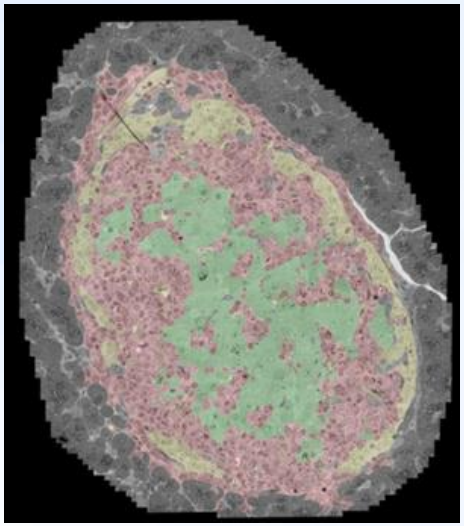
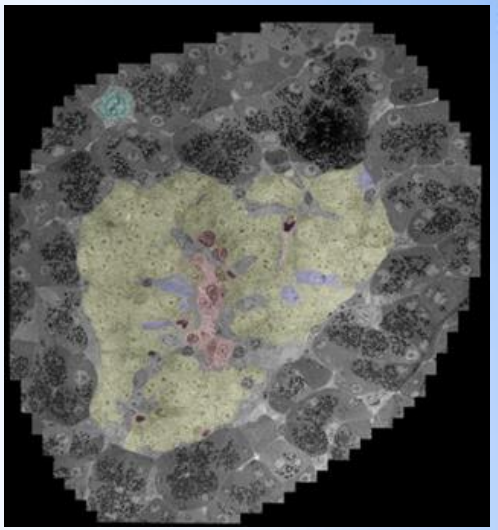


Pathogenesis of Type 1 diabetes



Does type 1 diabetes always lead to absolute insulin deficiency?

Thrower, S.L. and Bingley, P.J., 2011 adapted from Eisenbarth (1986)

1. Healthy β-cells with abundant insulin content

2. Infiltration of leukocytes and β-cell phagocytosis

3. Mass infiltration morphology

4. End stage diabetes count

Beta cell (green), Delta cell (blue), Alpha cell (yellow), Leukocytes (red), Vasculature (orange), Erythrocyte (magenta) and Duct (cyan). Ravelli (2013).

Diabetologia (2005) 48: 2221–2228
DOI 10.1007/s00125-005-1949-2

ARTICLE

J. J. Meier · A. Bhushan · A. E. Butler · R. A. Rizza · P. C. Butler

Sustained beta cell apoptosis in patients with long-standing type 1 diabetes: indirect evidence for islet regeneration?

Received: 15 February 2005 / Accepted: 3 June 2005 / Published online: 5 October 2005
© Springer-Verlag 2005

Beta cells were identified in 88% of individuals with type 1 diabetes.

-Unrelated to duration of disease or age at death
-Higher ($p<0.05$) in individuals with lower mean blood glucose.

ORIGINAL ARTICLE

Residual Insulin Production and Pancreatic β-Cell Turnover After 50 Years of Diabetes: Joslin Medalist Study

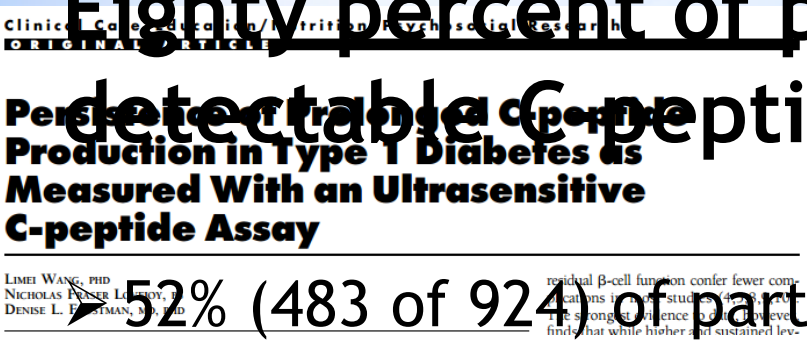
Hillary A. Keenan,[1,2] Jennifer K. Sun,[1,3,4] Jared Levine,[1,2] Alessandro Doria,[1,2] Lloyd P. Aiello,[1,3,4] George Eisenbarth,[5] Susan Bonner-Weir,[1,2] and George L. King[1,2]

33.0% undetectable (<0.03 nmol/l)
64.4% with minimal (0.03– 0.2 nmol/l),
2.6% with sustained (>0.2 nmol/l)

Ultrasensitive C-peptide Assay

Serum ≥ 0.003 nmol/l (3.3 pmol/l)
Or
Urine C-Peptide to Creatine Ratio
>0.001 nmol/mmol

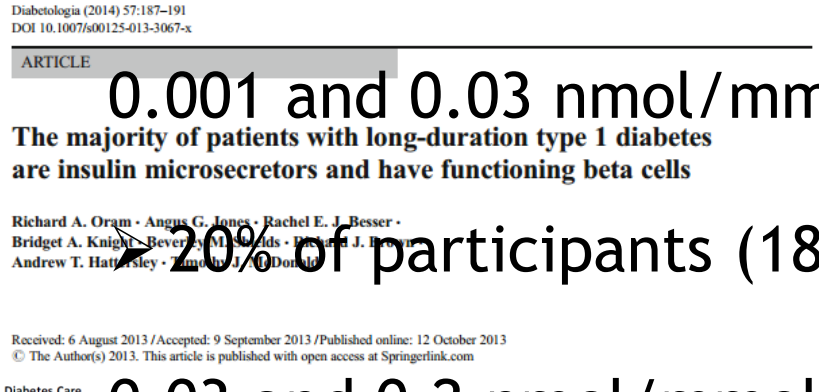
Eighty percent of participants had detectable C-peptide levels


Clinical Care/Education/Nutrition/Psychosocial Research
ORIGINAL ARTICLE

Persistence of Pancreatic Insulin Production in Type 1 Diabetes as Measured With an Ultrasensitive C-peptide Assay

LIMEI WANG, PHD
NICHOLAS PRATER LAWTON, BS
DENISE L. FEITMAN, MD, PHD

➢52% (483 of 924) of participants had a UCPCR between 0.001 and 0.03 nmol/mmol

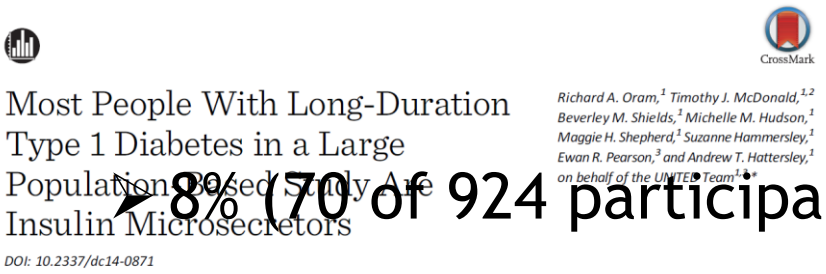

Diabetologia (2014) 57:187–191
DOI 10.1007/s00125-013-3067-x

ARTICLE

The majority of patients with long-duration type 1 diabetes are insulin microsecretors and have functioning beta cells

Richard A. Oram · Angus G. Jones · Rachel E. J. Besser · Bridget A. Knight · Beverley M. Shields · Richard J. Brown · Andrew T. Hattersley · Timothy J. McDonald

➢20% of participants (187 of 924) had a UCPCR between 0.03 and 0.2 nmol/mmol


Received: 6 August 2013 /Accepted: 9 September 2013 /Published online: 12 October 2013
© The Author(s) 2013. This article is published with open access at Springerlink.com

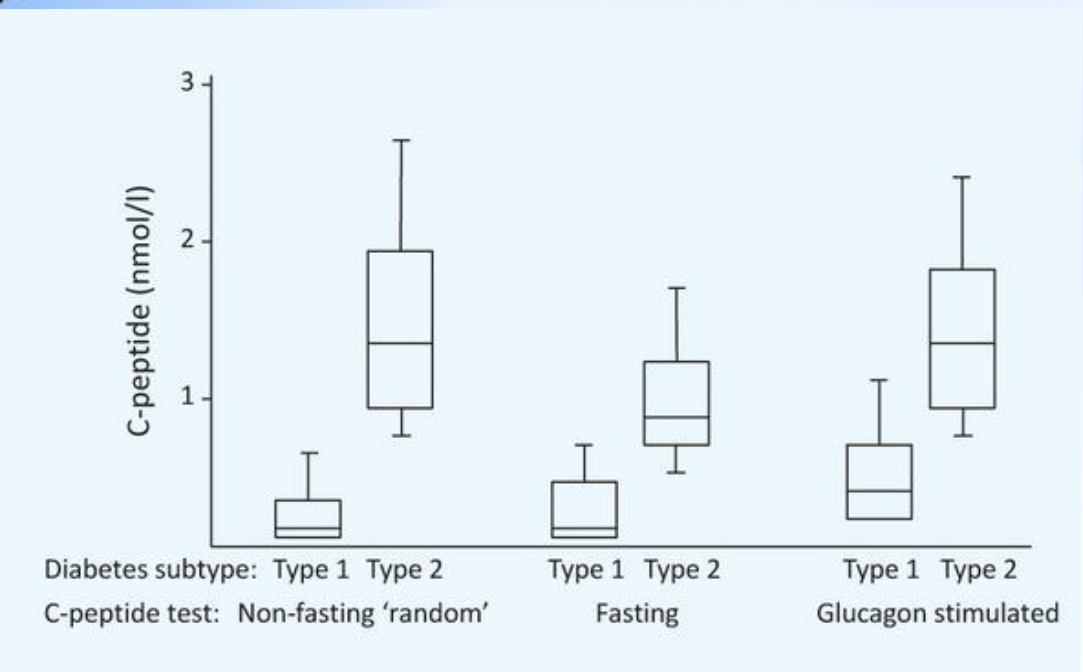
Diabetes Care 1

Most People With Long-Duration Type 1 Diabetes in a Large Population-Based Study Are Insulin Microsecretors

Richard A. Oram,[1] Timothy J. McDonald,[1,2] Beverley M. Shields,[1] Michelle M. Hudson,[1] Maggie H. Shepherd,[1] Suzanne Hammersley,[1] Ewan R. Pearson,[3] and Andrew T. Hattersley,[1] on behalf of the UNITED Team[1,*]

DOI: 10.2337/dc14-0871

➢8% (70 of 924 participants) had a UCPCR >0.2 nmol/mmol



UCPCR ranges in diabetes subtypes and controls (unpublished data)

	Males					Females				
	UCPCR (nmol/mmol)					UCPCR (nmol/mmol)				
Patient group	5th	25th	50th	75th	95th	5th	25th	50th	75th	95th
Controls	0.58	1.64	2.84	7.04	10.39	1.82	3	4.04	6.99	10.37
Type 1 diabetes										
>5 years duration	<0.02	<0.02	0.02	0.02	0.02	0.00	0.00	0.02	0.04	0.04
<5 years duration	0.02	0.55	1.24	1.79	5.78	0.02	0.55	1.24	1.79	5.78
Type 2 diabetes										
On OHA	0.35	1.6	2.87	4.08	7.80	1.28	2.34	3.85	5.68	9.43
On insulin	0.08	0.5	1.3	2.36	5.65	0.15	0.6	1.4	2.8	6.12

In healthy individuals the plasma concentration of C-peptide:

Fasting state = 0.3–0.6 nmol/l

Postprandial = 1–3 nmol/l

C-peptide and Diabetes complications

Diabetes Care and Complications Trial:

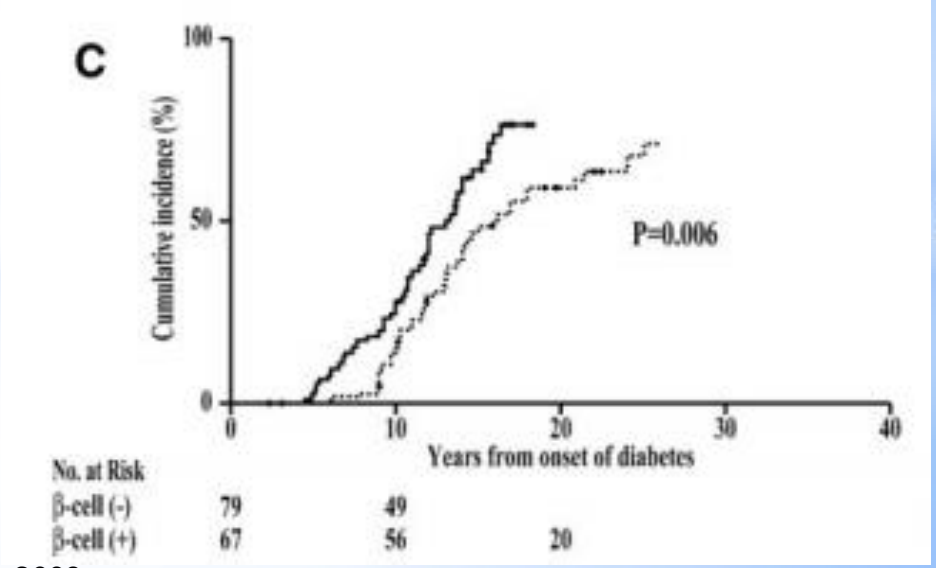
>0.2 nmol/l C-peptide = Lower fasting glucose and HbA1c

62% risk reduction in hypos in the intensive control group

Reduced development of retinopathy and nephropathy

Even individuals who are microsecreaters confer fewer diabetes related complications in most studies compared to absolute deficiencies.

- Associated with lower rates of hypoglycemia
- Lower incidence of retinopathy and nephropathy



Panero et al., 2009; Steffes et al., 2003; Nakanishi and Watanabe 2008

Time spent Hyperglycaemic (Klein, 1995)

Time spent Hypoglycaemic (Kalra et al., 2013)

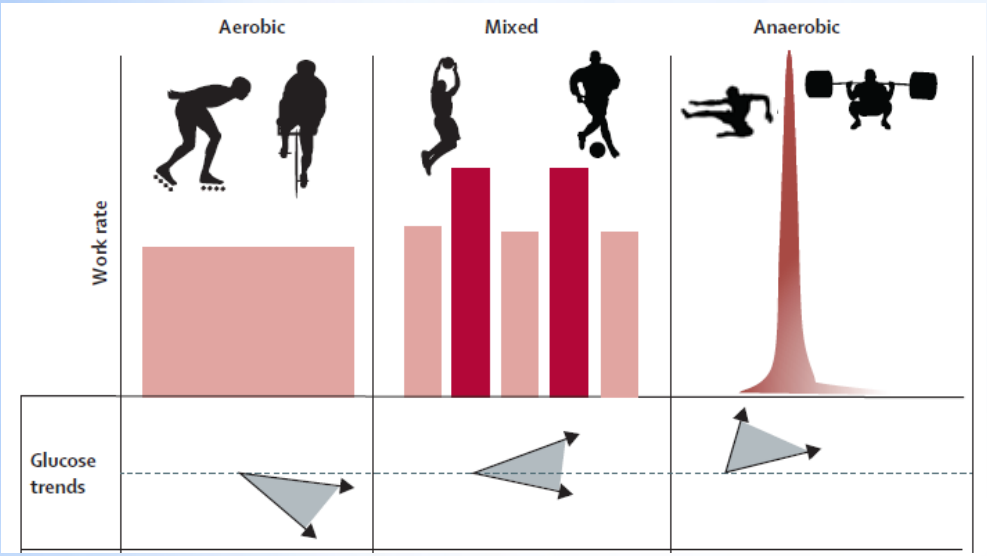
Glucose variation (Ceriello and Kilpatrick 2013)

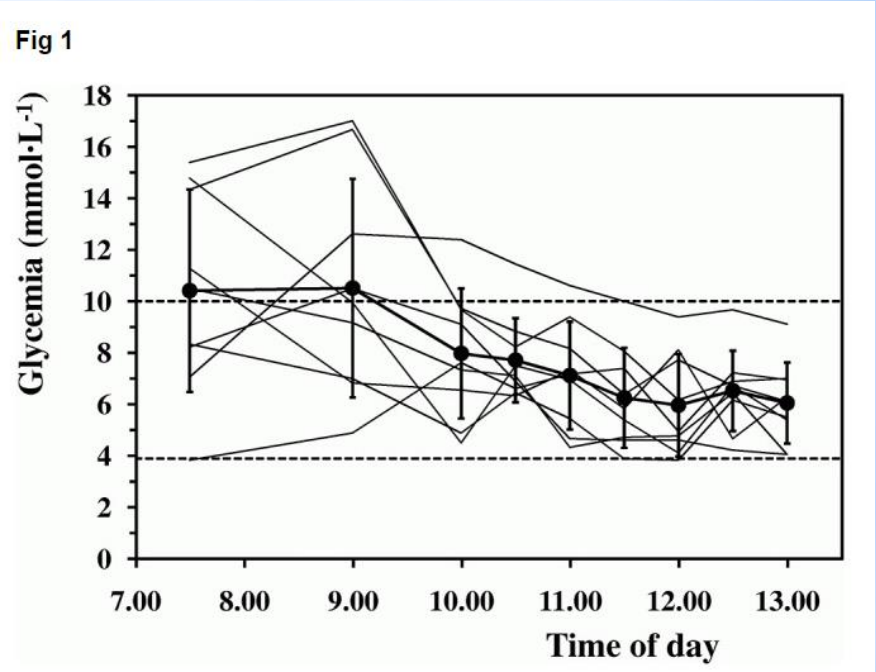
Are all associated with diabetes complications

Buckingham et al., (2015)

“In the first 2 years after diagnosis of type 1 diabetes, higher C-peptide levels are associated with increased sensor glucose levels in the target range and with lower glucose variability”

In general, aerobic exercise decreases glycaemia, anaerobic exercise increases glycaemia, and mixed activities are associated with glucose stability.





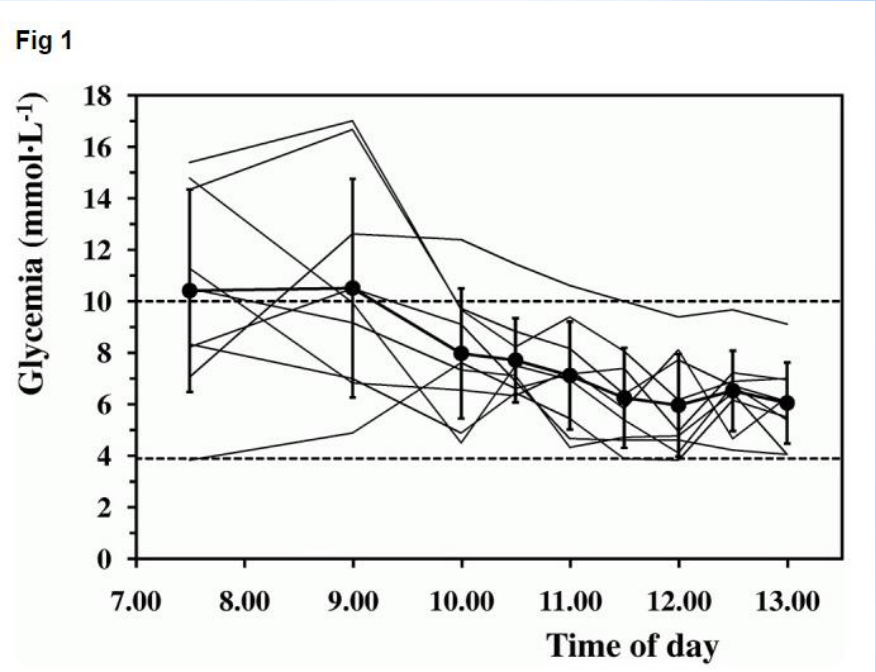
Large interindividual variation in the acute and chronic glycaemic response to exercise.

- Time spent in euglycaemia, hypoglycaemia and hyperglycaemia
- Glucose Variability
- HbA1C ↑→↓

Riddell et al., 2017

Individual responses are dependent on various additional factors, including:

- The duration and intensity of the activity
- Initial blood glucose concentrations
- Previous hypoglycaemic events
- Individual fitness
- Concentrations of insulin, glucagon, and other counter-regulatory hormones in the circulation
- The nutritional status of the individual

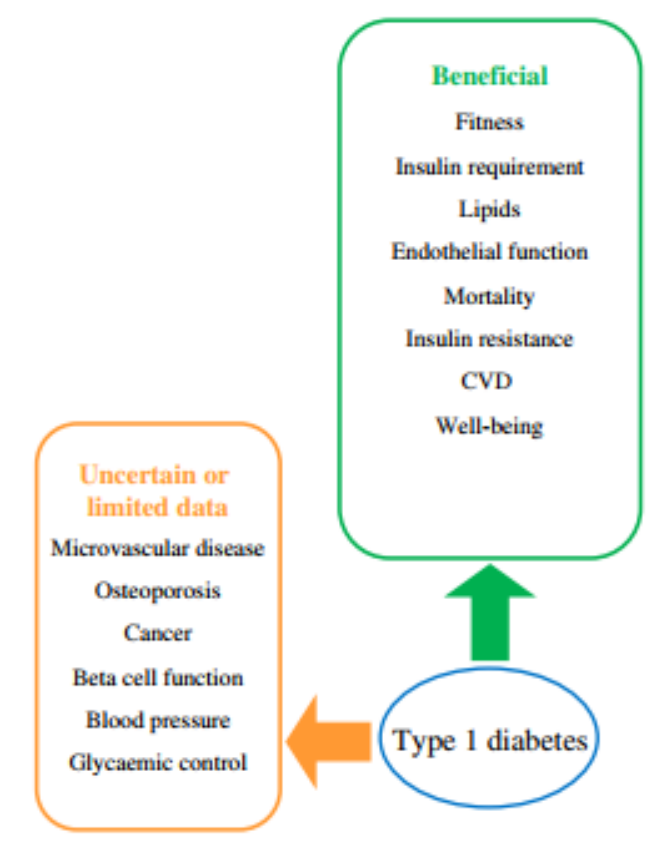


Riddell et al., 2017

Does remaining beta cell function also play a role?

Type 1 diabetes and exercise

Regular exercise has been found to improve:



Recruitment:

Classical presentation T1DM with insulin commencement at diagnosis
Diagnosis of at least 1 years
Stable on MDI/CSII for 6 months
Aged 18 – 65
No diabetic complications except background retinopathy
HbA1c < 86 mmol/mol

Screening 100 potential participants
2 hour post-prandial urine C-peptide creatinine ratio
Blinded CGM for 7 days
Questionnaire pack (HFS, HypoA-Q+Self Efficacy for Exercise)

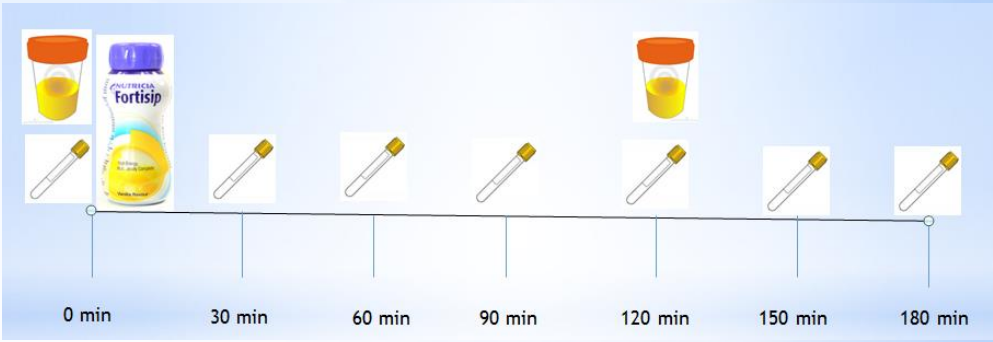
30 participants proceed to study
Range of C-peptide

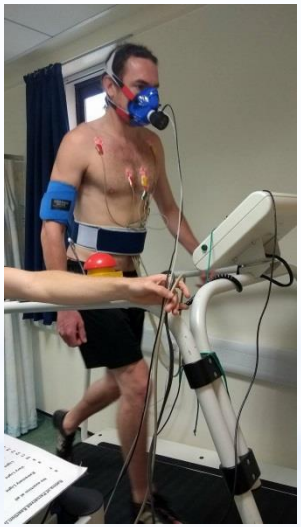
Baseline CRF Visit
MMTT
Body measurement/insulin dose
Blood samples (c-peptide and insulin)

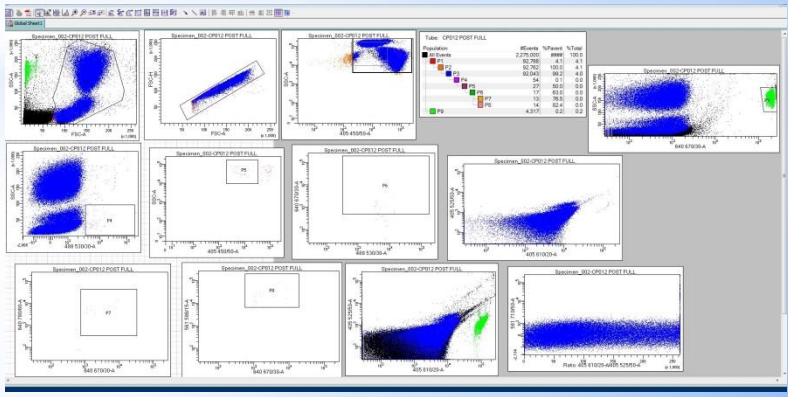
Return to CRF after > 48 hours
Health Screening
Treadmill walk with increase intensity every 3 minutes to maximum tolerated

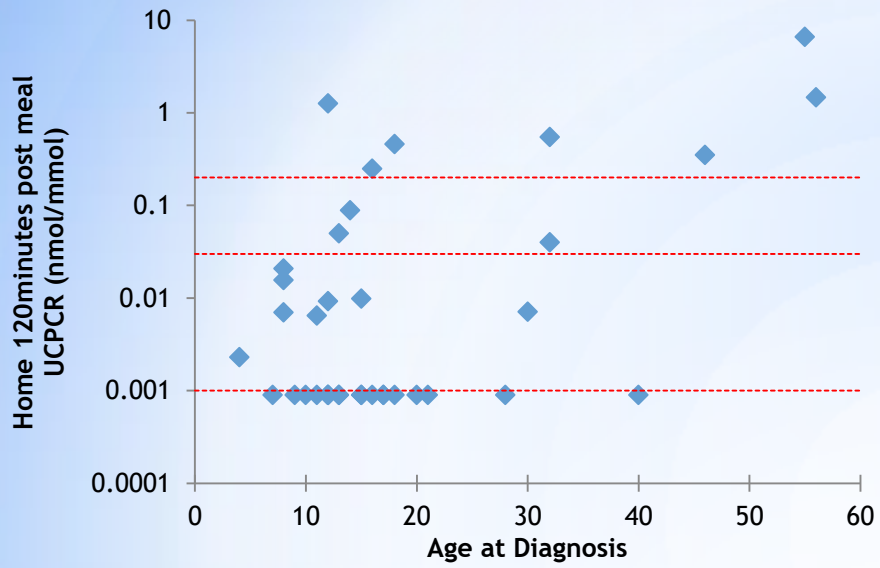
Return to CRF after > 7 days
Blinded CGM placed
Submaximal Exercise bout
Walking 45 minutes at 60% intensity pre-screening threshold
Blood sample pre, immediately post and 1 hour post exercise (endothelial progenitor cells, inflam cytokines, glucoregulatory hormones)

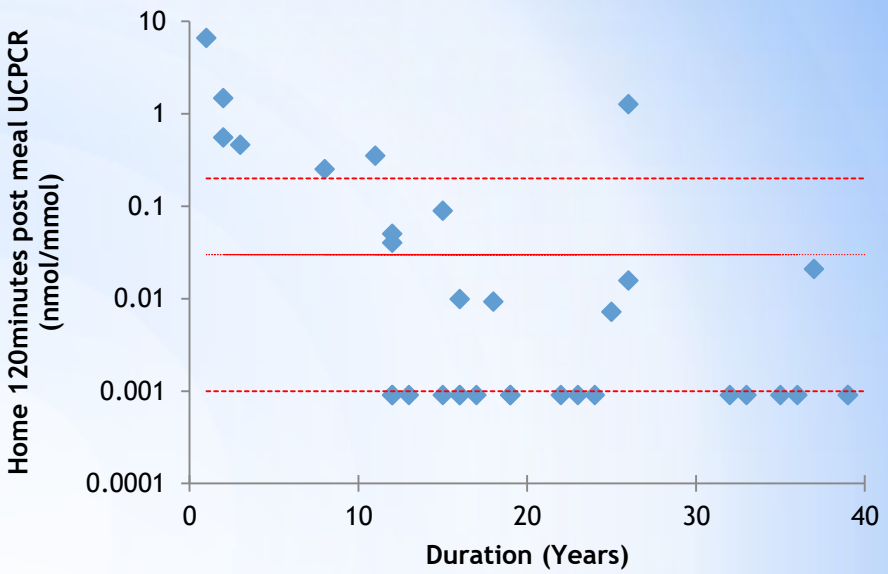
CGM monitoring 72 hours post-exercise
Insulin dose/diet diary

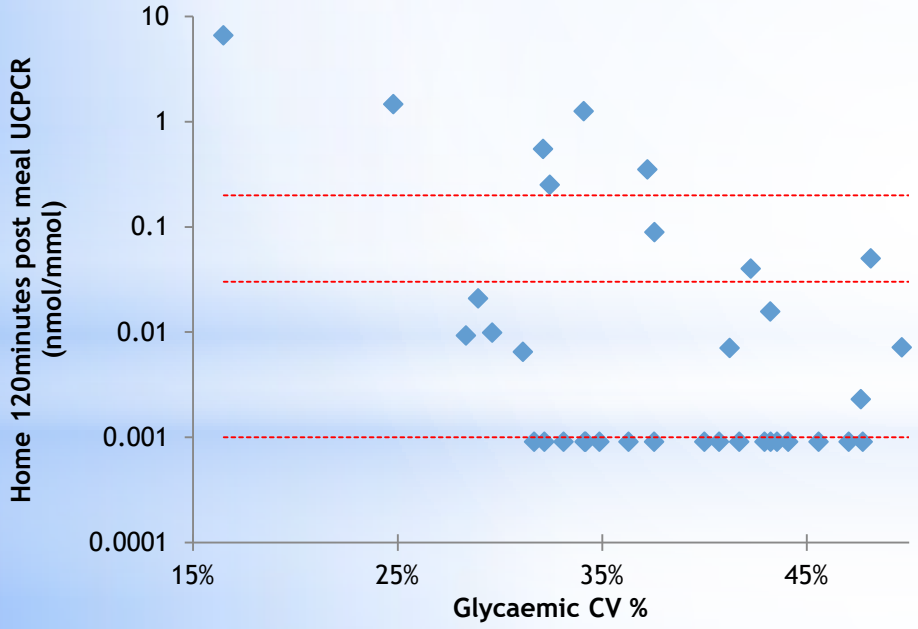


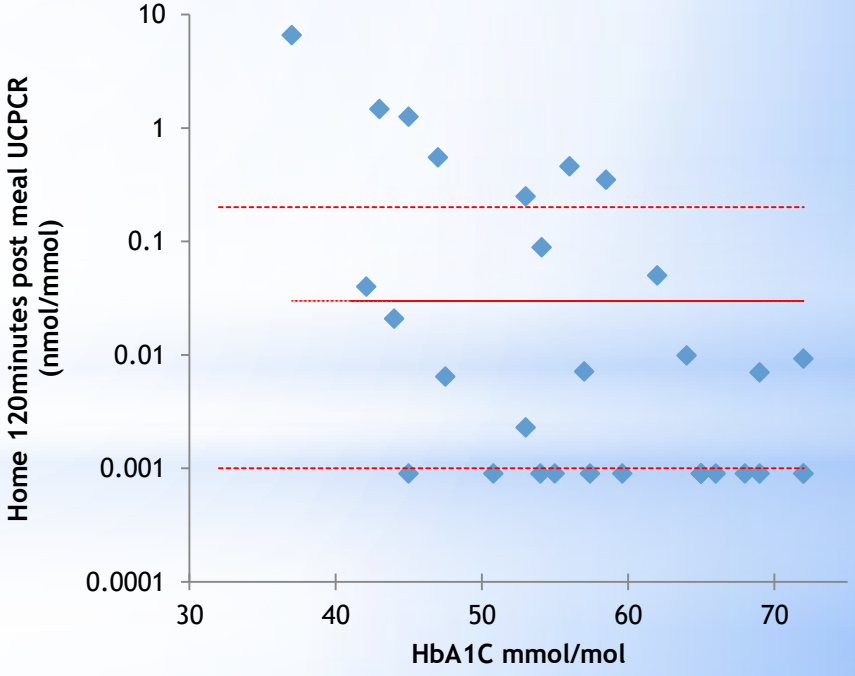












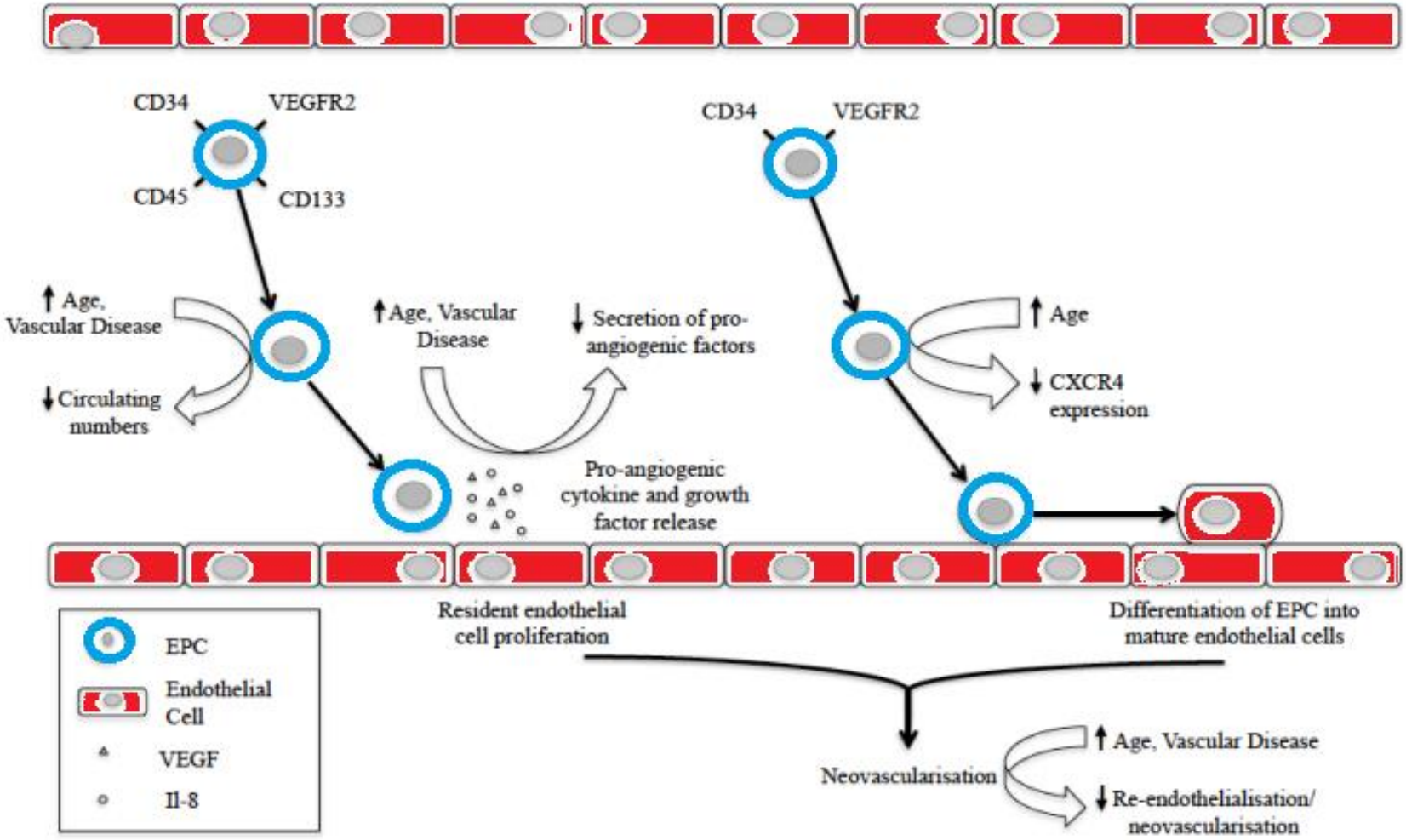
UCPCR values are plotted on a log scale to allow separation of the range of low levels found.

Venous blood samples

Analysed for:

- Circulating Endothelial Progenitor Cells (EPCs)
- Inflammatory markers (TNF-α, IL-6, C-Reactive protein)
- Glucose regularity hormones (Glucagon, Catecholamines)

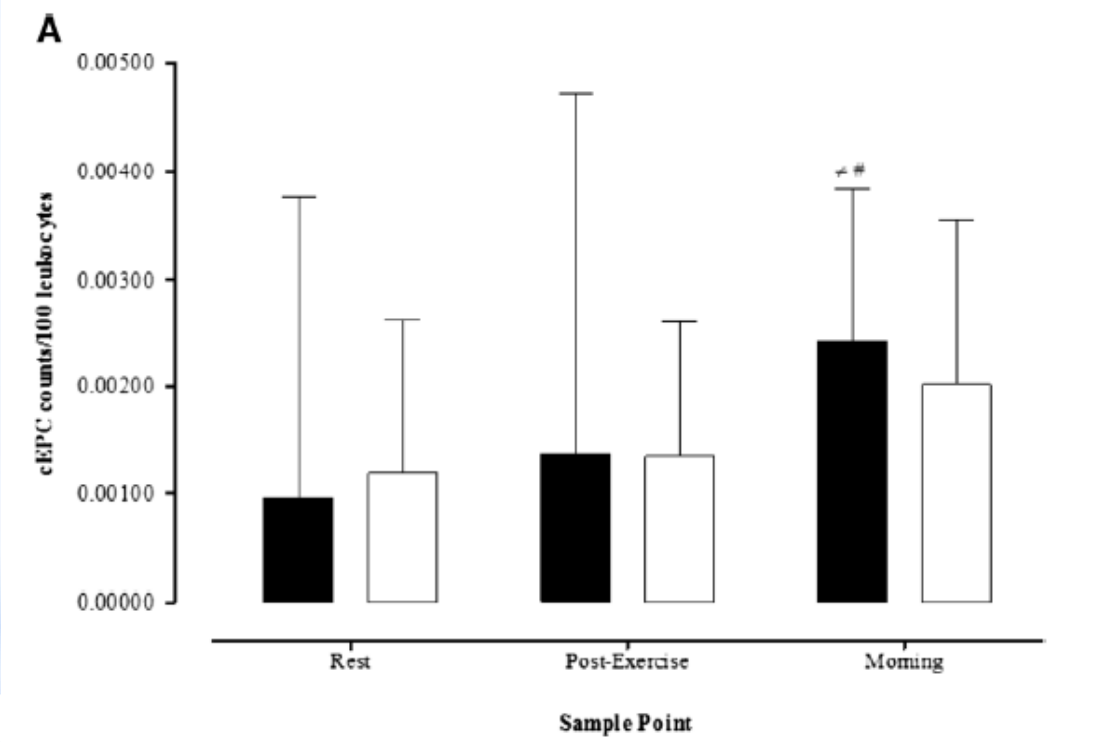
Endothelial Progenitor Cells



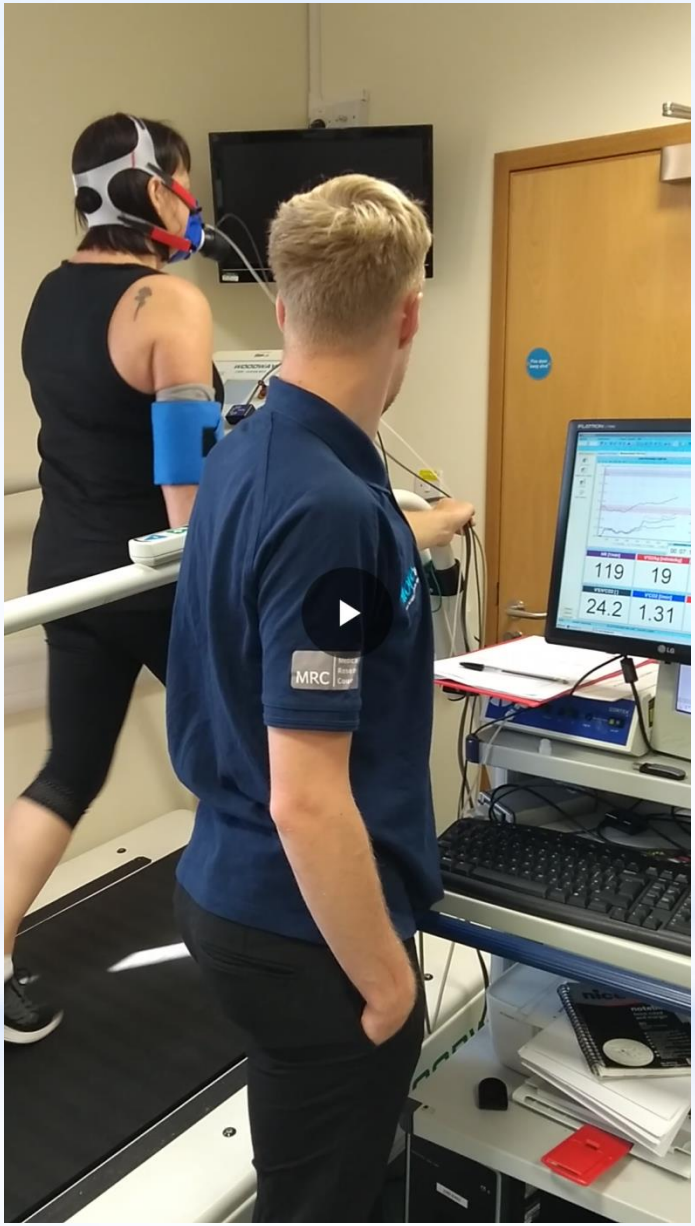
Type 1 Diabetes and EPCs

- Reduced circulating number of EPCs
- Reduced ability to mobilise EPCs from the bone marrow
- Hyperglycaemia impairs proliferation and survival
- Reduced migration and adhesion to areas of ischemia
- Reduced incorporation into endothelial cells

Type 1 diabetes, Exercise and EPCs



West et al., 2015


MRC
119
19
24.2
1.31