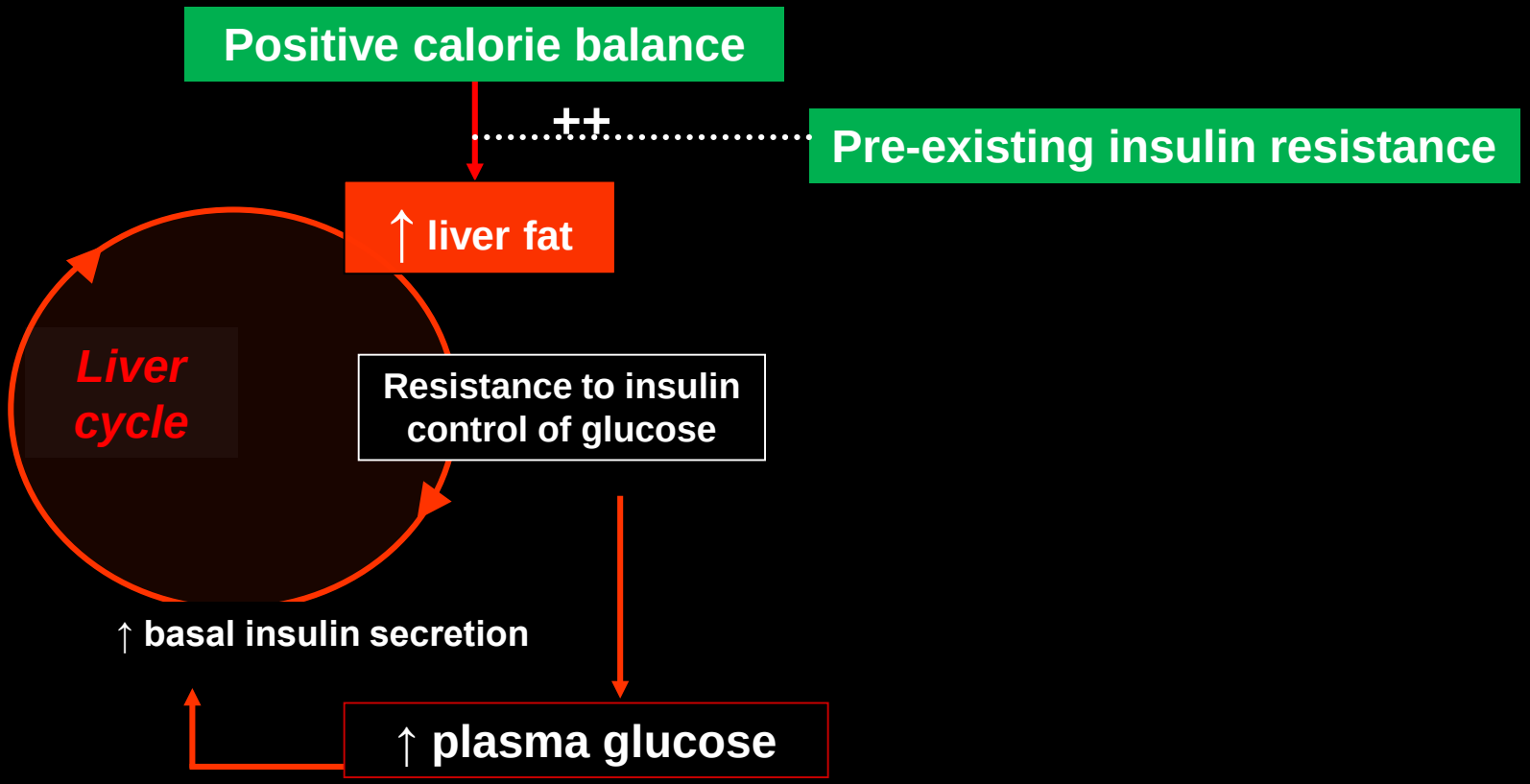
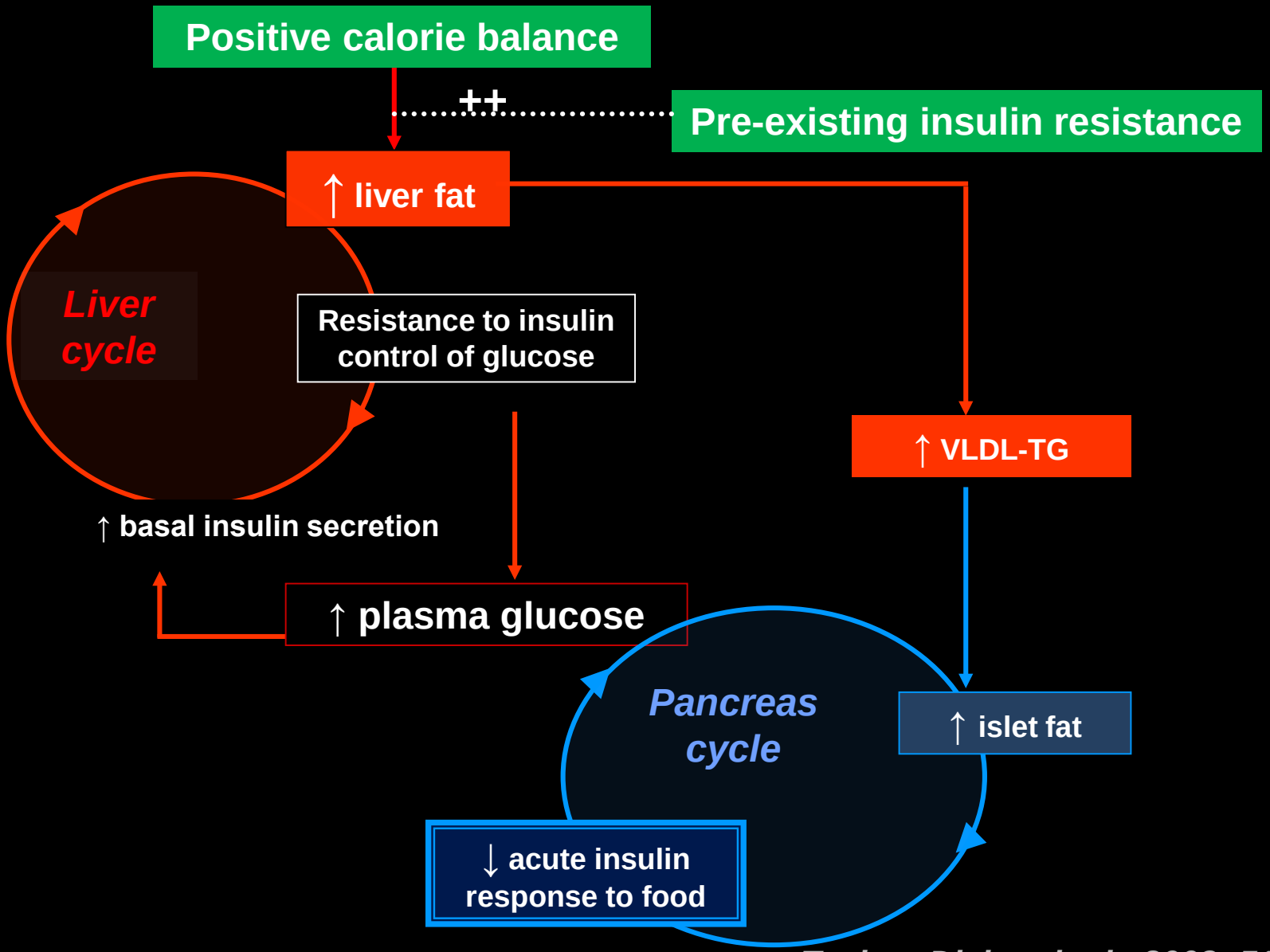
The twin-cycle hypothesis: type 2 diabetes



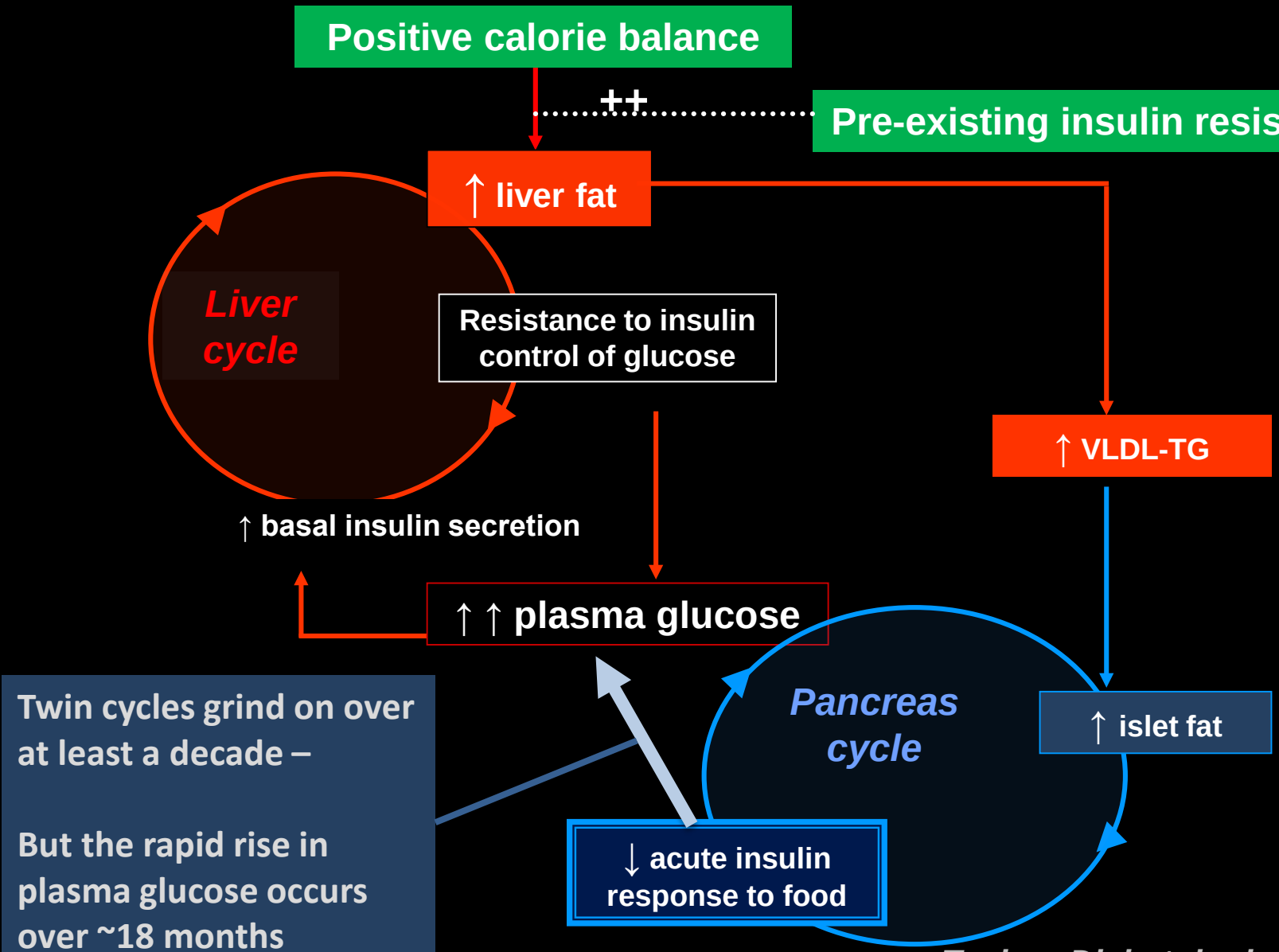
Taylor, Diabetologia 2008; 51: 1781

The twin-cycle hypothesis: type 2 diabetes



Taylor, Diabetologia 2008; 51: 1781

The twin-cycle hypothesis: type 2 diabetes



Twin cycles grind on over at least a decade –

But the rapid rise in plasma glucose occurs over ~18 months

Taylor, Diabetologia 2008; 51: 1781

The twin cycle hypothesis

Substantial weight loss in people with type 2 diabetes will:

Liver

Decrease fat – improve insulin action and normalise overnight blood sugar

and

Pancreas

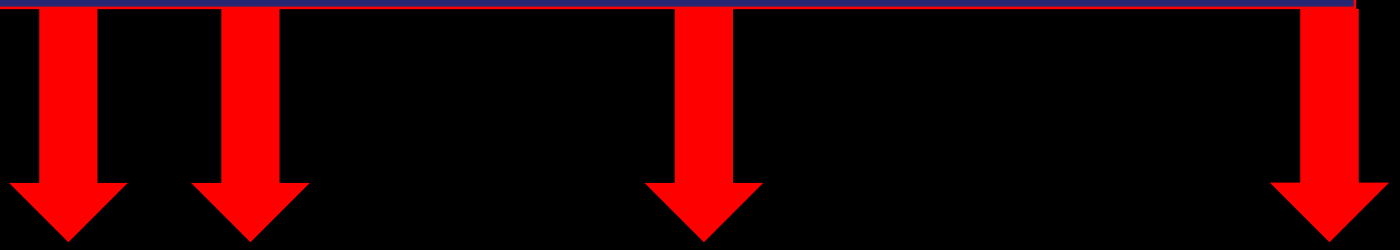
Decrease fat – normalise the insulin response to eating

The Counterpoint Study

(Counteracting Pancreatic inhibitiOn of INsulin secretion by Triglyceride)

Tests of:

- Beta cell function
- Liver and muscle insulin sensitivity
- Liver and pancreas fat

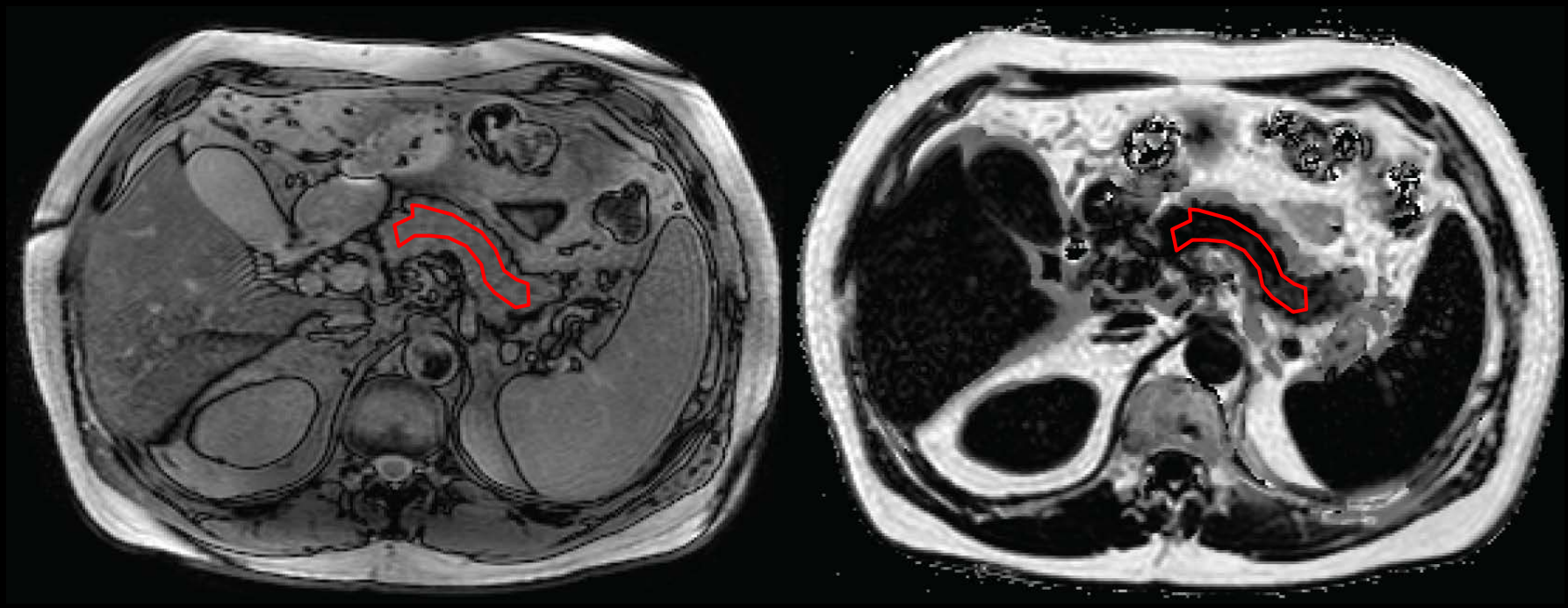


Very low calorie diet (~800 kcal/day)

0 1 4 8

Weeks

New magnetic resonance method allows measurement of organ fat content



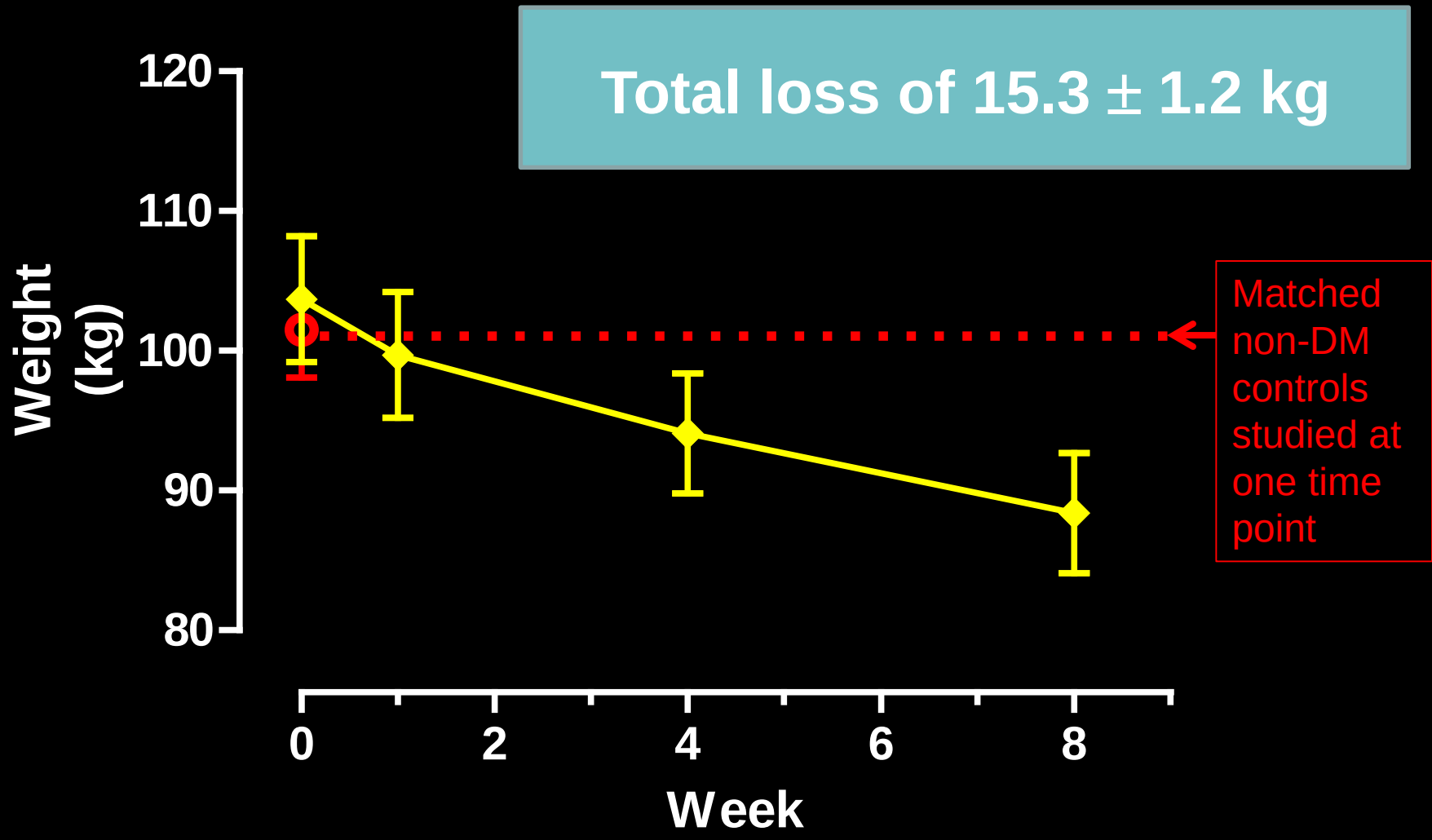
Detailed anatomical MRI scan

Fat map co-localised with scan

Bland-Altman reproducibility coefficients: Liver 0.5; Pancreas 0.9

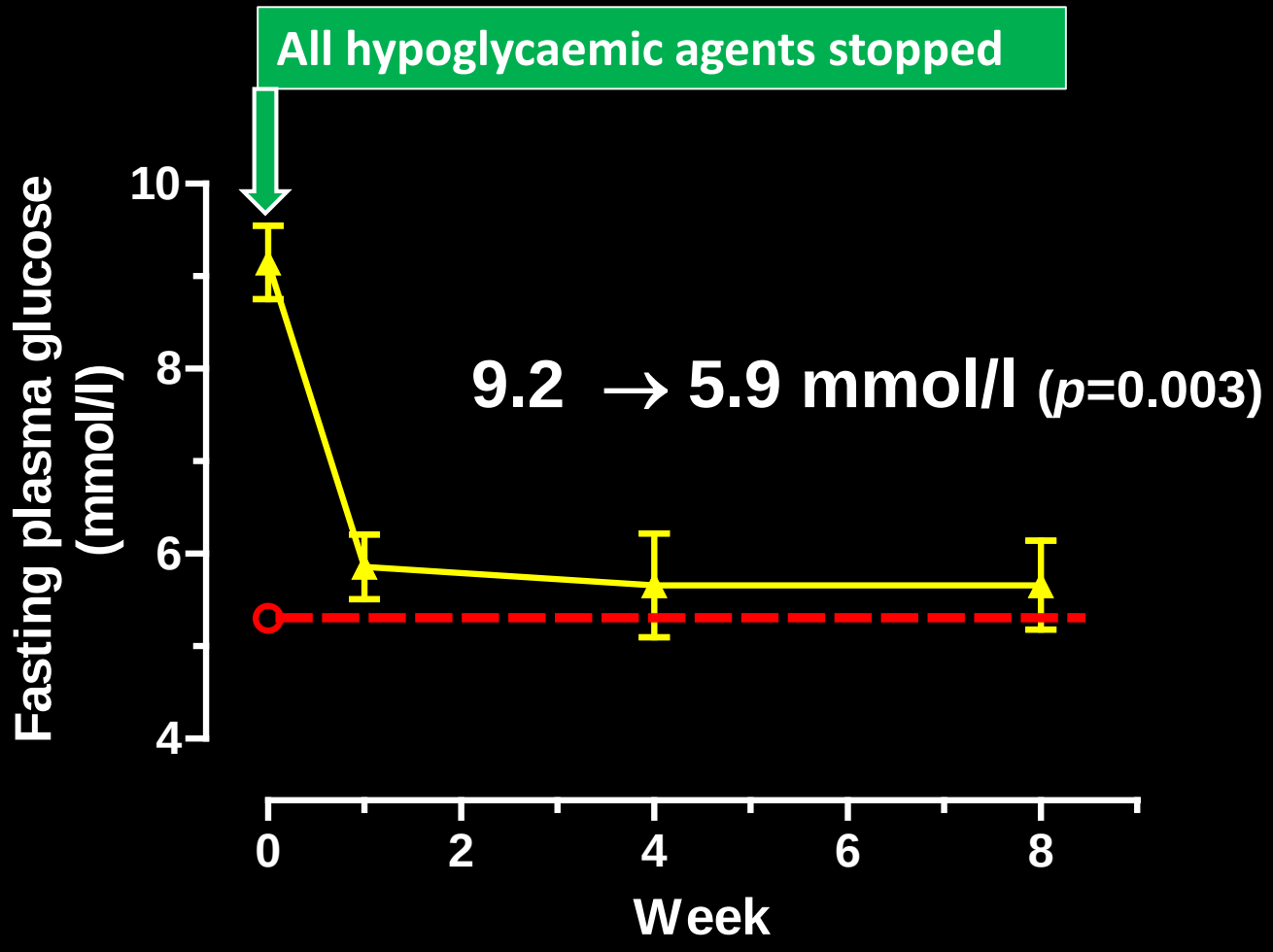
Method based on 3-point Dixon developed by Dr Kieren Hollingsworth

Body weight change during Counterpoint



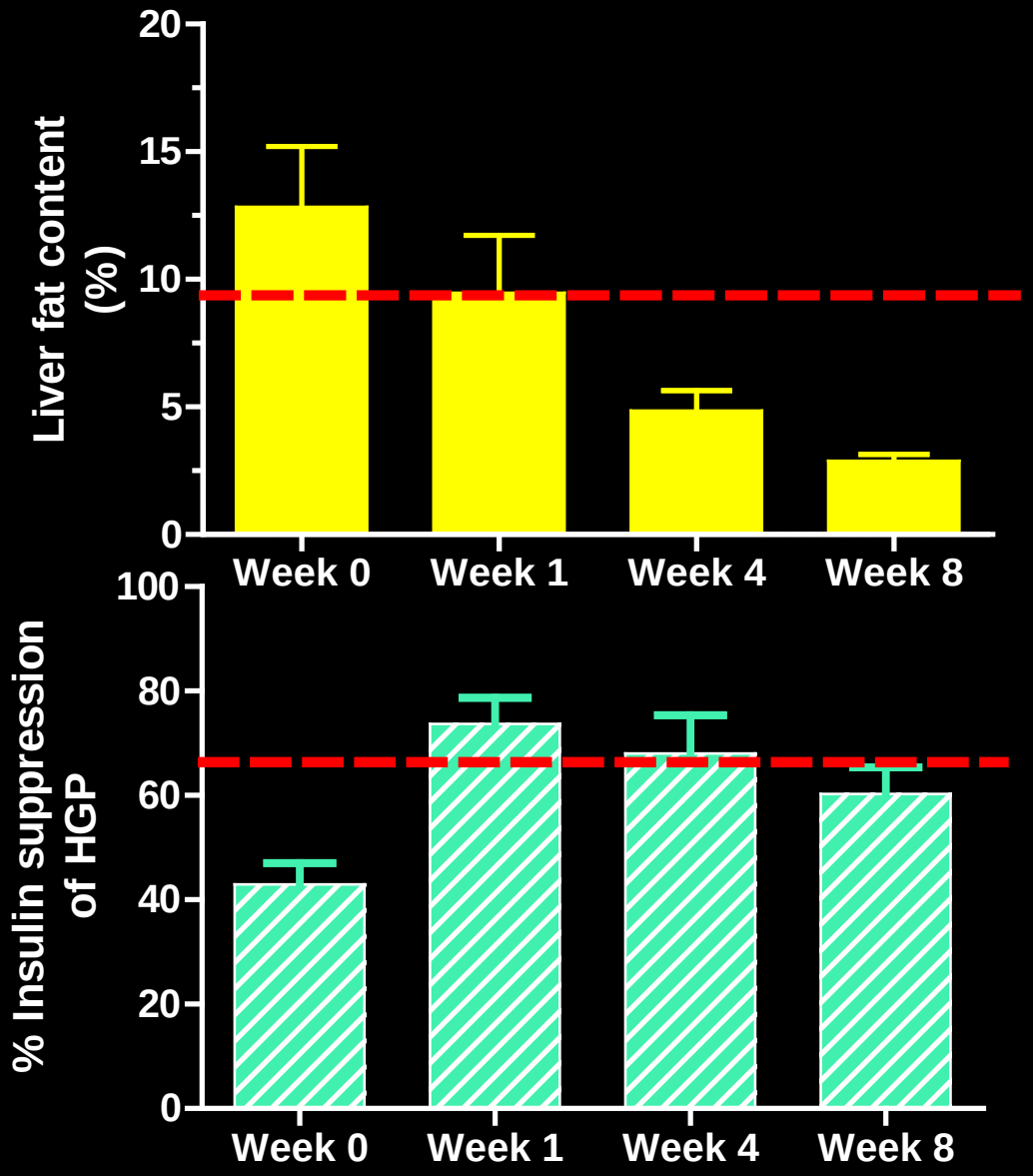
Lim et al, Diabetologia 2011

Counterpoint: Effect of VLCD on fasting glucose



Lim et al, Diabetologia 2011

Liver fat and liver insulin sensitivity - Counterpoint

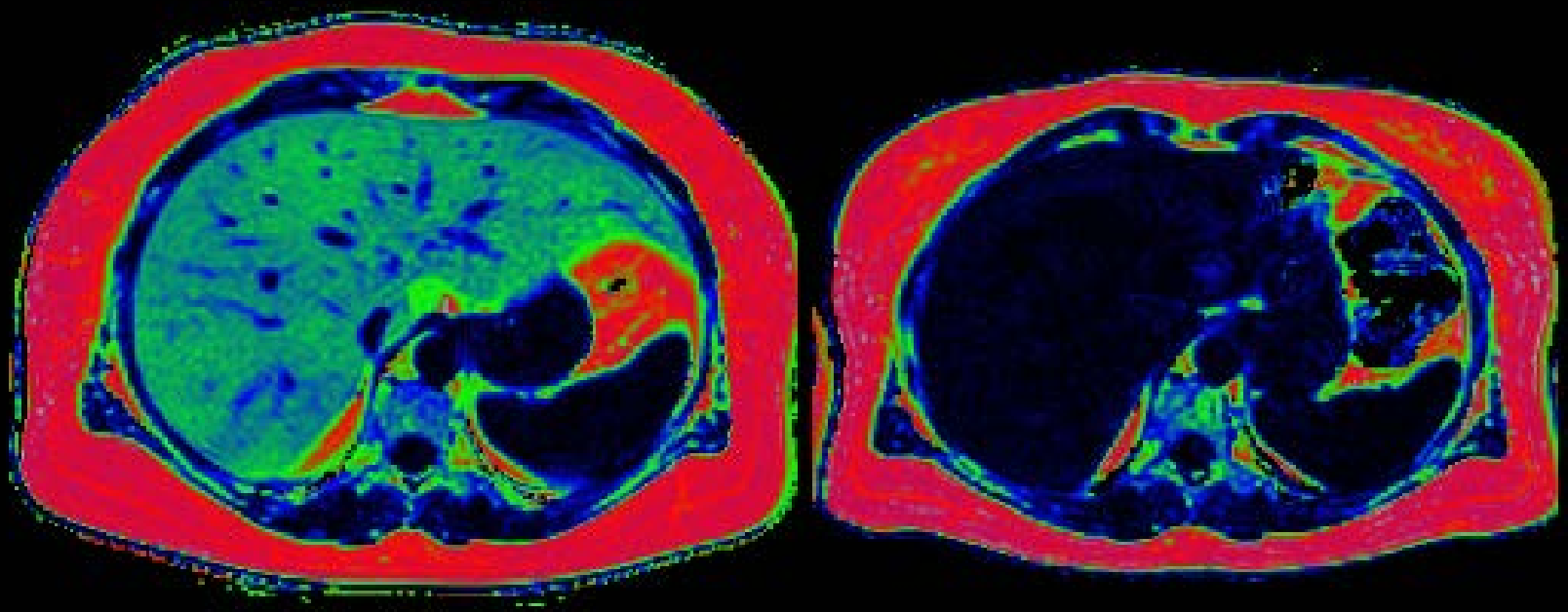


Dotted red lines show non-diabetic matched control data

As liver fat normalised - so did liver insulin sensitivity

Lim et al, Diabetologia 2011

Change in liver fat during 8 weeks of low calorie diet and reversal of Type 2 diabetes to normal



Colour key:
100%
0%

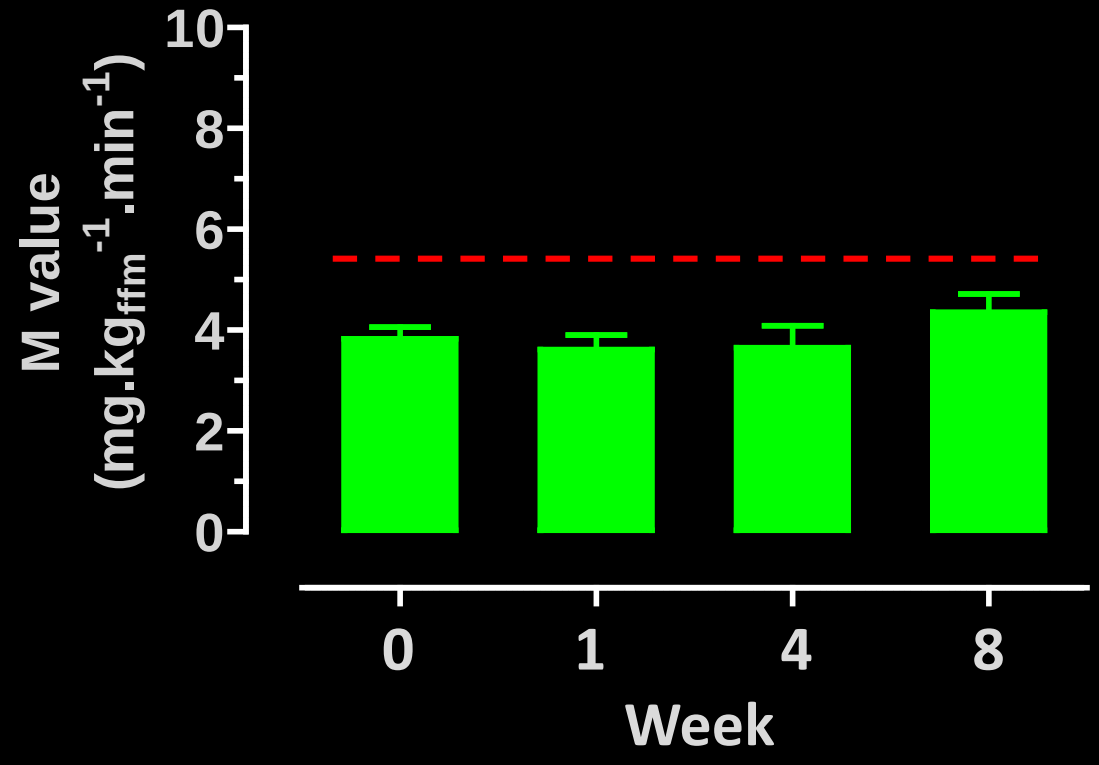
Baseline scan – liver is green

= 36% liver fat

8 weeks scan – liver is black

= 2% liver fat

Muscle insulin sensitivity assessed by isoglycaemic hyperinsulaemic clamp during Counterpoint



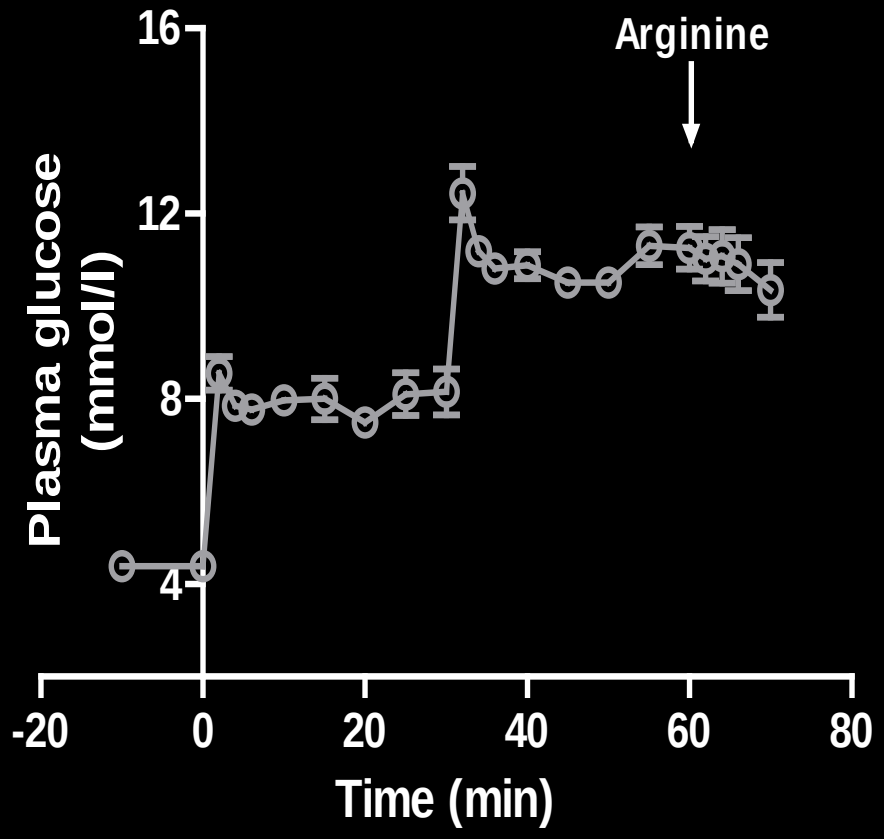
No change in muscle despite reversal of diabetes

Lim et al, Diabetologia 2011

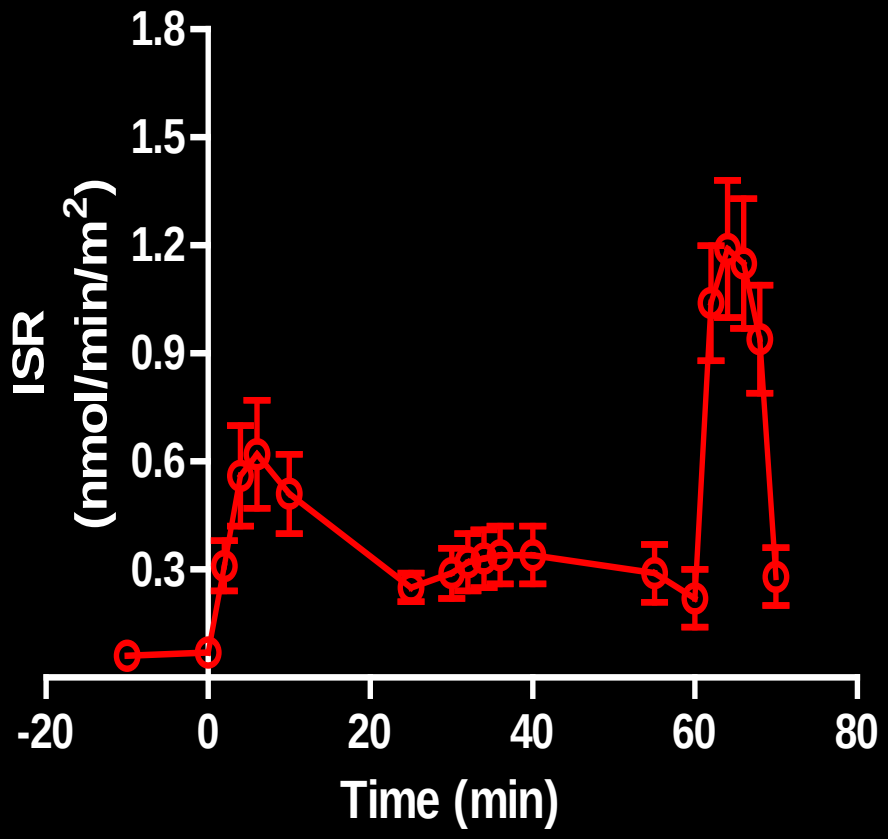
Beta cell function: Control subjects

Stepped Insulin Secretion Test with Arginine (SISTA)

IV glucose infused to achieve this plasma glucose profile:



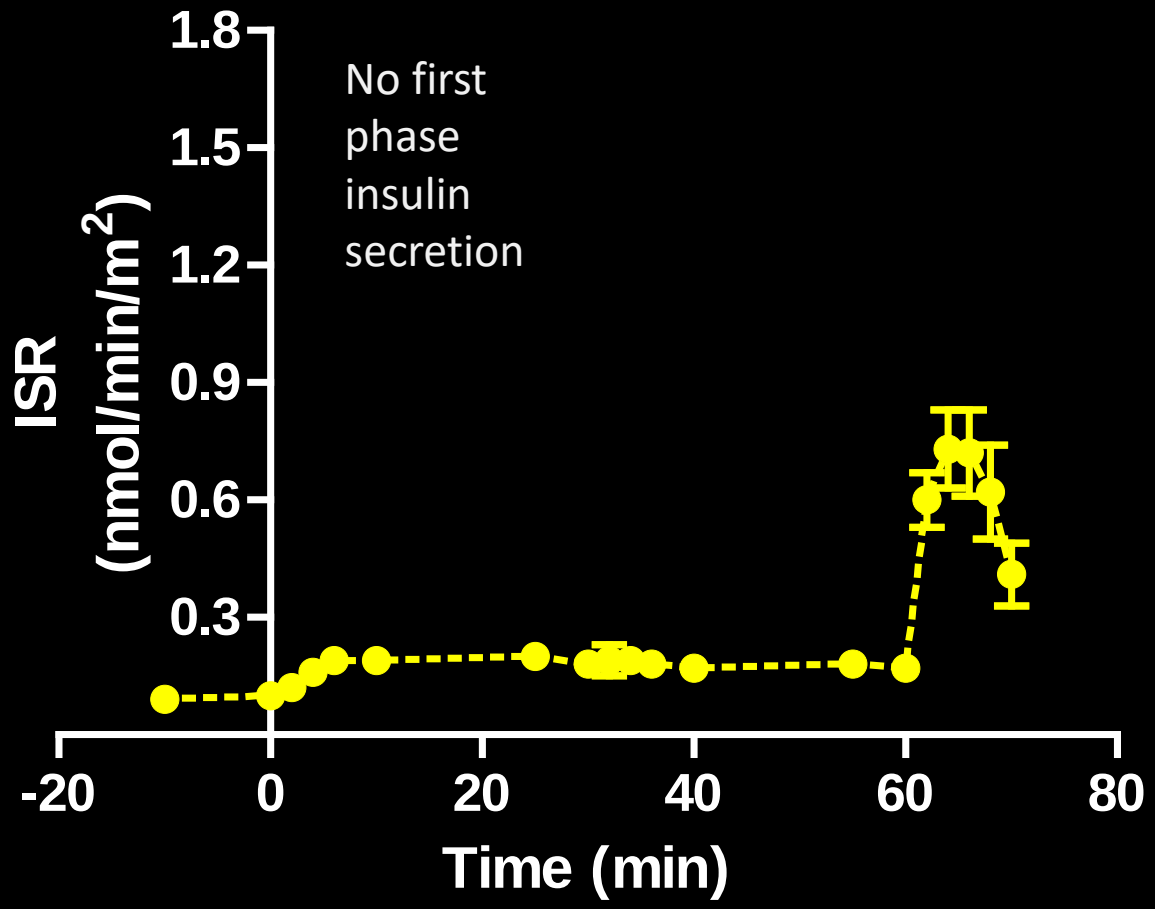
Observed insulin secretion rate:



Lim et al, Diabetologia 2011

Beta cell function: Diabetes subjects

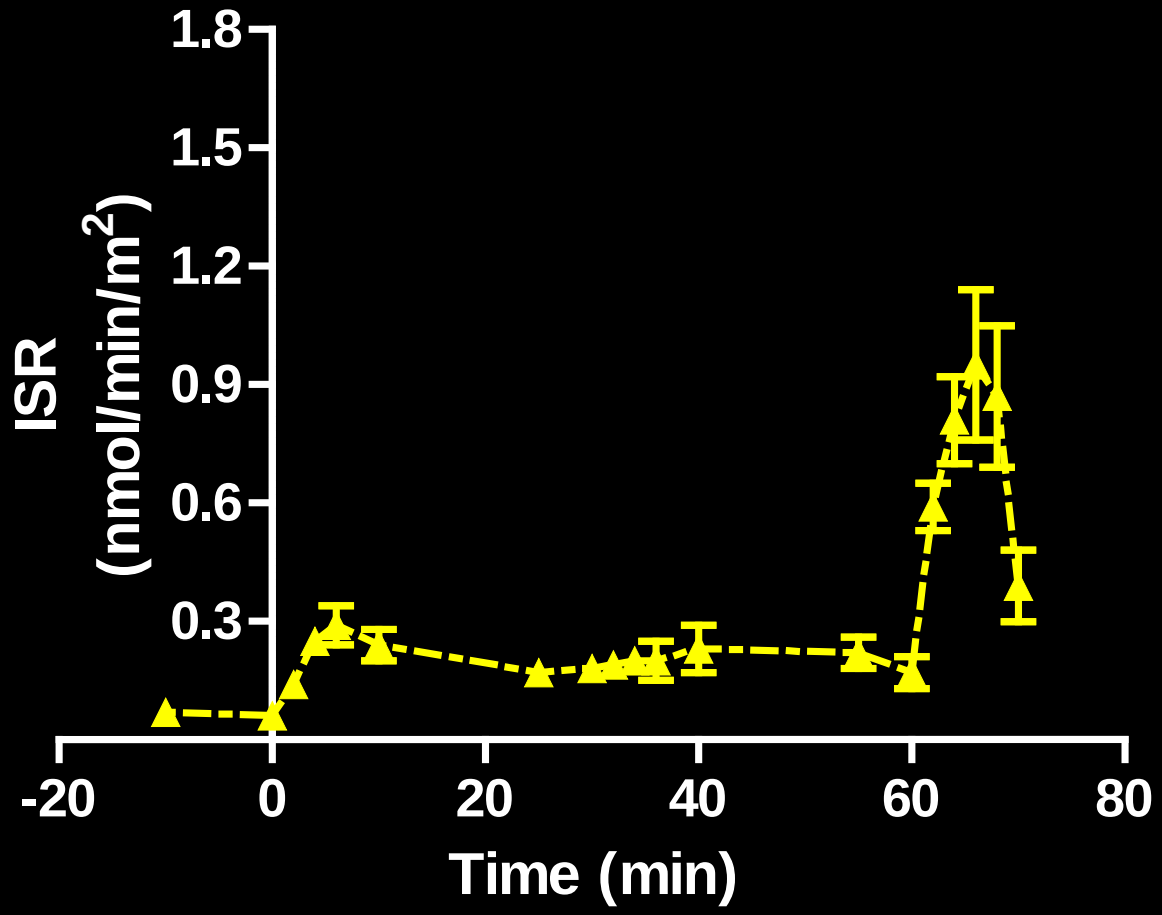
Baseline



Lim et al, Diabetologia 2011

Beta cell function: Diabetes subjects

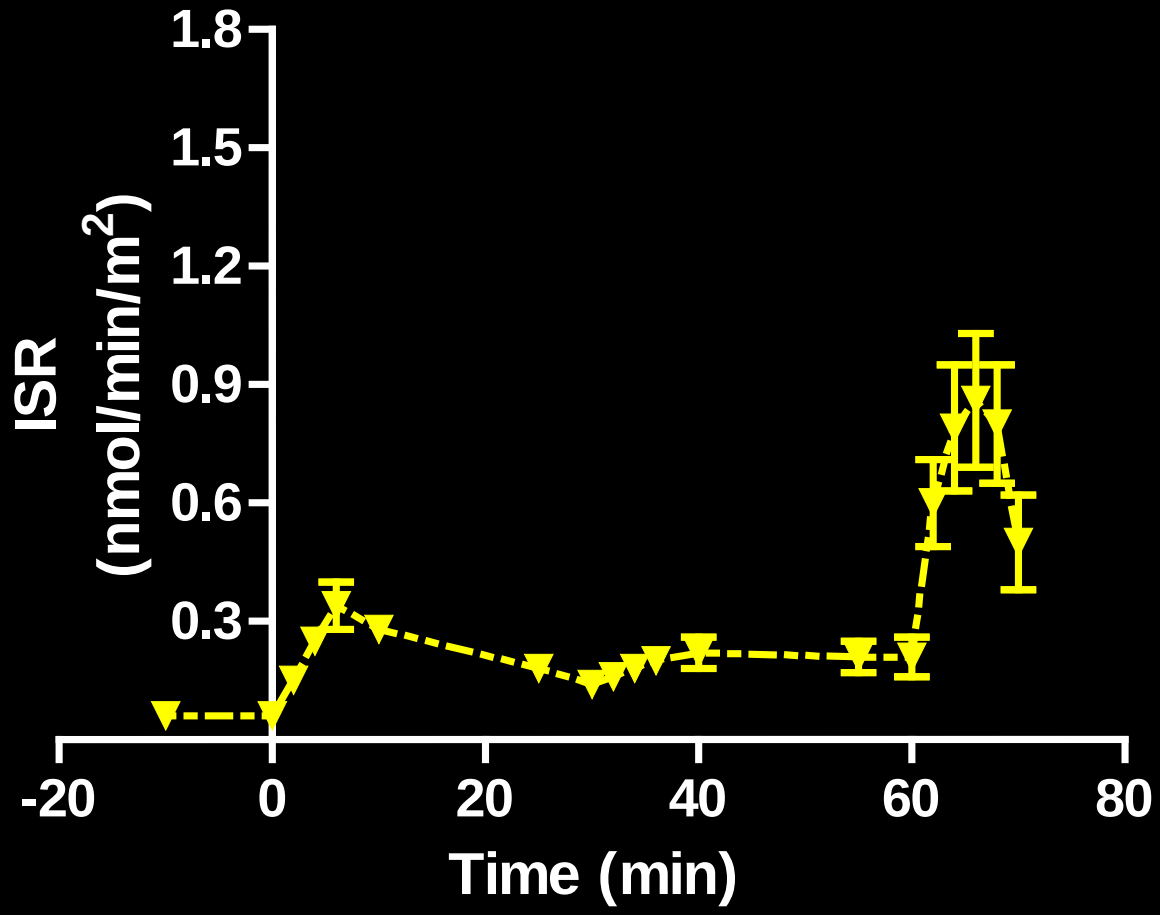
Week 1



Lim et al, Diabetologia 2011

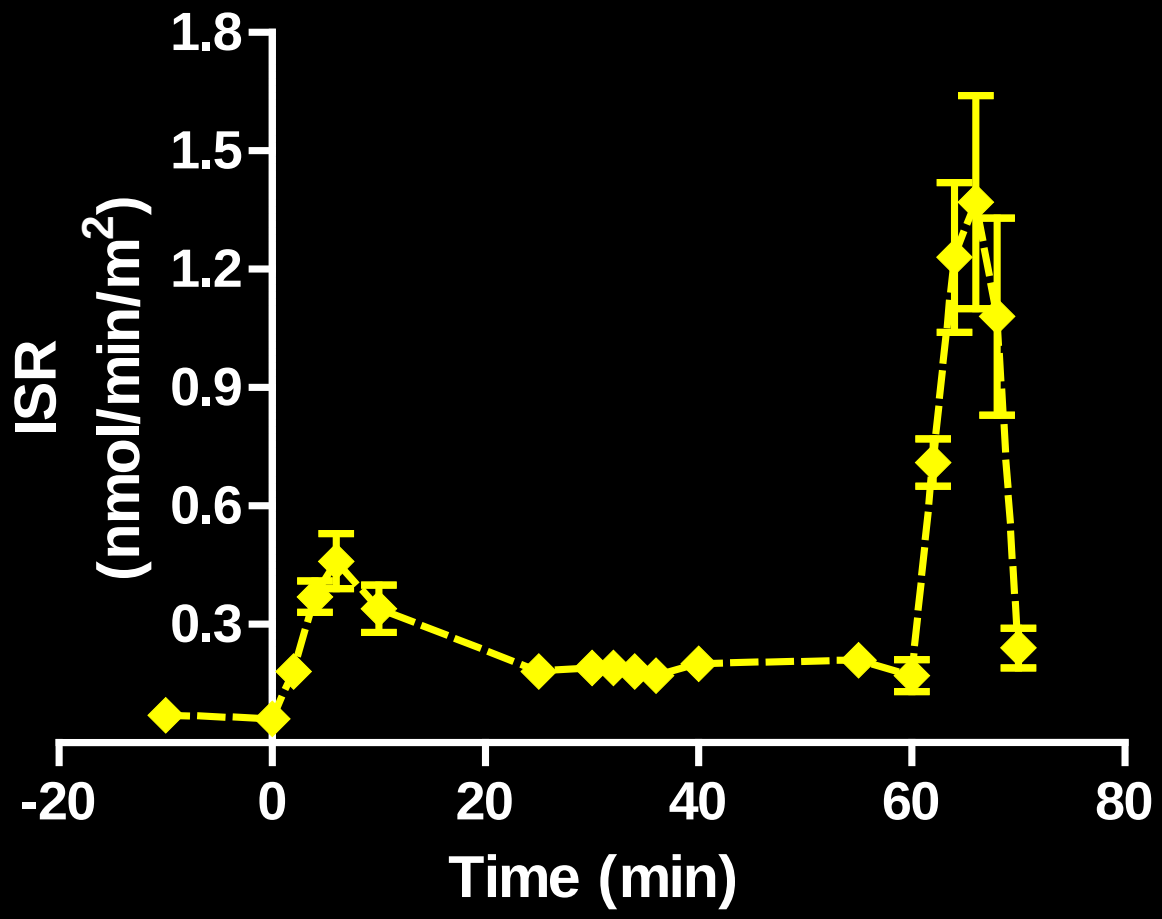
Beta cell function: Diabetes subjects

Week 4



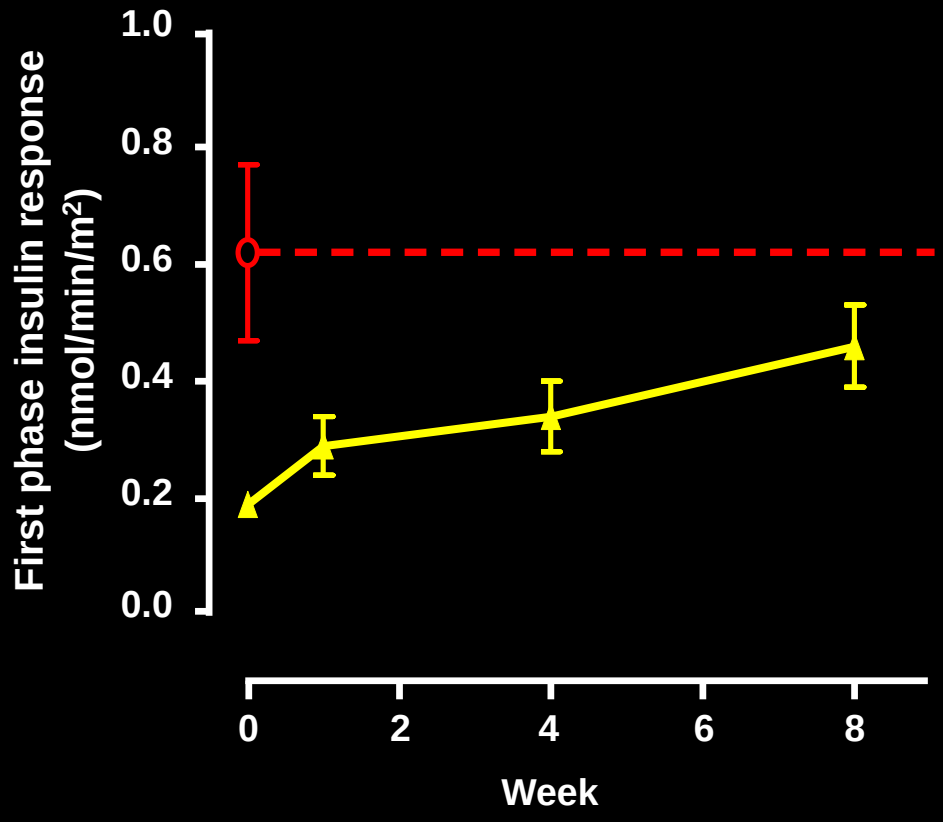
Lim et al, Diabetologia 2011

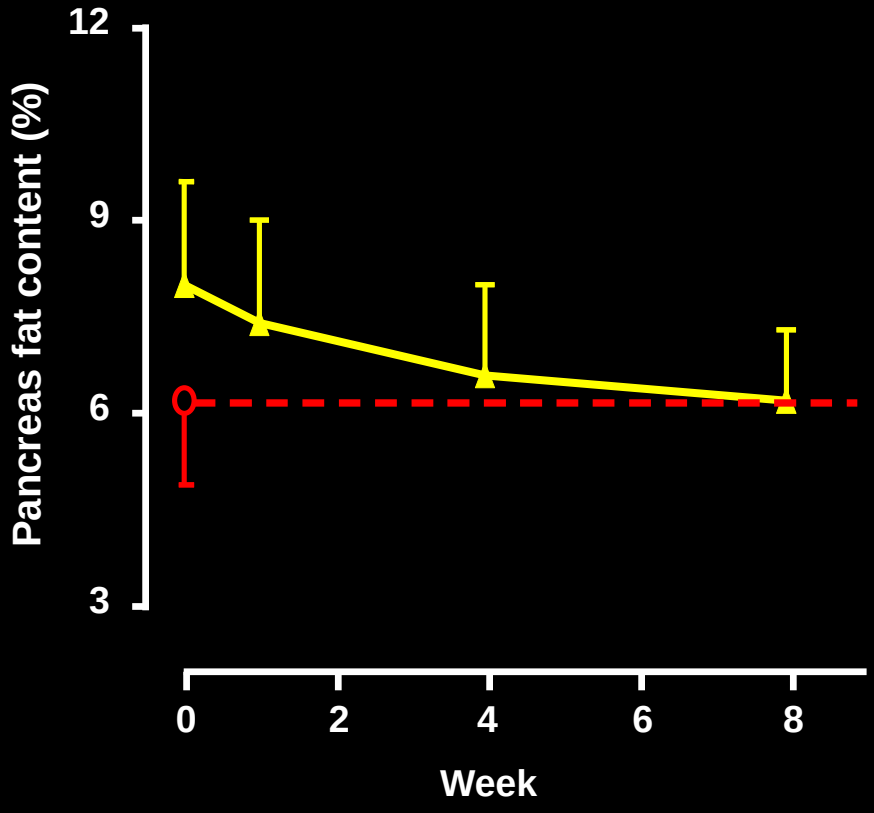
Beta cell function: Diabetes subjects



Lim et al, Diabetologia 2011

Change in beta-cell function and pancreas fat





Lim et al. Diabetologia 2011; 54: 2506–2514

Reversing the twin cycles of type 2 diabetes

Type 2 diabetes is a simple condition of fat excess to which some people are more susceptible than others

Health-motivated people can reverse their diabetes

This knowledge must not be used as a stick with which to beat people who do not want to change their lives

The twin cycle hypothesis

Substantial weight loss in people with type 2 diabetes will:

Liver

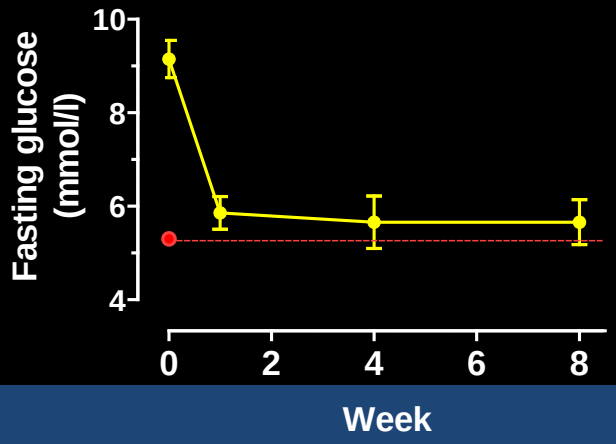
Decrease fat – improve insulin action and normalise overnight blood sugar

and

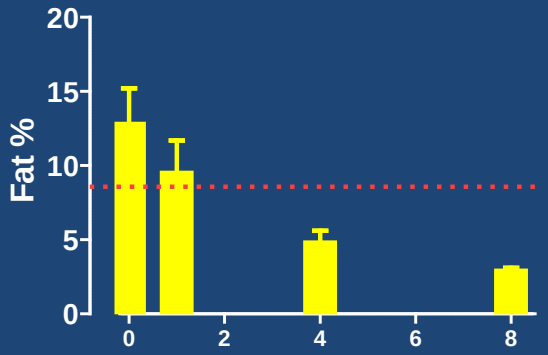
Pancreas

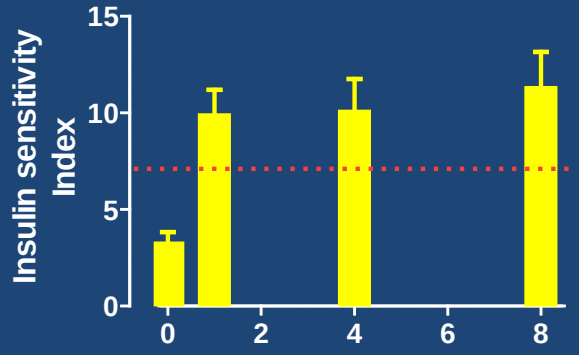
Decrease fat – normalise the insulin response to eating

The Counterpoint study – Type 2 diabetes, 800kcal diet

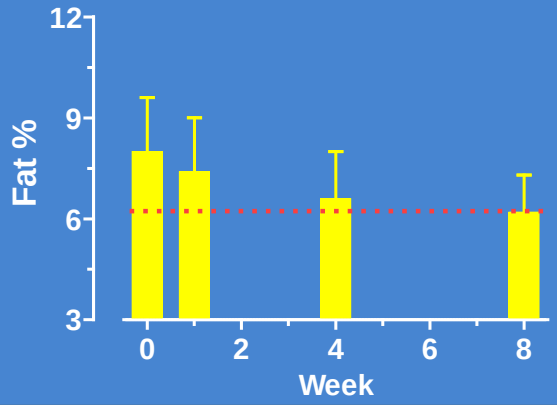


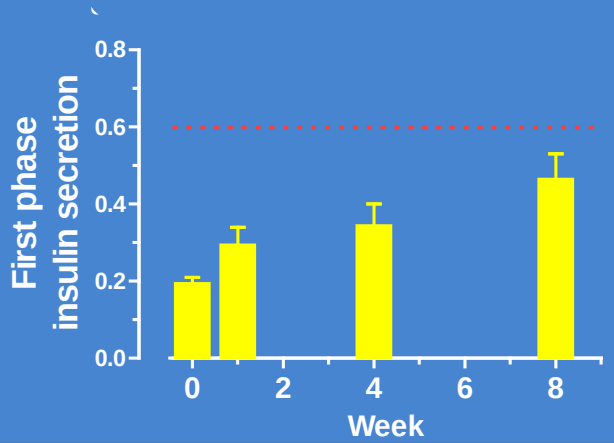
Liver



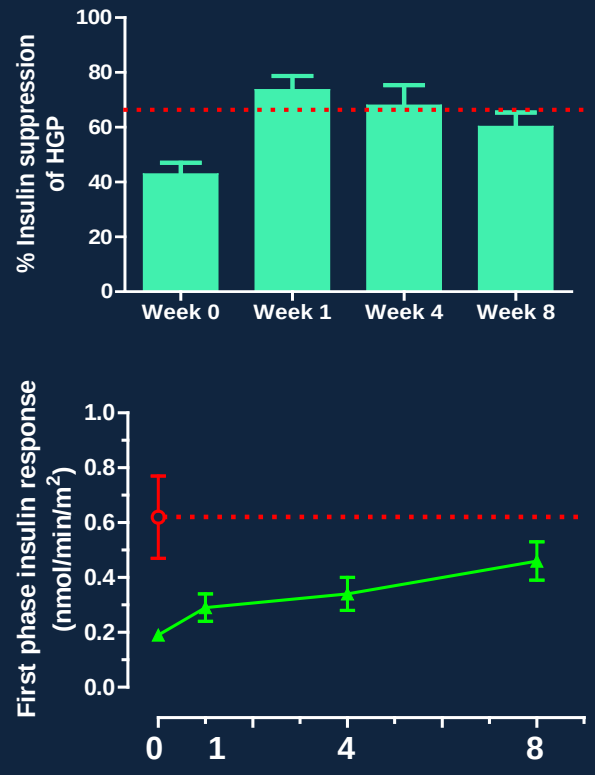


Pancreas





Reversibility of type 2 diabetes



The pathophysiological defects in the liver and pancreas are reversible – if diabetes duration <4yr

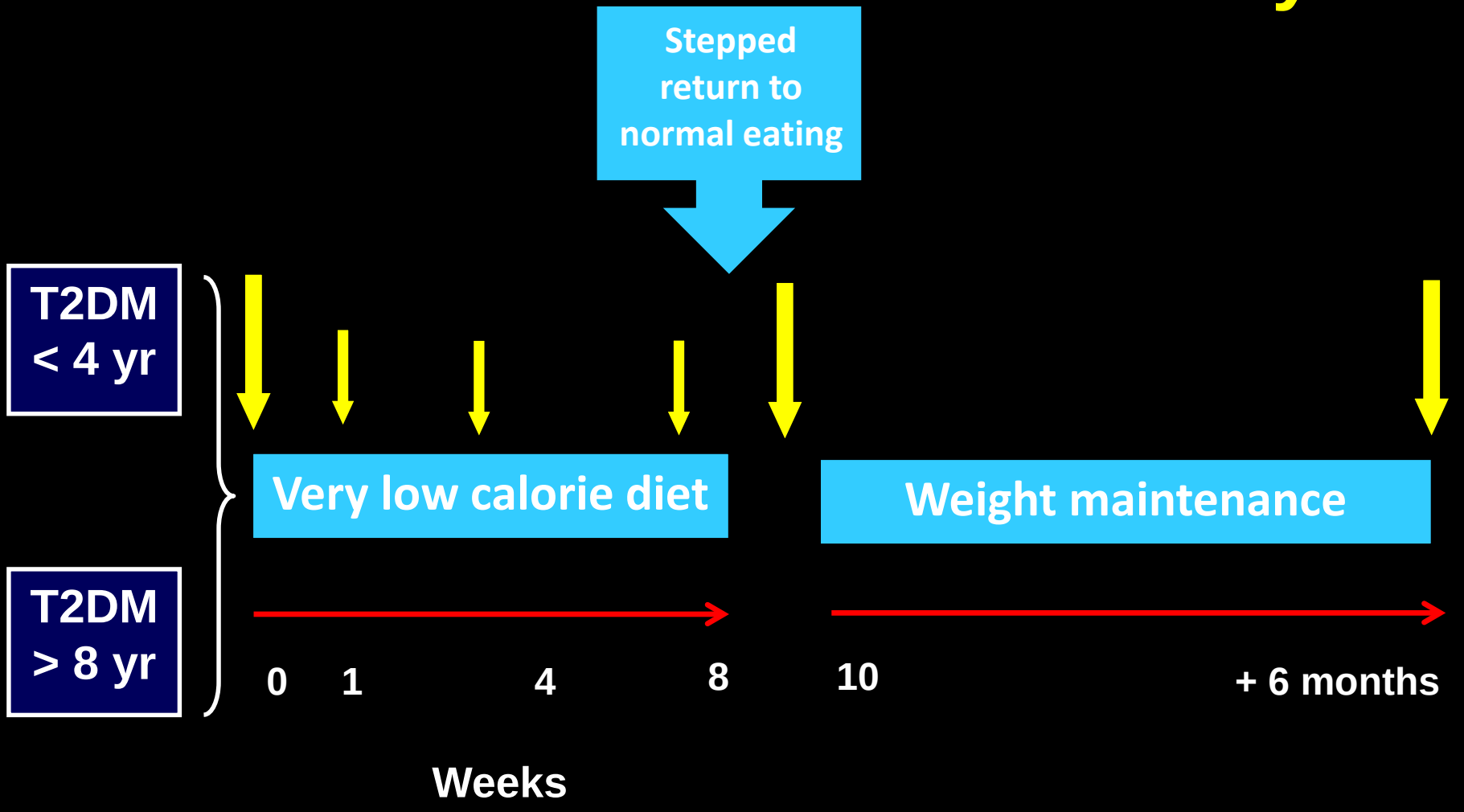
Can long duration type 2 diabetes also be reversed?

The Counterbalance Study –

Counteracting BetA cell failure by Long term Action to Normalize Calorie intakE

Questions:
Can people with longer duration type 2 diabetes reverse to normal?
Is the reversal of type 2 diabetes durable if body weight remains stable?

Protocol for CounterBalance study

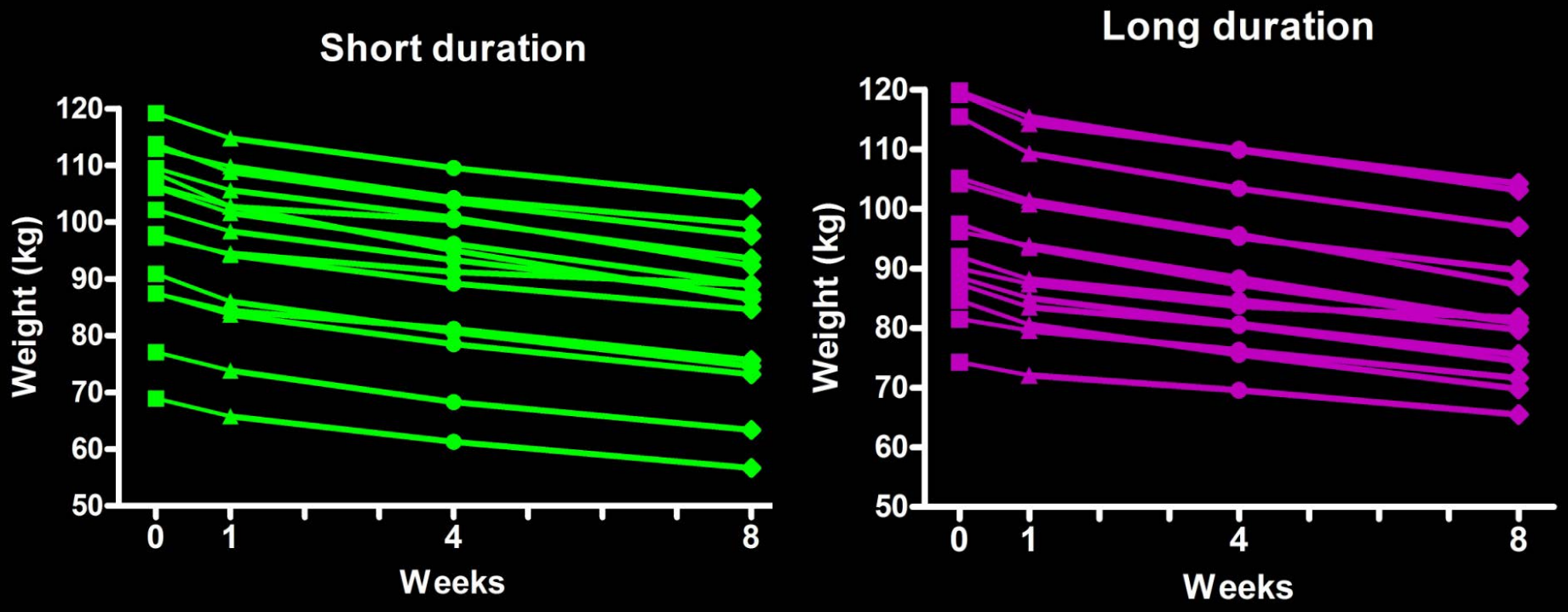


Counterbalance Subjects

Diabetes duration	0-4y (n=15)	8-23y (n=14)
Age (yr)	52.1 ± 2.6	61.6 ± 2.0
Weight (kg)	99.0 ± 3.7	96.9 ± 3.8
BMI (kg/m^2)	34.6 (27.6-38.0)	33.0 (29.4-45.7)

Steven et al Diabetic Med 2015

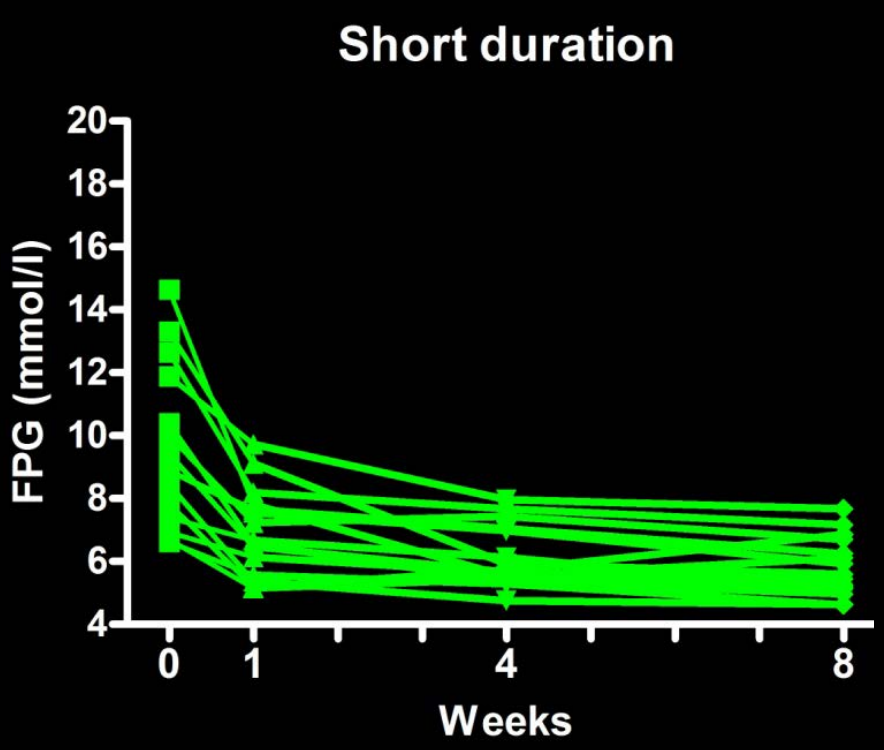
Results: weight loss during diet

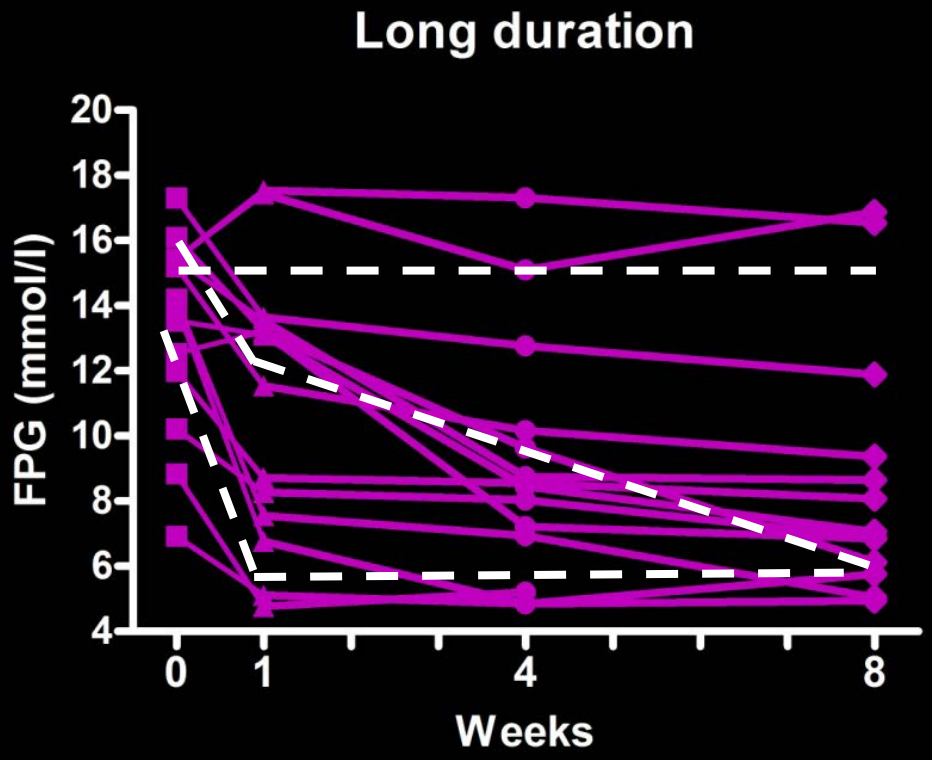


Weight loss: 14.6 ± 0.8 % vs. 14.5 ± 0.7 %

p=0.662

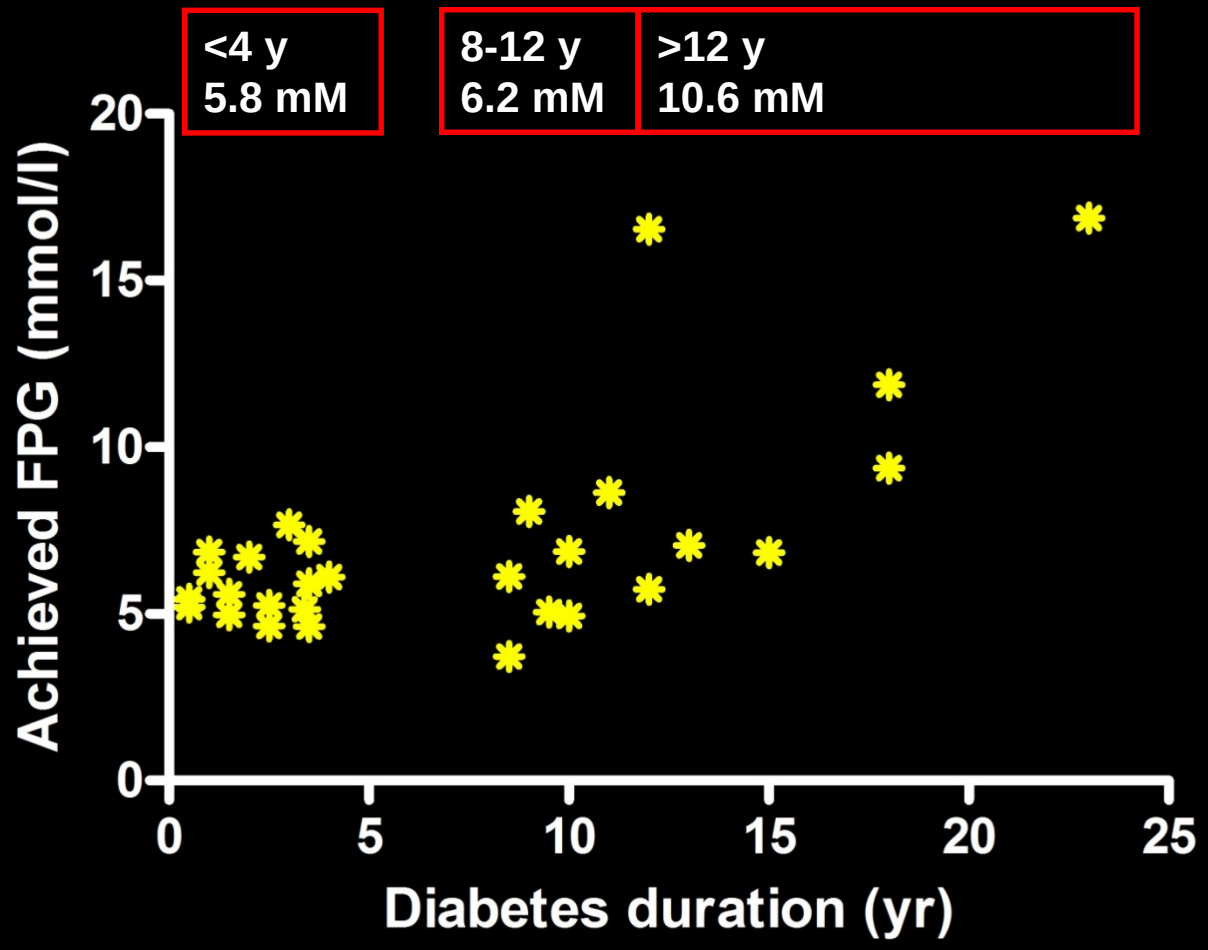
Fasting plasma glucose during diet





Steven et al Diabetic Med 2015

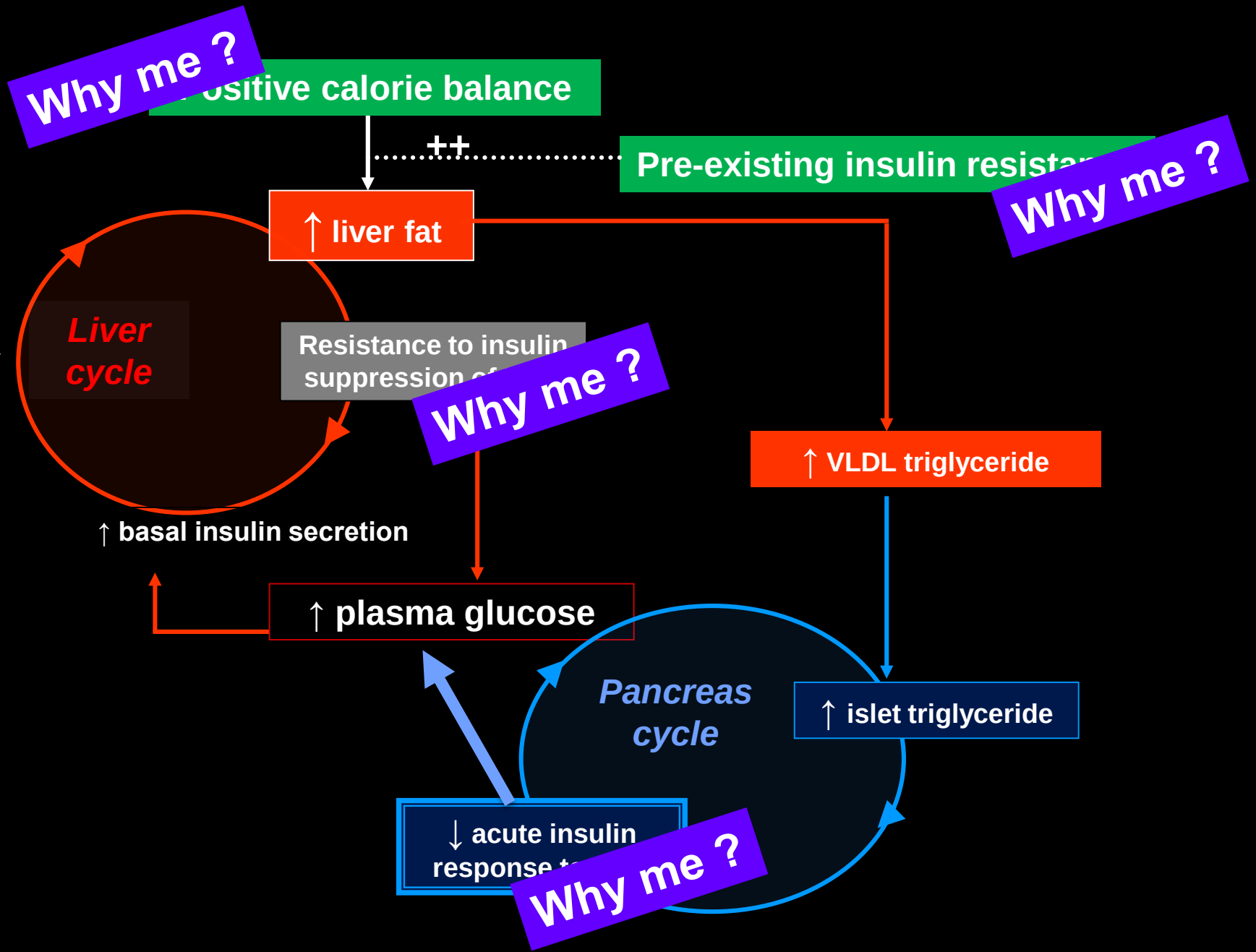
By diabetes duration



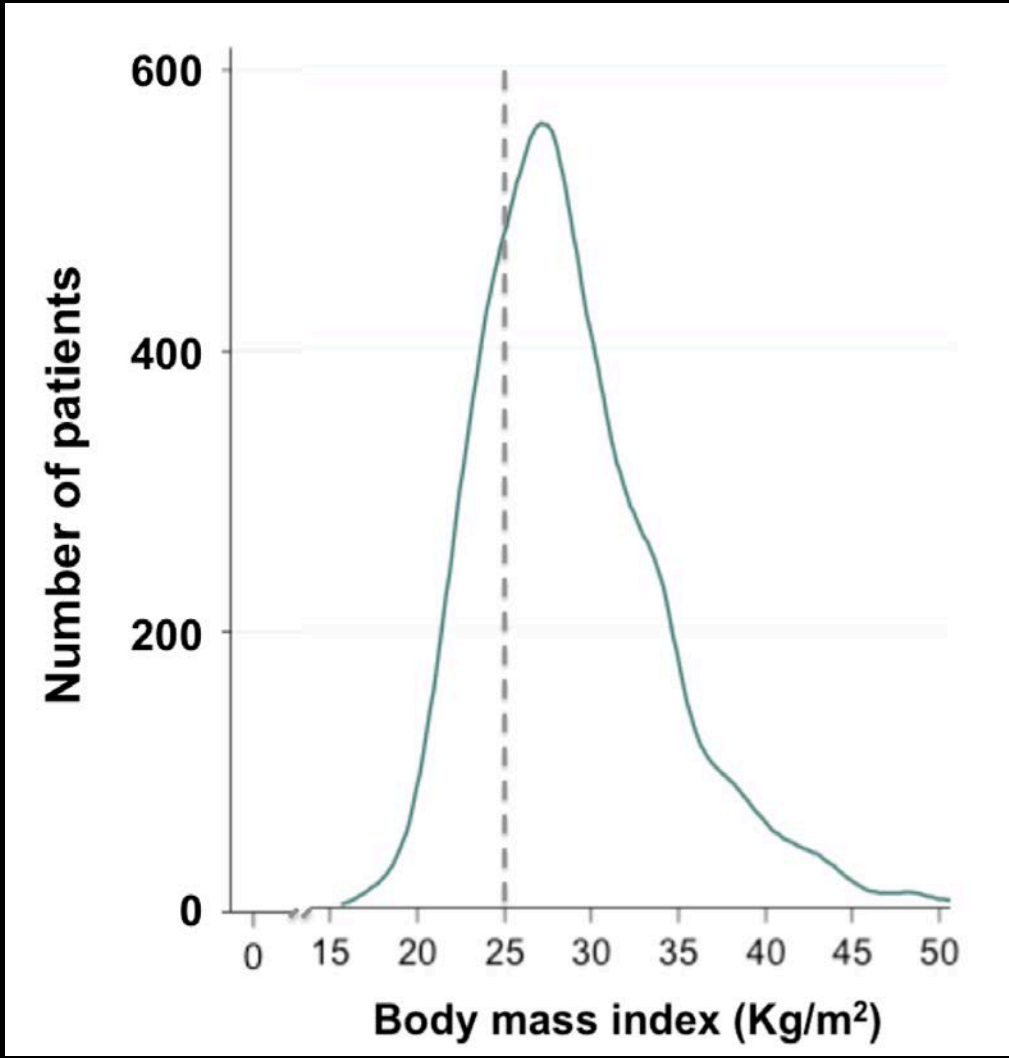
Spearman 0.501; p=0.006

Steven et al Diabetic Med 2015

Aetiology of type 2 diabetes: twin-cycle hypothesis

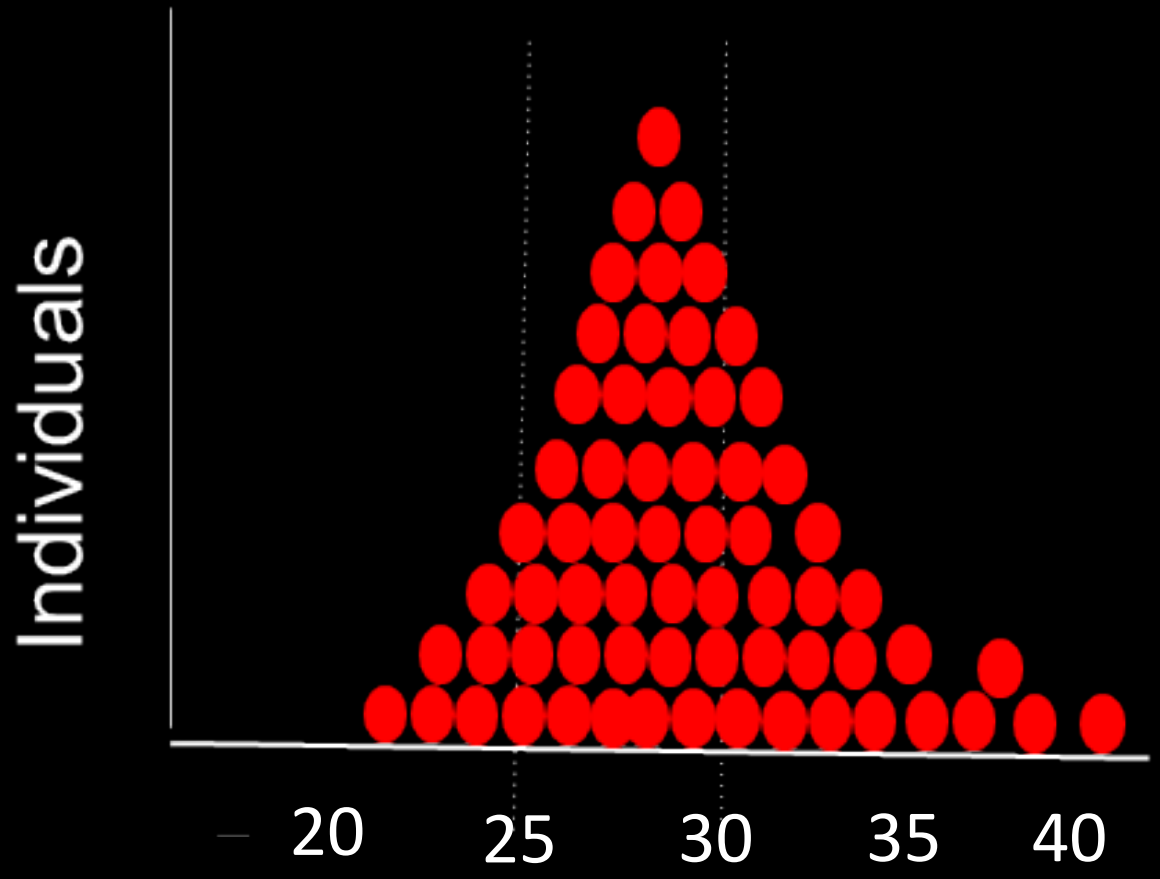


BMI distribution of participants – Start of UK Prospective Diabetes Study



Taylor & Holman, Clin Sci **128: 405-410** *2015*

BMI distribution of individuals with type 2 diabetes



Taylor & Holman, Clin Sci **128: 405-410** *2015*

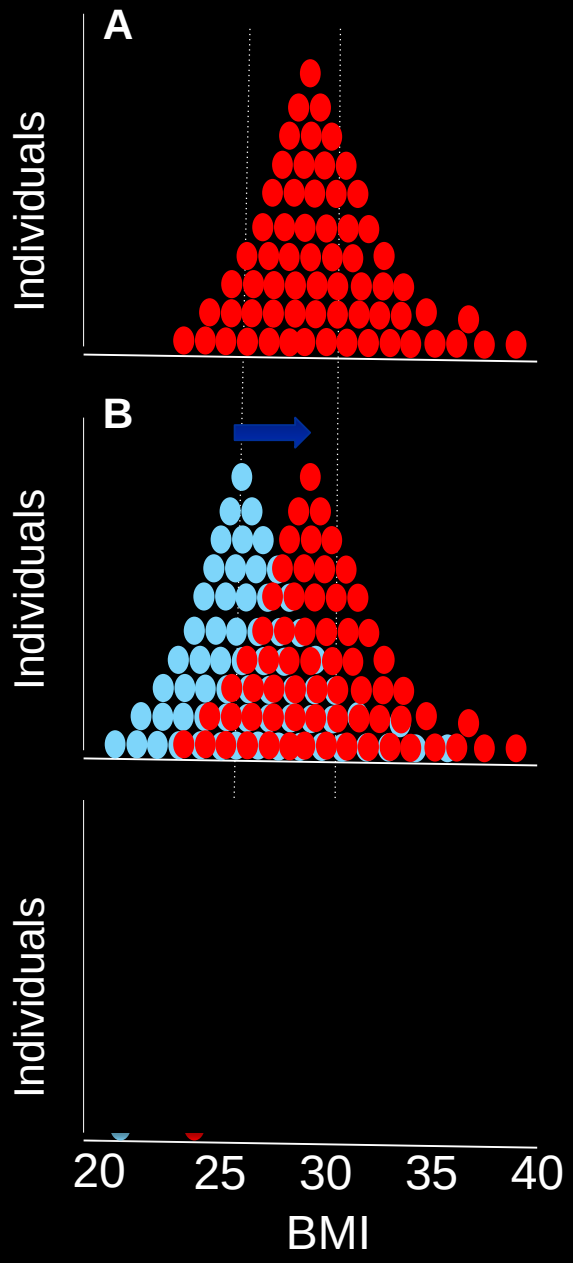
Personal vs population

The top panel shows the BMI distribution of individuals at diagnosis of type 2 diabetes.

However, a generation ago, the alter egos of those people would have been ~15 mg lighter and would not have had diabetes (blue dots).

OR –

If those people with T2DM lose 15kg, they lose their type 2 diabetes

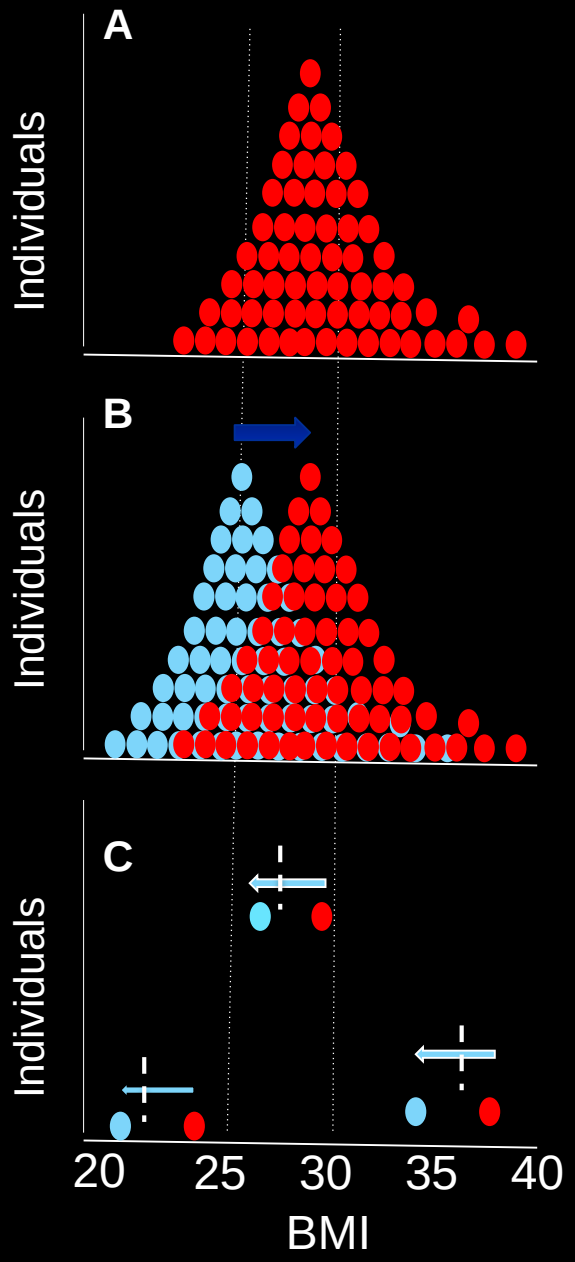


Taylor & Holman, Clin Sci **128: 405-410** *2015*

Personal vs population

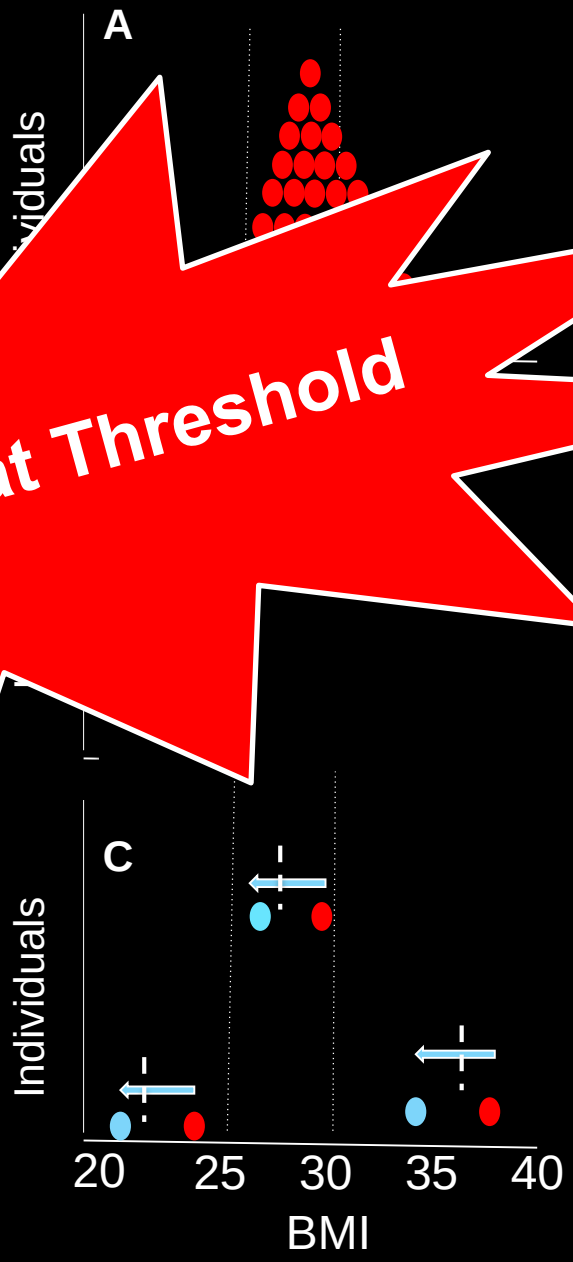
Take 3 individuals for example.
Each lost 15kg and reversed their diabetes. But by BMI criteria they remain obese, overweight and normal respectively.

Each individual must have crossed a threshold of fat mass, personal to them.



Taylor & Holman, Clin Sci **128: 405-410** *2015*

Personal vs population

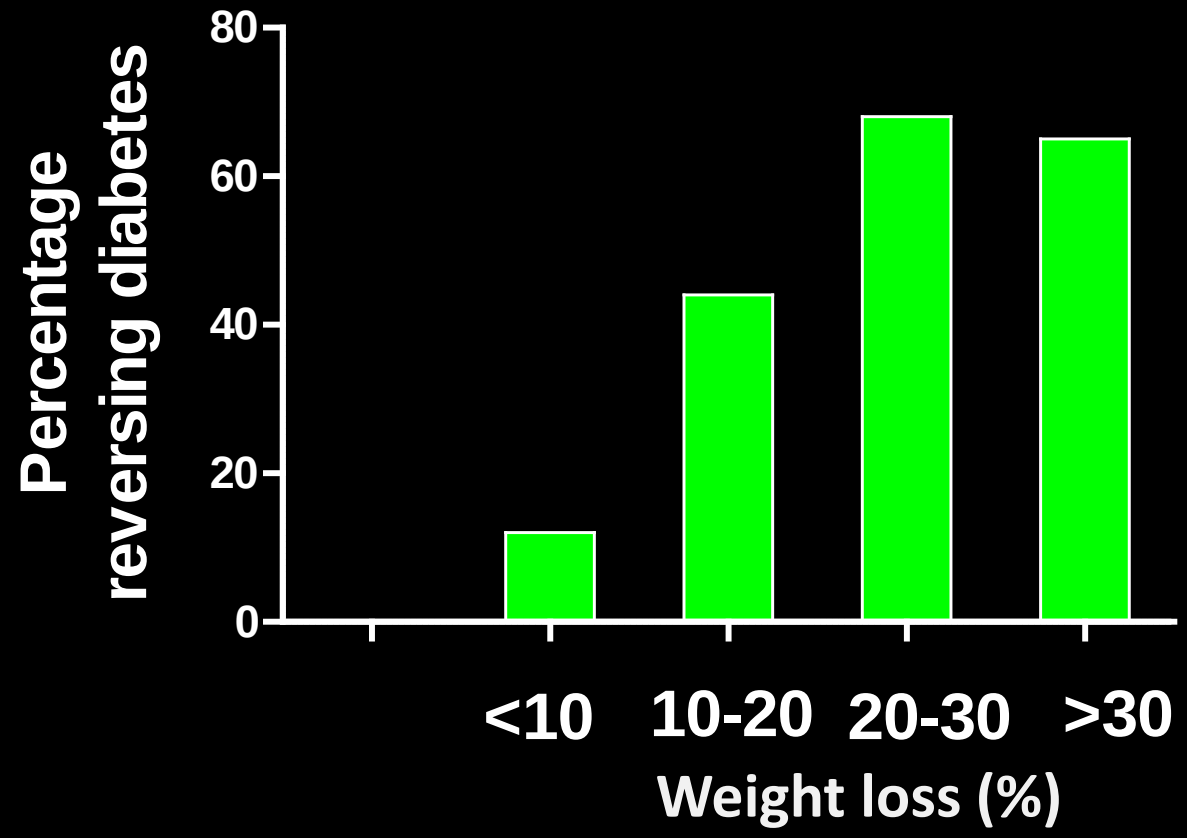


The Personal Fat Threshold

explains the "Why me" factor – indivduals have personal capacity to store fat safely. If the PFT is exceeded, T2DM slowly develops.

Taylor & Holman, Clin Sci **128: 405-410** *2015*

Amount of weight lost and effect on reversal of diabetes – 92 people after bariatric surgery



Steven, Carey, Small & Taylor; Diabetic Med 2014

The Pancreas Study –

Question:
Is the decrease in triglyceride content of the pancreas specifically related to type 2 diabetes and it reversal?
Or is it merely a generalised effect of loss of fat from the body?

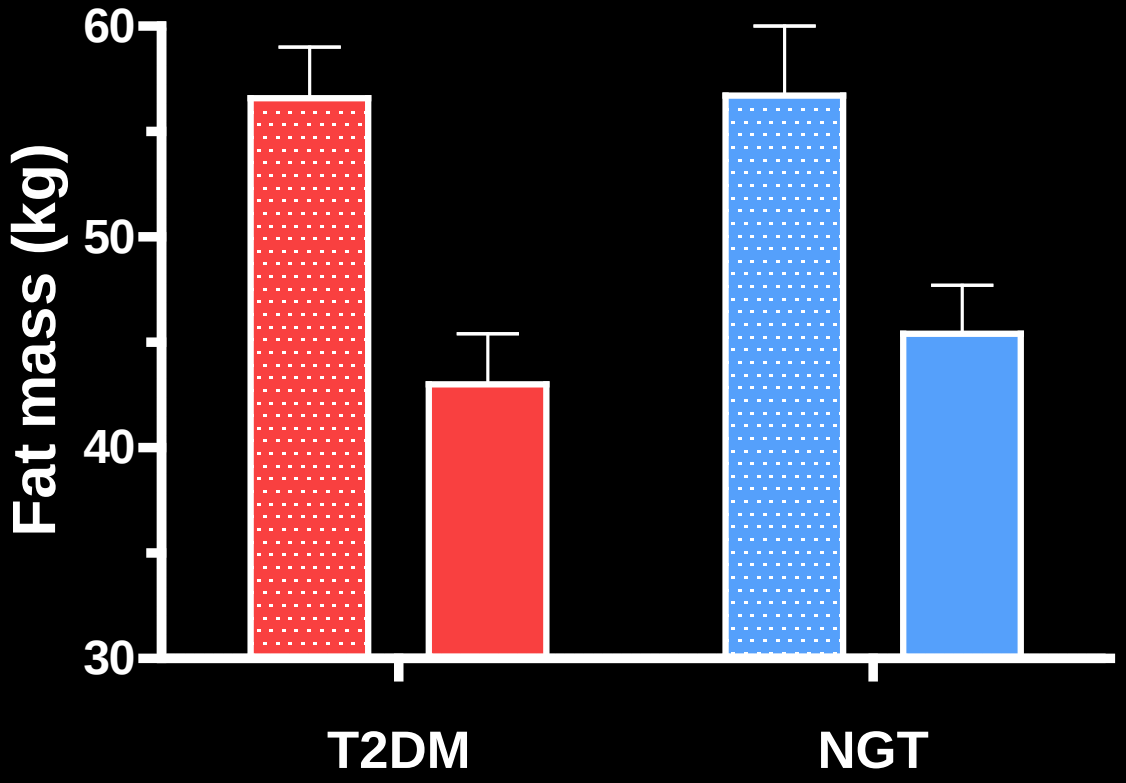
Design:
Compare pancreas triglyceride in matched groups of people with and without type 2 diabetes undergoing identical weight loss

Baseline subject characteristics

	Type 2 DM n=18	NGT N=9
Age (yr)	49.1 ± 1.6	46.3 ± 2.1
Weight (kg)	121.0 ± 3.0	114 ± 5.0
BMI (kg/m^2)	42.7 ± 0.7	41.3 ± 1.0

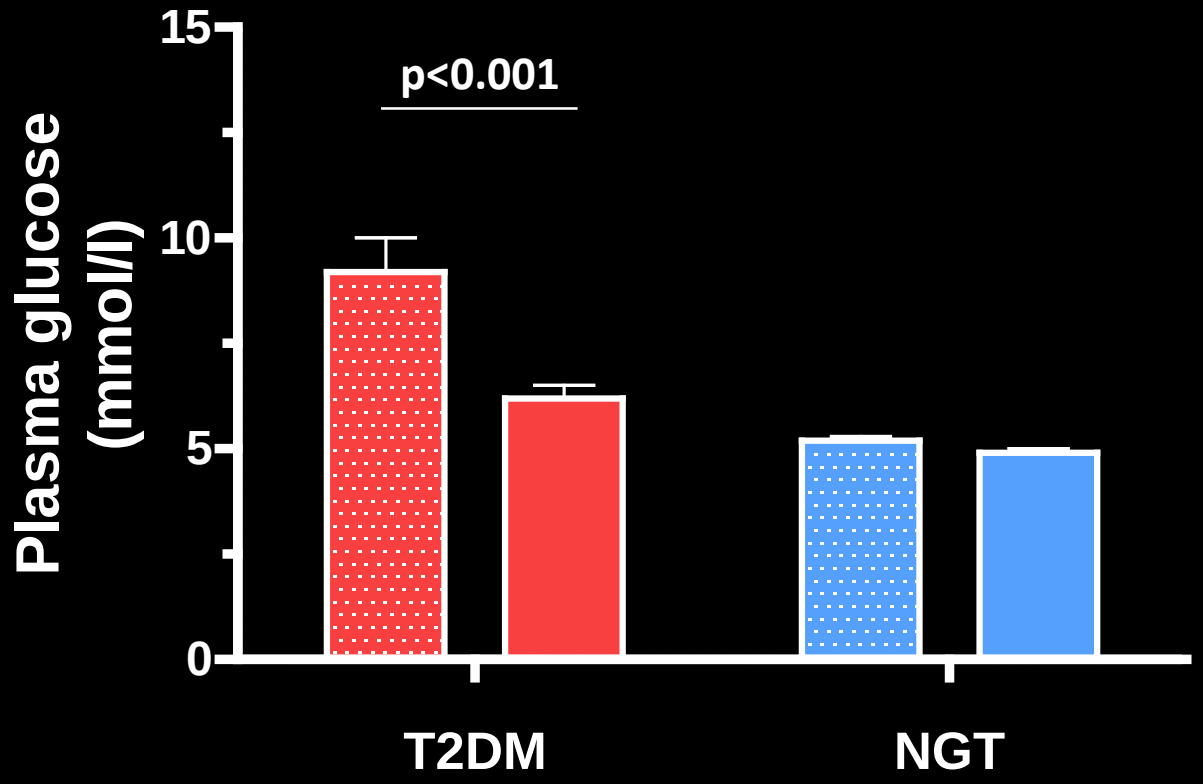
Steven et al, Diabetes Care 39(1):158-65; *2016*

Fat mass in type 2 diabetic and normal glucose tolerance groups – before and after weight loss



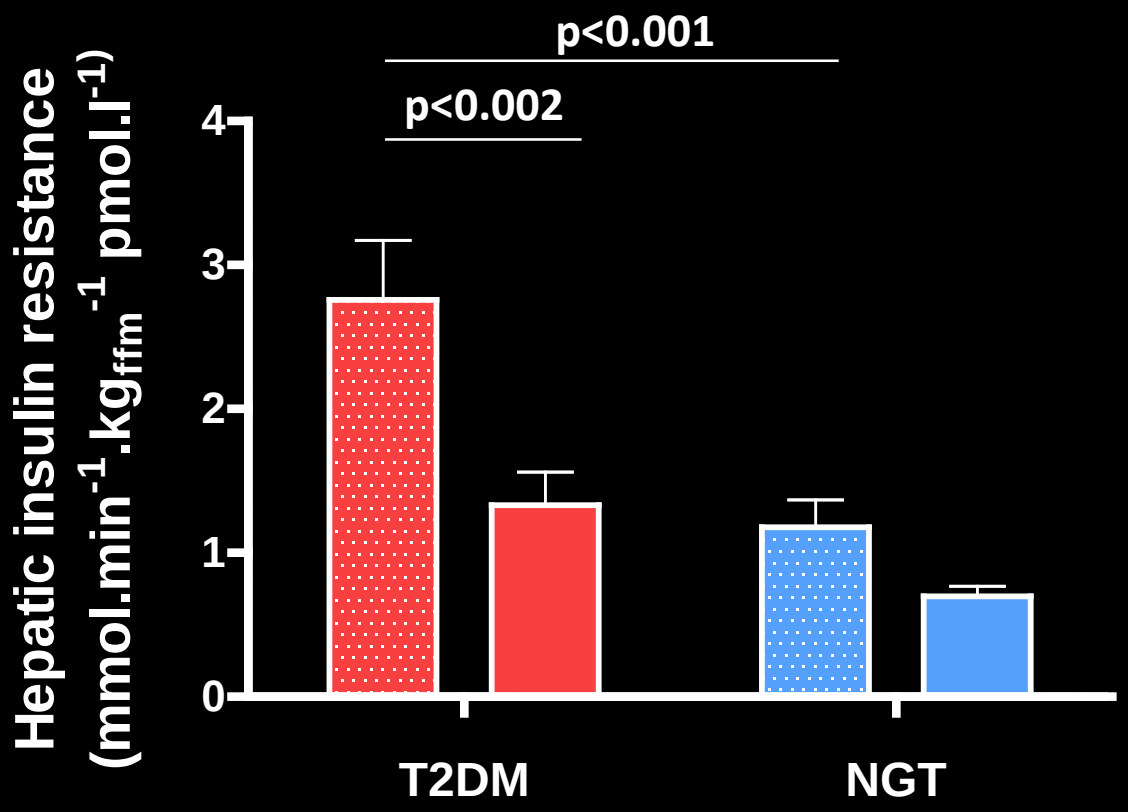
Decrease body weight	13.6±0.7%	12.8 ± 0.8%

Fasting plasma glucose in T2DM and NGT – Before and after weight loss



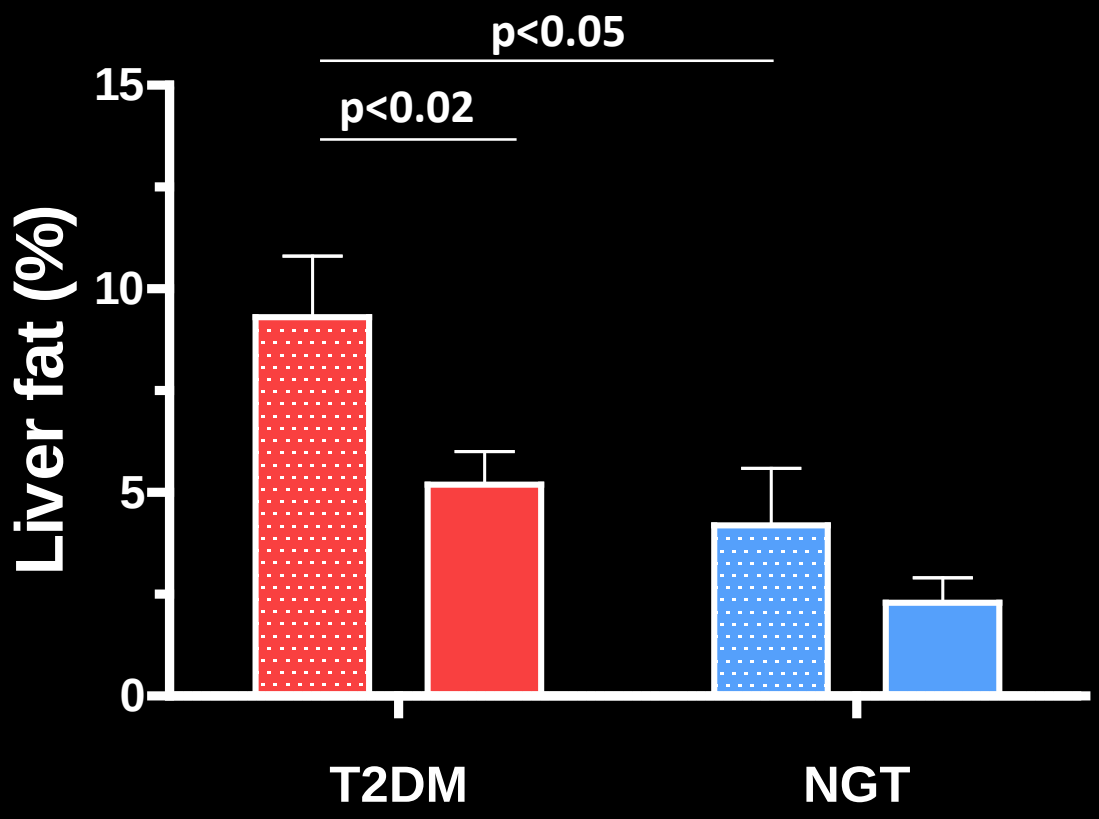
Steven et al, Diabetes Care 39(1):158-65; *2016*

Hepatic insulin resistance in T2DM and NGT – before and after weight loss



Steven et al, Diabetes Care 39(1):158-65; *2016*

Liver fat in T2DM and NGT – before and after weight loss

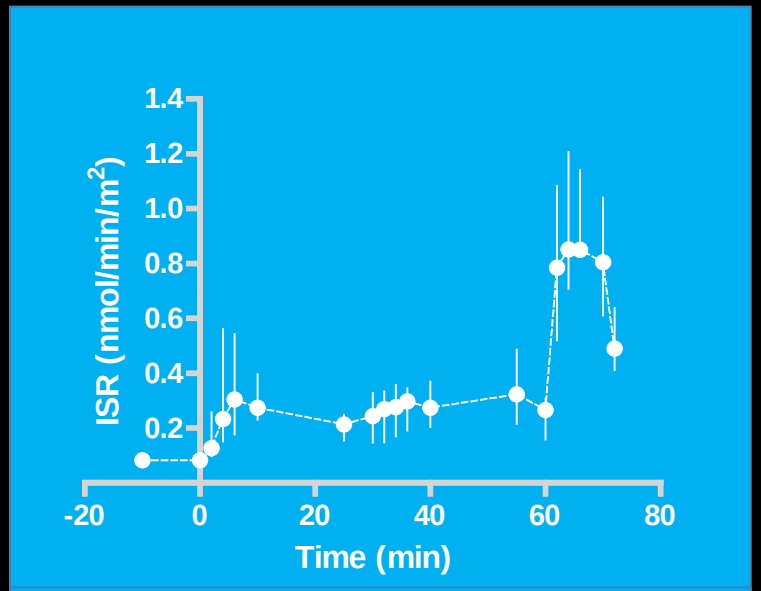


Steven et al, Diabetes Care 39(1):158-65; *2016*

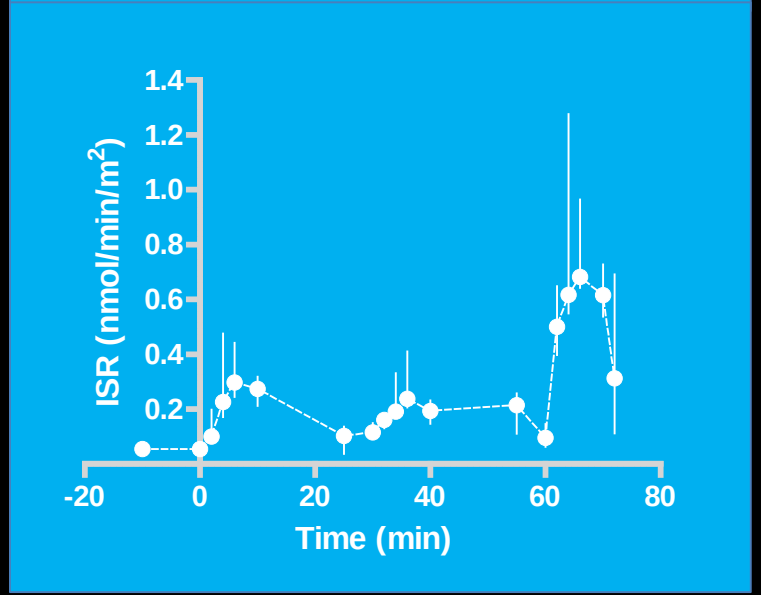
Insulin secretion before and after weight loss

NGT

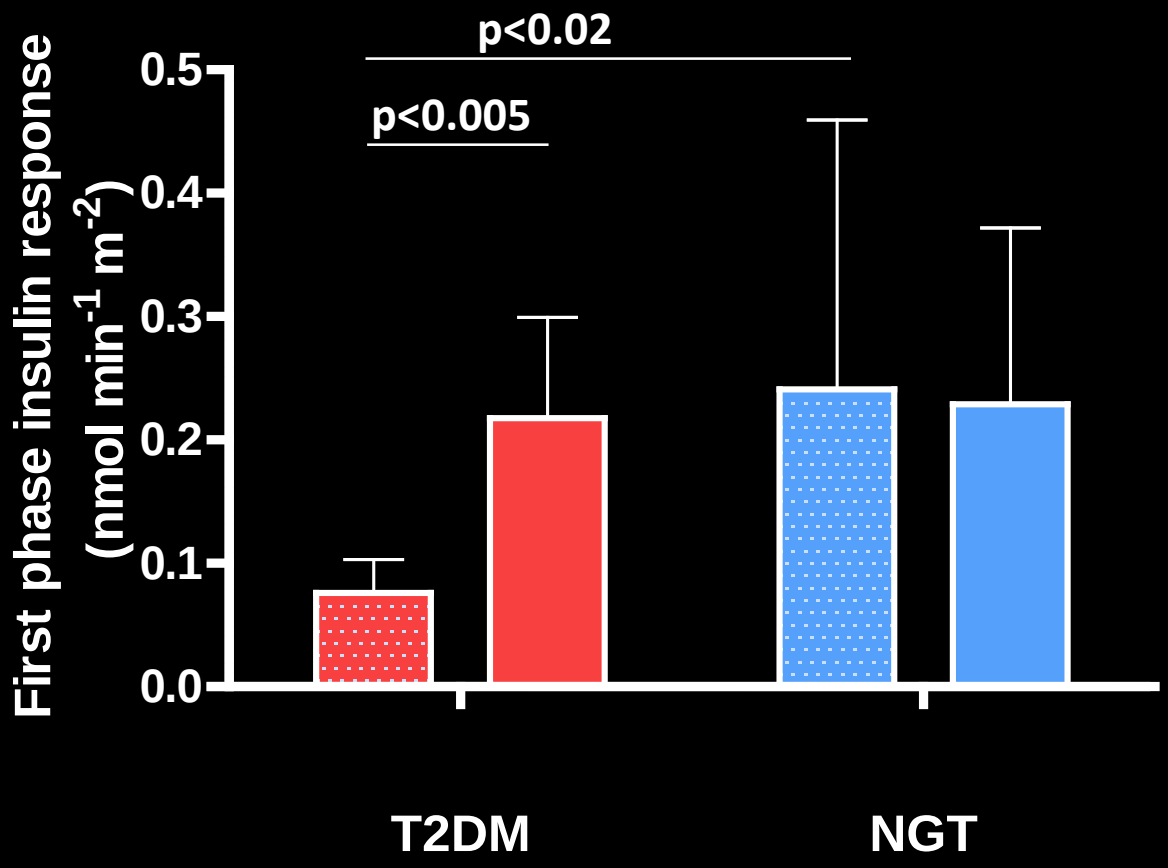
Baseline



8 weeks

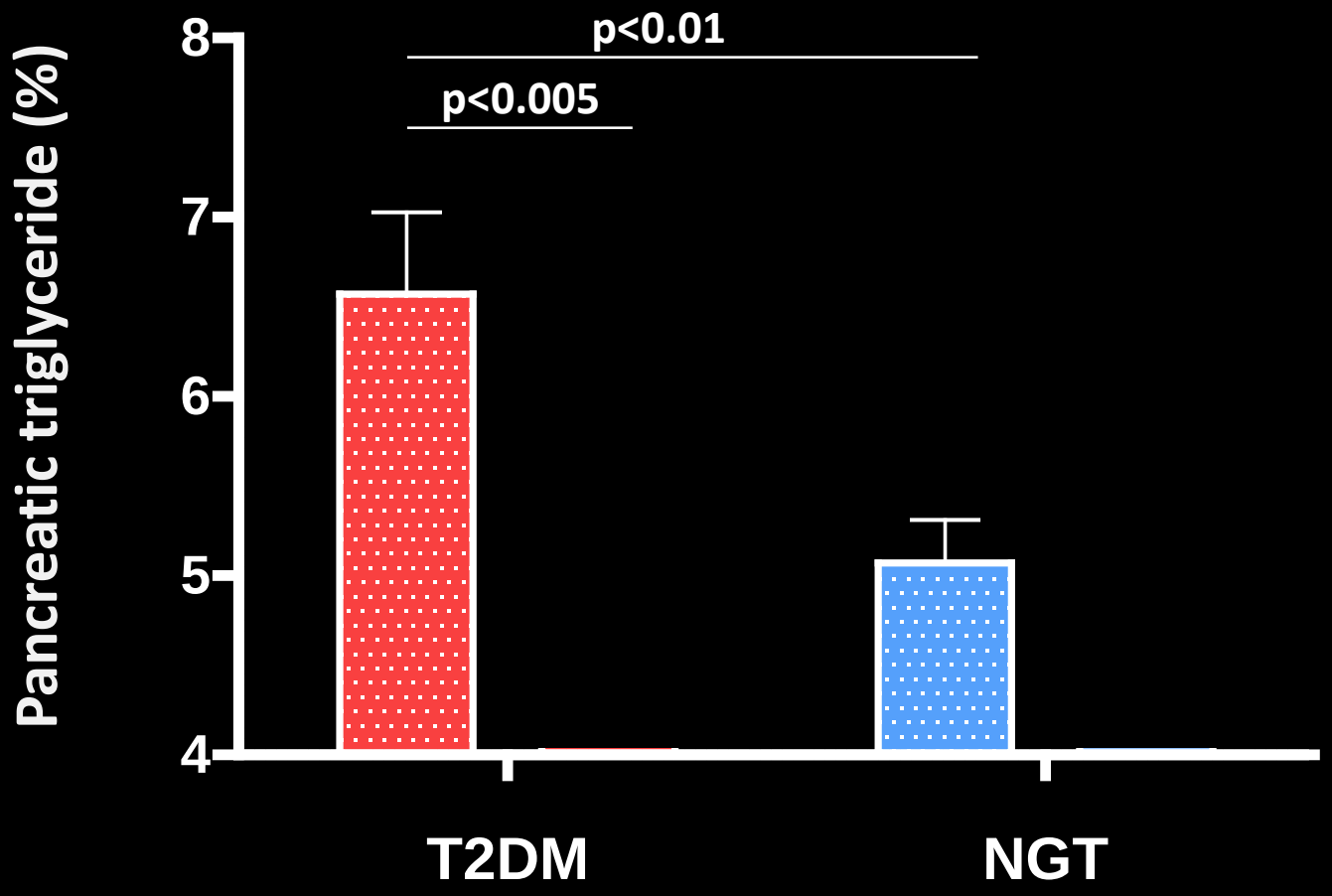


First phase insulin secretion in T2DM and NGT – before and after weight loss



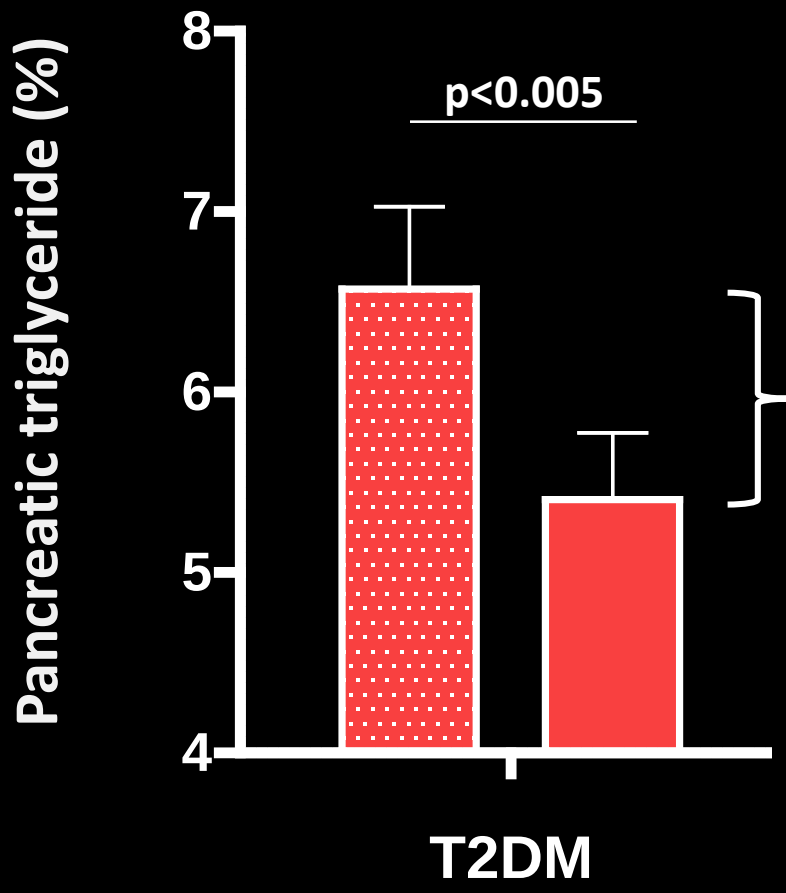
Steven et al, Diabetes Care 39(1):158-65; *2016*

Pancreatic triglyceride in T2DM and NGT – before and after weight loss



Steven et al, Diabetes Care 39(1):158-65; *2016*

Pancreatic triglyceride in T2DM before and after weight loss



Decrease of 1.2%
Mean pancreas volume ~50ml

This represents ~0.6 grams of fat

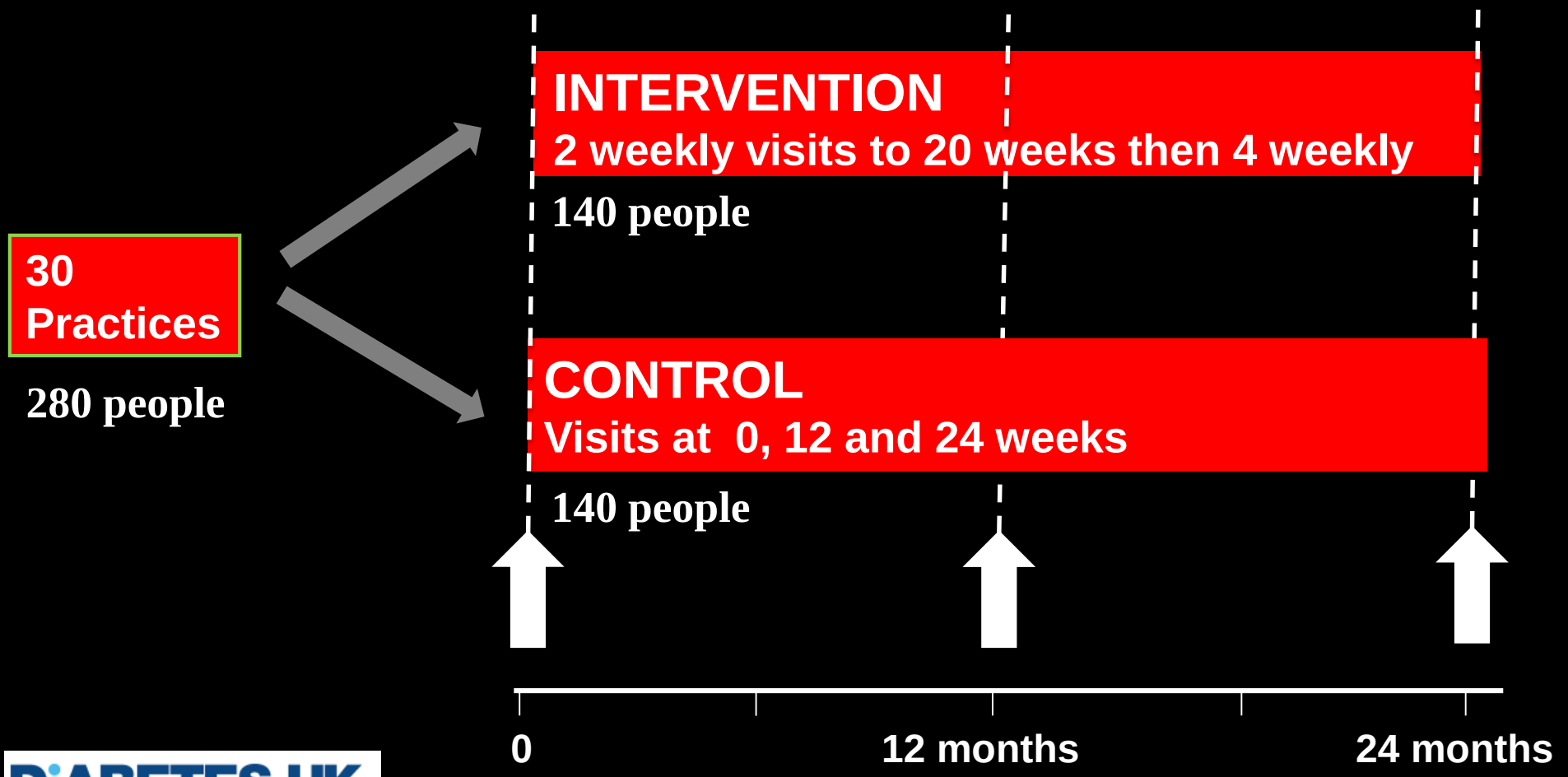
Steven et al, Diabetes Care 39(1):158-65; *2016*

Conclusions

Weight loss over 8 weeks brings about loss of pancreatic triglyceride specifically in type 2 diabetes

It is likely that type 2 diabetes is caused by less than 1 gram of fat in the pancreas

DiRECT – a study in routine NHS General Practice



DiABETES UK
CARE. CONNECT. CAMPAIGN.

DiRECT – a study in routine NHS General Practice