The twin-cycle hypothesis: type 2 diabetes

Positive calorie balance 

↑ liver fat

Pre-existing insulin resistance

++

Liver cycle

Resistance to insulin control of glucose

↑ basal insulin secretion

↑ plasma glucose

Taylor, Diabetologia 2008; 51: 1781
The twin-cycle hypothesis: type 2 diabetes

Positive calorie balance

Pre-existing insulin resistance

Liver cycle

- ↑ liver fat
- ↑ basal insulin secretion
- ↑ plasma glucose

Pancreas cycle

- ↑ VLDL-TG
- ↑ islet fat
- ↓ acute insulin response to food

Resistance to insulin control of glucose
The twin-cycle hypothesis: type 2 diabetes

Positive calorie balance

↑ liver fat

Pre-existing insulin resistance

↑ VLDL-TG

Liver cycle

↑↑ plasma glucose

Pancreas cycle

↑ islet fat

↓ acute insulin response to food

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
Substantial weight loss in people with type 2 diabetes will:

**Liver**
- Decrease fat – improve insulin action and
- normalise overnight blood sugar

**Pancreas**
- Decrease fat – normalise the insulin response to eating

The twin cycle hypothesis
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)

Weeks

0 1 4 8
New magnetic resonance method allows measurement of organ fat content

Bland-Altman reproducibility coefficients: Liver 0.5; Pancreas 0.9

Detailed anatomical MRI scan

Fat map co-localised with scan

Method based on 3-point Dixon developed by Dr Kieren Hollingsworth
Body weight change during Counterpoint

Total loss of 15.3 ± 1.2 kg

Weight (kg)

Week

Matched non-DM controls studied at one time point

Lim et al, Diabetologia 2011
Counterpoint: Effect of VLCD on fasting glucose

All hypoglycaemic agents stopped

Fasting plasma glucose (mmol/l)

9.2 → 5.9 mmol/l (p=0.003)

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

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

 ISR (nmol/min/m²)

Baseline

No first phase insulin secretion

Lim et al, Diabetologia 2011
Beta cell function: Diabetes subjects

Week 1

ISR (nmol/min/m²)

Time (min)

Lim et al, Diabetologia 2011
Beta cell function: Diabetes subjects

Week 4

 ISR (nmol/min/m²)

Time (min)

Lim et al, Diabetologia 2011
Beta cell function: Diabetes subjects

Week 8

ISR (nmol/min/m²)

Time (min)

Lim et al, Diabetologia 2011
Change in beta-cell function and pancreas fat

First phase insulin response (nmol/min/m^2)

Pancreas fat content (%)

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

**Pancreas**
- Decrease fat – normalise the insulin response to eating

*and*
The Counterpoint study – Type 2 diabetes, 800kcal diet

Liver

- Fat %
- Insulin sensitivity Index

Pancreas

- Fat %
- First phase insulin secretion
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

- **T2DM < 4 yr**
  - Very low calorie diet
  - Stepped return to normal eating
  - Weeks: 0, 1, 4, 8

- **T2DM > 8 yr**
  - Very low calorie diet
  - Weight maintenance
  - Weeks: 0, 1, 4, 8, 10, + 6 months

**Weeks**
<table>
<thead>
<tr>
<th>Diabetes duration</th>
<th>0-4y (n=15)</th>
<th>8-23y (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>52.1 ± 2.6</td>
<td>61.6 ± 2.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>99.0 ± 3.7</td>
<td>96.9 ± 3.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.6 (27.6-38.0)</td>
<td>33.0 (29.4-45.7)</td>
</tr>
</tbody>
</table>
Results: weight loss during diet

Short duration

Long duration

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

p=0.662
Fasting plasma glucose during diet

**Short duration**

**Long duration**

Steven et al Diabetic Med 2015
By diabetes duration

Spearman 0.501; p=0.006

<4 y 5.8 mM
8-12 y 6.2 mM
>12 y 10.6 mM

Steven et al Diabetic Med 2015
Aetiology of type 2 diabetes: twin-cycle hypothesis

Positive calorie balance

↑ liver fat

↑ plasma glucose

↑ liver fat

↑ basal insulin secretion

Pre-existing insulin resistance

Resistance to insulin suppression of HGP

↑ VLDL triglyceride

↑ islet triglyceride

↓ acute insulin response to food

Liver cycle

↑ VLDL triglyceride

Pancreas cycle

Pre-existing insulin resistance

↓ acute insulin response to food

Liver cycle

Why me?
BMI distribution of participants – Start of UK Prospective Diabetes Study
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.
Personal vs population

explains the “Why me” factor – individuals 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 its 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

<table>
<thead>
<tr>
<th></th>
<th>Type 2 DM n=18</th>
<th>NGT N=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.1 ± 1.6</td>
<td>46.3 ± 2.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>121.0 ± 3.0</td>
<td>114 ± 5.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>42.7 ± 0.7</td>
<td>41.3 ± 1.0</td>
</tr>
</tbody>
</table>

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

Decrease body weight

T2DM: 13.6±0.7%
NGT: 12.8 ± 0.8%
Fasting plasma glucose in T2DM and NGT – Before and after weight loss

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

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

Insulin secretion before and after weight loss

Baseline

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

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

Pancreatic triglyceride in T2DM before and after weight loss

Pancreatic triglyceride (%)

- Mean pancreas volume ~50ml
- Decrease of 1.2%
- This represents ~0.6 grams of fat

\[ p < 0.005 \]

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

**INTERVENTION**
2 weekly visits to 20 weeks then 4 weekly
140 people

**CONTROL**
Visits at 0, 12 and 24 weeks
140 people

30 Practices
280 people
DiRECT – a study in routine NHS General Practice

What proportion of people with type 2 diabetes can be returned to ongoing normal health?

What psychological factors lead to success?

What metabolic changes ensure continuing normal metabolism?