Proving the Twin Cycle Hypothesis: 2011 - The COUNTERPOINT study

Type 2 diabetes 0-4 years duration

All OHA stopped; 800kcal/day started

Liver fat 30%↓; Plasma TG↓50%; Liver insulin sensitivity normal

Slow increase in beta cell function

Fasting plasma glucose (mmol/l)

Lim E-L et al, Diabetologia 2011; 54: 2506
Type 2 Diabetes

Etiology and reversibility

Roy Taylor, MD, FRCP

Reversal of type 2 diabetes to normal metabolic control by either bariatric surgery or hypocaloric diet allows for the time sequence of underlying pathophysiologic mechanisms to be observed. Type 2 diabetes has to progress despite treatment, with 50% requiring insulin therapy (1). This seemingly in
The personal fat threshold hypothesis

Individuals have differing susceptibility to fat excess
The personal fat threshold
The personal fat threshold
ReTUNE protocol – Step-wise weight loss in T2DM

Baseline BMI 21-27 kg/m²

Weight loss (%)

Weeks

Studies

Taylor et al, Clin Sci 2023; 137:1333-46
### Participants

*T2DM duration <6y; BMI 21-27kg/m²*

<table>
<thead>
<tr>
<th></th>
<th>T2DM (n=20)</th>
<th>Controls (n=20)</th>
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</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>59.0 ± 7.0</td>
<td>58.0 ± 10.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8 ± 1.7</td>
<td>21.5 ± 0.5*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.8 ± 12.6</td>
<td>61.5 ± 2.2*</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>13/7</td>
<td>13/7</td>
</tr>
<tr>
<td>Duration of diabetes (y)</td>
<td>2.8 ± 1.9</td>
<td>-</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>54 ± 6</td>
<td>37 ± 3</td>
</tr>
</tbody>
</table>

*Post-weight loss matching

N=24: 4 found not to be T2DM - 2 monogenic DM + 2 type 1 DM
Weight loss

We noted significant weight loss over the weeks with a***p<0.001***

***p<0.001

Taylor et al, Clin Sci 2023; 137:1333-46
% Body fat – 32% at baseline; 28% at 1 year [controls 25%]

Taylor et al, Clin Sci 2023; 137:1333-46
Liver fat

**p<0.01

Taylor et al, Clin Sci 2023; 137:1333-46
Plasma VLDL triglyceride and total triglyceride

* p<0.05  ** p<0.01  *** p<0.001

Taylor et al, Clin Sci 2023; 137:1333-46
Measure of *de novo* lipogenesis

![Graph showing changes in Plasma TG 48:1 (μmol/l) over time. The x-axis represents weeks (0, 8, 16, 24, 52) and the y-axis represents Plasma TG 48:1 (μmol/l). The graph includes error bars and statistical significance markers (**, ***, ***) at certain points.](Taylor et al, Clin Sci 2023; 137:1333-46)
Change in Insulin Secretion

* p<0.02
*** p=0.005

Taylor et al, Clin Sci 2023; 137:1333-46
Change in HbA1c

![Bar chart showing the change in HbA1c over weeks.](chart.png)

Taylor et al, Clin Sci 2023; 137:1333-46
70% of ‘slim’ people achieved remission with weight loss

Taylor et al, Clin Sci 2023; 137:1333-46
Slimmer people have no problem in preventing weight regain under similar follow up.

- **Baseline BMI 27-45**
- **Baseline BMI 21-27**

Taylor et al, Clin Sci 2023; 137:1333-46
Implications for T2DM management in ‘normal’ and raised BMI

Information at diagnosis

Offer a choice - ?return to health

Approach to target-driven weight loss

Choice of hypoglycaemic agent

Taylor R. Type 2 Diabetes: Etiology and Reversibility. Diabetes Care 2013; 36:1037-
Taylor et al, Clin Sci 2023; 137:1333-46
What is T2DM?

T2DM is a state of excess fat inside liver and pancreas

In people with susceptible beta cells

Lim et al Diabetologia 2011; Steven et al Diabetes Care 2016; Steven et al Diabetes Care 2016; Taylor et al Cell Metabolism 2018; Al-Mrabe et al 2020 Cell Metabolism; ReTUNE 2023
ReTUNE confirms the Personal Fat Threshold –

*If a person has T2DM they are too heavy for their own body*