Summary: Why type 2 diabetes is reversible?

- Liver fat: ↑
- Liver fat export: ↑
- Pancreas fat: ↑
- Beta cell damage: ↑

↓

- Liver fat: ↓
- Liver fat export: ↓
- Pancreas fat: ↓
- Beta cell damage: ↓
DiRECT – a study in routine NHS General Practice

INTERVENTION
15kg weight loss then maintain
157 people

CONTROL
Best management by guidelines
149 people

49 Practices

Leslie et al. 2016 BMC Family Practice 17:20
## Baseline data: analysed participants

(100%)

<p>| | | | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Total number</strong></td>
<td>298</td>
<td><strong>Duration of T2DM (y)</strong></td>
<td>3.1 (SD 1.7)</td>
</tr>
<tr>
<td><strong>Men / women</strong></td>
<td>59% / 41%</td>
<td><strong>HbA1c (mmol/mol)</strong></td>
<td>59 (SD 14) (7.6%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>54 (SD 7)</td>
<td><strong>Diet alone</strong></td>
<td>24%</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>men 106 (SD 16)</td>
<td><strong>I drug</strong></td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td>women 91 (SD 13)</td>
<td><strong>2+ drugs</strong></td>
<td>28%</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>35 (SD 4)</td>
<td><strong>Blood Pressure</strong></td>
<td>135/85</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Smoking (current)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Former</strong></td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Never</strong></td>
<td>50%</td>
</tr>
</tbody>
</table>

Intervention and Control groups well balanced for all criteria
Results: weight changes over 12 months

Lean et al, Lancet 2017
Remissions at 12 and 24 months

Lean et al. *Lancet Diab & Endo* 2019; 7: 344
Remissions by 24-month weight loss: entire study population

- <5kg: 5%
- 5-10kg: 29%
- 10-15kg: 60%
- ≥15kg: 70%

≥10kg loss: 64% are in remission

24-months

Lean et al Lancet Diab & Endo 2019; 7: 344
Weight management is critical for T2D remission

Lean et al. *Lancet Diab & Endo* 2019; 7: 344
Baseline determinants of return to non-diabetic glucose control (Tyneside cohort)

<table>
<thead>
<tr>
<th></th>
<th>Responder</th>
<th>Non-responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53 ± 1</td>
<td>53 ± 2</td>
</tr>
<tr>
<td>Weight</td>
<td>101 ± 3</td>
<td>102 ± 4</td>
</tr>
<tr>
<td>Sex</td>
<td>17/23</td>
<td>9/9</td>
</tr>
<tr>
<td>HbA1c</td>
<td>58±2</td>
<td>63±2*</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>108±10</td>
<td>77±9*</td>
</tr>
</tbody>
</table>

Duration of diabetes

Taylor et al, Cell Metabolism 2018 28(4):547-556
Protocol for pathophysiological studies

Stop anti-diabetic drugs

Baseline  →  Post-weight loss  →  12 months

Weight loss  →  SFR  →  Responders

HbA1c <48mmol/mol + FPG <7.0mM

Non-responders

Taylor et al, Cell Metabolism 2018 28(4):547-556
Methodology – Fat quantification by MRI

Liver fat: 22.3%
Baseline
Male/58 Years
BMI: 37.9 KG/m²

Liver fat: 0.9%
Post weight loss
BMI: 28.5 KG/m²

Lim et al, Diabetologia 2011 54:2506-2514
Changes in liver and pancreas fat

- Non-Responders
- Responders
- Relapsers

Liver fat (%)

- Months

Pancreas fat (%)

- Months
Change in hepatic triglyceride export

- VLDL1 TG production rate (mg/kg/day)
- VLDL1 TG pool (mg)
- Responders
- Controls
- Nonresponders
Change in plasma VLDL1-TG and total triglyceride

- **Plasma VLDL1-TG**
- **Total Plasma TG**

- **Responders**
- **Controls**
- **Nonresponders**

Graphs showing changes over 24 months.
Effect of degree of weight loss on plasma TG

Fasting plasma VLDL-TG (mmol/mol)

Fasting total plasma TG (mmol/l)

- W. loss<15%
- W. loss>15%

Months

0 4 8 12 16 20 24

0.0 0.2 0.4 0.6 0.8 1.0 1.2

0 4 8 12 16 20 24

0.0 0.5 1.0 1.5 2.0 2.5
Change in acute insulin secretion

Median ± interquartile

Taylor et al, Cell Metabolism 2018 28(4):547-556
Change in maximal insulin secretion

Median ± interquartile

Taylor et al, Cell Metabolism 2018 28(4):547-556
Dedifferentiation explains the beta cell in type 2 diabetes

Reversible if metabolic stress removed

Metabolic stress

Healthy beta cell

Loss of specialised function

Null cell

Pinnick 2010; Talchai 2012; White 2013; White, Diabetes Care 2016
The Twin Cycle Hypothesis: Aetiology of Type 2 diabetes

Pre-existing insulin resistance

Positive calorie balance

Liver cycle

↑ liver fat

↑ basal insulin secretion

Resistance to insulin control of glucose

↑ plasma glucose

Pancreas cycle

↑ VLDL-TG in blood

↑ islet fat

↓ acute insulin response to food

Subcutaneous stores full

Taylor R, Diabetologia 2008; 51: 1781
“Diet” for weight loss

Simple
Practical
Spouse/partner on board
Time limited and planned
No additional exercise

Compensatory eating renders exercise counterproductive during weight loss

Taylor R & Barnes AC, Diabetologia 2018; 61:273-83
**Behaviours-regulation strategies** (examples)
- Avoidance,
- Distraction
- Breaking the goal down
- Drinking water
- Modifying the diet
- Reminding oneself of the goals
- Planning,
- Removing food from environment
- Social disclosure
- Weighting up pros and cons

**Facilitators**

**Barriers**
- Emotional and cognitive barriers
  - Boredom with the regime
  - Life events and stress
  - Body shape dissatisfaction
  - Lack of self-efficacy
  - Lack of social support
- Environmental barriers
  - Presence of shops with food
  - Traveling
  - Going out and socializing
  - Lack of opportunity to speak with other participants
- Process barriers
  - Dissatisfaction with outcomes
  - Dislike of the product
  - Hunger, cravings, and lapses
- Destabilisation
  - Re-designing of the “Foodrobe”

*Rehakova L et al, Diabetic Medicine 2017; 34: 1554-67*
Summary: Why type 2 diabetes is reversible?

Liver fat ↑
Liver fat export ↑
Pancreas fat ↑
Beta cell damage ↑

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