Clinical aspects of long term remission of type 2 diabetes

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Disclosures – Roy Taylor

- Member of UK government (SACN) working group on low carbohydrate diets – all opinions in this lecture are personal
- Author of book: Life Without Diabetes
- Lecture fees from Novartis, Lilly & Janssen
- Research funding from Diabetes UK
“Diet” for weight loss

Simple
Practical
Spouse/partner on board
Duration limited and planned
No additional exercise during this time
“Diet” for weight loss

- Simple
- Practical
- Spouse/partner on board
- Duration limited and planned

Compensatory eating renders exercise counterproductive during weight loss.
Weight loss then weight maintenance

Step 1  Low calorie weight loss
       600kcal/day liquid formula diet + nonstarchy vegetables
       (or 800kcal/day liquid formula only)

Step 2  Step-wise return to normal eating
       Replace liquid formula with normal food, one meal at a time. Aiming for ±1500kcal/day

Step 3  Long term support to limit calorie intake and encourage increased physical activity
Effect of very low calorie diet on fasting glucose
The COUNTERPOINT study

Type 2 diabetes
0-4 years duration

All hypoglycaemic agents stopped

Lim E-L et al, Diabetologia 2011; 54: 2506
Effect of very low calorie diet on fasting glucose
The COUNTERPOINT study

**Type 2 diabetes 0-4 years duration**

**At 7 days:**
- 30% fall in liver fat
- Normalisation of liver insulin sensitivity

**Over 8 weeks:**
- Gradual fall in pancreas fat
- Gradual return of first phase insulin response

*Lim E-L et al, Diabetologia 2011; 54: 2506*
Counterpoint:
Change in intra-pancreatic fat & first phase insulin secretion

Lim et al. Diabetologia 2011; 54: 2506
CounterBALANCE – Does duration of T2DM matter?

Effect of VLCD then 6 months isocaloric eating on first phase insulin secretion

Steven et al, Diabetes Care 2016; 39:808
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Responders               Non-responders

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CounterBALANCE – Does duration of T2DM matter?

Effect of VLCD then 6 months isocaloric eating on first phase insulin secretion

Responders               Non-responders

Duration (years)              3.8±1.0 9.8±1.6

HbA1c (%)                  7.1 5.8 5.9  8.4 8.0 7.8

Steven et al, Diabetes Care 2016; 39:808
Look Ahead – Multivariate analysis to identify effect of duration of type 2 diabetes on odds ratio of remission

Gregg EW et al, JAMA 2012; 308:2489
Remissions at 12 and 24 months

Lean et al. *Lancet Diab & Endo* 2019; 7: 344
DiRECT: Decreased VLDL-TG output from the liver

[Graph showing plasma VLDL1 TG (mmol/l) over months for Non-responders and Responders.]

Al-Mrabe et al, Cell Metabolism 2020; 31:233-249
DiRECT: Pancreas fat content in T2DM falls will weight loss irrespective of remission

Al-Mrabeh et al, Cell Metabolism 2020; 31:233-249
Remission depends on capacity of beta cells to recover once lipid excess is removed

*** p<0.001 vs. baseline,
** p<0.01 vs. baseline,
* p<0.05 vs. baseline
Remission depends on capacity of beta cells to recover once lipid excess is removed.

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Al-Mrabe et al. Cell Metabolism 2020; 31:233-249
The pancreas in T2DM is 25% smaller than normal. Does it return towards normal size with remission?

Macauley et al, PLOS One 2015; 10:e0126825
Al-Mrabe et al, Diabetologia 2016; 59:1753
With weight regain: observing T2DM develop

Graphs showing the change in Plasma VLDL1 TG and Change pancreas fat over 0-24 months.

- **Responders** (green line)
- **Relapsers** (blue line)

For more details, refer to Al-Mrabe et al. Cell Metabolism 2020; 31:233-249
With weight regain: observing T2DM develop.

** p<0.01 vs. baseline, *** p<0.001 vs. baseline
# p<0.05 vs. 5 months, ## p<0.05 vs. 5 months

Al-Mrabeo et al, Cell Metabolism 2020; 31:233-249
The twin cycle hypothesis

Negative calorie balance 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

*Taylor Diabetologia 2008; 51: 1781*
The Twin Cycle Hypothesis: Aetiology of Type 2 diabetes

Positive calorie balance

Pre-existing insulin resistance

Liver cycle

↑ liver fat

↑ basal insulin secretion

Resistance to insulin control of HGP

↑ plasma glucose

Pancreas cycle

↓ acute insulin response to food

↑ VLDL-TG in blood

↑ islet fat

Subcutaneous stores full

Taylor R, Diabetologia 2008; 51: 1781
Pre-diabetes, diabetes and post-diabetes

- **Pre-diabetes**
  - **HbA1c**:
    - 28
    - 48
    - 68
  - **High lipids**
  - **High BP**

- **Post-diabetes**
  - **QRISK 23%, heart age 71y**

- **Reversal**
  - of underlying pathophysiology
  - **Low risk**
    - QRISK 7%, heart age 56y
Look Ahead – Multivariate analysis to identify major factors underlying remission of type 2 diabetes (11.5% at 1y)

**Weight loss**
- Lo
- Mid
- Hi

**Increased fitness**
- Lo
- Mid
- Hi

**Tertiles**

**Odds ratio of remission**

- Weight loss: Lo, Mid, Hi
  - Lo: p <0.001
  - Mid: p <0.001
  - Hi: p <0.001

- Increased fitness: Lo, Mid, Hi
  - Lo: p <0.01
  - Mid: p = 0.39
  - Hi: p = 0.39

Gregg EW et al, JAMA 2012; 308:2489
Website on how-to-do-it

go.ncl.ac.uk/diabetes-reversal
Remission of type 2 diabetes follows:
weight-loss induced ↓ in hepatic VLDL-TG output,
decrease in intra-pancreatic fat
and return of beta cell function

Long term remission permits return of
full functional beta cell mass