**Type 2 diabetes reversal**

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<td>Complete List of Authors:</td>
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<td>diabetes, diet, nutrition, food, diabetes reversal</td>
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Type 2 diabetes

Liver fat ↑

Liver fat export ↑

Pancreas fat ↑

Beta cell function ↓

Remission

Liver fat ↓

Liver fat export ↓

Pancreas fat ↓

Beta cell function ↑

Relapse

VLDL

101x101mm (300 x 300 DPI)
THE NUTRITIONAL BASIS OF TYPE 2 DIABETES REMISSION

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Standfirst Statement

Type 2 diabetes, once thought to be irreversible and progressive, is a state of excess fat in the liver and pancreas and can be reversed to normal in both European and non-European populations by weight loss and avoidance of weight regain.

Do you think that type 2 diabetes (T2DM) is a lifelong, inevitably progressive condition? If so, you are out of date! This review summarises the new understanding of T2DM and the potential for its remission in both European and non-European populations. It also describes the key considerations for effective dietary advice for long-term weight maintenance and mitigation of T2DM from a population perspective.

1. How can remission be achieved?

A series of hypothesis-driven clinical studies over the last 12 years has clarified the mechanisms which cause T2DM. These processes can be put into reverse in short duration T2DM by restriction of food energy to achieve weight loss of around 15kg. For people within the first 10 years of diagnosis of T2DM, around 1 in 2 people can stop all diabetes medication and return to non-diabetic glucose control. The elusive aetiology of T2DM can now be understood. During the return to normal glucose control, the underlying processes undergo exactly the reverse of what happened as the disease developed and these have now been defined.

To test the underlying hypothesis (Section 2 below), a sure-fire way of achieving around 15kg weight loss was required, and one of the most striking findings of the Counterpoint Study was the acceptability of a low calorie liquid diet for a short, planned period of time. The widespread acceptability of this approach was confirmed in the primary care based DIRECT Study in which almost 30% of everyone invited took up the invitation to participate.

However, any way of achieving the necessary degree of weight loss can bring about remission. In the UK Prospective Diabetes Study, normalisation of fasting glucose was reported in 15% following the initial dietary weight loss phase. The Look-AHEAD study was not targeted at achieving remission, but the modest weight loss achieved remission in 11.5% of the intensive lifestyle group. In addition to the low fat/low calorie plan in Look-AHEAD, the low carbohydrate diet is another recognised way of achieving the degree of weight loss necessary for remission. Merely providing the information on the degree of weight loss required for remission can allow motivated people to achieve this for themselves. Bariatric surgery necessitates nil-by-mouth for a period followed by much reduced food intake and achieves around 64% remission at 2 years.

2. What happens in the body to cause T2DM and bring about remission?

In 2008 the Twin Cycle Hypothesis postulated that there were vicious cycles of fat accumulation, in liver and pancreas respectively, which lead to the development of T2DM over at least a decade. This hypothesis predicted that major calorie restriction would lead to a rapid fall in liver fat, normalisation of liver insulin sensitivity and decrease to normal of glucose production by the liver.

In a nutshell, T2DM is characterised by accumulation of more fat in the liver than an individual can tolerate. Different people have different personal fat thresholds, and this explains why only 50% of people diagnosed with T2DM are obese and some have ‘normal’
The excess fat within liver cells causes insulin resistance and this entirely resolves if liver fat levels fall to low normal. Then the hormone can act normally again, restraining the previous outpouring of glucose from the liver into the blood and causing very rapid normalisation of fasting blood glucose. Because the liver supplies triglyceride to the rest of the body, the sudden fall in liver fat causes the high rate of supply to fall to normal. As a result, fat levels inside the pancreas gradually decrease, along with all ectopic fat depots. Gradually, normal insulin response to eating is restored.

This initial study was conducted in people with T2DM diagnosed within 4 years prior to recruitment, while the next study demonstrated that remission was steadily less likely with increasing duration. That set the scene for a randomised controlled trial in primary care of a low calorie diet compared with conventional management according to best practice guidelines. The DiRECT study demonstrated that non-medical primary care staff could achieve remission of T2DM for 2 years in 36% of the whole group initially recruited. Remission is now defined as HbA1c <48mmol/mol after weight loss, off all oral anti-diabetic medications, on two occasions six months apart (Box 1).

DIRECT also showed that after rapid weight loss then 2 years of structured weight maintenance, people in remission showed a complete return to normal of maximal insulin secretion rates. This complete return to normal functional beta cell mass is remarkable. Previously, both clinical and histological studies on the pancreas showed that beta cell capacity declined to around 50% by the time of diagnosis, and death or apoptosis of the beta cells had been assumed. But we now know that excess fat exposure of beta cells causes metabolic stress and that the cells de-differentiate, losing ability to secrete insulin most likely via downregulation of the genes controlling insulin production. This demonstration of return to normal in a large group of people who used to have T2DM lays to rest the notion of irreversible beta cell loss. Some individuals are known to remain in remission for many years provided weight regain is avoided. Implicit in the definition of remission is freedom from anti-hyperglycaemic medication, as specified in the definition of remission adopted in the UK (Box 1).

It is important to emphasize that any sustained decrease in calorie intake is able to remove the excess intra-organ fat. For example, the enforced sudden decrease in food intake after bariatric surgery brings about remission by the same underlying mechanisms as voluntary dieting.

3. Dietary advice – key components

Low carbohydrate versus low calorie
There is much noise and confusion about the ‘best’ macronutrient composition. Low-fat diets were favoured with the assumption that ‘fat makes you fat’ given that fat contains the highest density of calories (9 kcal per gram), compared with carbohydrate and protein (4 kcal per gram), coupled with concerns about cardiovascular risks of high fat diets. On the other hand, there is increasing interest in low- or very low-carbohydrate diets because, among the macronutrients, carbohydrate is the primary contributor to post-prandial glycaemia. The major evidence comparing low calorie and low carbohydrate diets is summarised in Table 1.

It is clear from RCTs of general, not diabetes specific, populations that either type of diet can be effective for weight loss as long as participants can adhere to the diet. Slightly greater weight loss up to 1y was achieved with a low-carbohydrate diet than with a low-fat diet, with a modest difference around 1kg body weight, but the scanty RCT evidence at 2 years showed no difference. In contrast, a non-randomised study with intensive follow-up has reported that a very low carbohydrate approach can achieve and sustain weight loss of 12kg at 2 years. Moreover, a 2 year follow-up of a cohort in a British General Practice (not
restricted to T2DM) reported decrease in median weight of 8.3kg at 2 years.\textsuperscript{24} For glycaemic control, a non-randomised study reported 58% of participants achieving HbA1c \textless48mmol/mol (<6.5%) but metformin therapy was not discontinued.\textsuperscript{25} It must be noted, however, that RCT evidence differs from non-randomised or uncontrolled studies reporting data on completers rather than by intention to treat and cannot be directly compared. It is beyond the scope of this article to cover details of study design but in the hierarchy of evidence framework RCTs are considered as providing the highest quality of evidence provided they are feasible. One RCT to our knowledge reported remission rates on a low carbohydrate diet; it studied patients with poorly controlled glycaemia and found diabetes remitted with continued metformin in 11% of participants compared with 0% in the comparator intervention of diabetes group medical visits \textsuperscript{26}.

There is a variety of opinion too on definitions. What constitutes ‘low-carbohydrate’ varies widely across studies from <45% of total energy\textsuperscript{27} to ketogenic levels of intake of under 50g/day (<10% of energy).\textsuperscript{23} A standardised definition for low carbohydrate terminology is shown in Box 2.

Dietary adherence is always problematic, with substantial differences in prescribed and attained macronutrient intakes. The take-home message is that the best diet for longer-term success will be one which is easiest for an individual to adhere to in the long term.

Dietary restriction through eating strategies
Portion control is an age-old strategy as is the concept of fasting: short-term dietary self-restraint was traditionally associated with religious faith practices. Intermittent fasting, on the other hand, has become popularized more recently. Daily or alternate day fasting aims for \sim25% lower intake; 5:2 diet reduces intake to 500 to 700 calories per day for 2 days each week; while daily time-restricted feeding limits eating to within a 6 to 8 hour window per day. For instance, omit breakfast and consume food only between 12 noon and 6pm. Intermittent fasting may also have longer term impacts for health and longevity.\textsuperscript{28} Challenges such as hunger and cravings on fasting days could be too great for many despite evidence that these diminish over time.\textsuperscript{28}

Dietary quality
In addition to quantity, the quality or type of food and dietary patterns are important since food is eaten within overall socio-cultural contexts. A focus solely on the amount of macronutrients or energy may be over simplistic, because different food sources impact physiological pathways differently including appetite, satiety, hunger and diet-induced thermogenesis. Reducing all carbohydrates indiscriminately may take away certain benefits to be had from the consumption of fibre and wholegrain. Decades of research has clarified the importance of considering not total fat but distinguishing between saturated, unsaturated and \textit{trans} unsaturated fat for cardiometabolic disease.\textsuperscript{29-31} Further scientific progress has clarified that even saturated fat as a sub-group of fat is not sufficiently discriminatory for health effects; individual saturated fatty acids differ in their association with T2DM.\textsuperscript{32} Moreover, dairy and meat are typically high in saturated fat and protein but some types of dairy such as fermented dairy (yoghurt) are associated inversely with cardiometabolic disease risk, highlighting the importance of food sources rather than a sole focus on the macronutrient type..

Advice on foods consumed within an overall dietary pattern may facilitate longer term adherence, and there is evidence for benefits of Mediterranean-type diets for a number of health outcomes. That is not to say that the Mediterranean-dietary pattern is singularly superior or easy to adhere to. Other dietary patterns or diet quality indices are also effective, such as the DASH diet, the healthy eating index, Nordic diet, and vegetarian or other meal plans, but more research is needed. There is also emerging consensus that avoidance of
ultraprocessed foods and a move to the consumption of fresh, whole foods has health benefits including for weight and glycaemic control.

In sum, food based dietary guidelines that move beyond a focus on macronutrients and consider overall dietary and social contexts would communicate our current knowledge on nutrition and health more comprehensively.

4. Remission of T2DM in ethnically diverse and global populations

The majority of the studies on remission of T2DM carried out in western countries involved few non-white participants, and ethnically differing background nutritional patterns have to be considered. Look AHEAD included ~38% non-white participants (mainly Hispanic and African-American). Remission was observed in proportion to weight loss (11.5% at year 1 and 7.3% at year 4, with weight loss of 8.6% and 4.7% respectively) and no association of ethnicity with remission was observed. A large community based analysis from the Kaiser Permanente Northern California Registry showed higher likelihood of remission in African Americans compared with the white population, with overall 7 year remission of 4.6% in those with < 2 years duration of T2DM. A similar retrospective survey of people over 65 years observed higher 8 year rates of non-surgical remission in Asian and Hispanic compared with white and African American groups.

South Asians achieve remission after a low calorie liquid diet similarly to white Europeans. A 2 year prospective study of a low calorie diet and advice to walk daily in a young South Asian population with recent onset T2DM showed 75% remission at 3 months, and 69% at 2 years. FPG was 5.6mmol/l with HbA1c <5.7% in 53% at 3 months and 47% at 2 years and FPG was 5.6-6.9mmol/l with HbA1c 5.7% - 6.4% in 22% at both time points. Similar observations at 3 months were made in a Thai population. At 12 weeks, diabetes remission was achieved in 79% (by an average weight loss of 10kg) and at 12 months remission was maintained in approximately 30%. In Diadem-1, remission was observed in 61% of a Middle Eastern population.

A recent study in Barbados on a predominantly African-Caribbean population observed comparable rates of weight-loss induced remission to those documented in DIRECT. This was achieved over 8 weeks by use of a hypocaloric liquid diet (760kcal) with withdrawal of diabetes medication on day 1 of the diet. Nine of 11 (82%) of those who lost ≥ 10 kg achieved non-diabetic fasting blood glucose levels compared with 6 of 14 (43%) who lost < 10 kg.

In Indian populations, there was also evidence for remission of prediabetes by weight loss and physical activity, with significant improvements in insulin resistance and beta cell function.

5. Long term remission and influences on dietary intakes – lending a helping hand?

The US national registry of free-living weight-loss maintainers over 10y has provided important insights into nutritional and other factors. Weight regain was fastest in the early years of follow-up, with decreasing rates over each of first 5 years followed by stable maintenance over the subsequent 5y, suggesting that weight-loss maintenance requires less effort over time. In the Look-AHEAD trial, an observational analysis among 4503 adults with T2D showed that at 4 years 7.3% of those randomised to an intensive lifestyle intervention, with a balanced calorie reduction approach were in remission. Many personal factors
influence what we eat and therefore how well weight loss was maintained: age, sex, genetics, ethnicity, body fat status, level of physical activity, and family and social culture to name a few. But there are also profound wider influences on food intake. These included food availability, accessibility, cost, advertising, ready availability of fast-food take-aways and home delivery options and price promotions for processed energy-dense foods.

Continued support from healthcare professionals, irrespective of composition of food advised, is one strategy to increase the avoidance of long-term weight regain and achieve sustained diabetes remission. In DIRECT a 'rescue plan' of partial or total meal replacement was offered for weight regain greater than 2kg or 4kg respectively. More research is needed, but observational evidence indicates that successful weight-loss maintenance over 10y requires sustained dietary change, maintained physical activity and frequent self-weighing.

Population strategies including education, dietary guidelines, and empowerment to make healthy food choices, such as clear food labelling, are necessary but not yet universally available. Clear evidence supports the case for other population ‘nudge’ interventions including taxation, restriction of fast food outlets near schools and reducing the size and appeal of large-sized food portions, packages and tableware to impact on quantities of food and beverages consumed. Another potentially clinically and economically effective strategy is food prescription to promote healthier eating. Pilot data from the US on people with uncontrolled T2DM and food insecurity shows substantial reductions in HbA1c in those enrolled to receive fresh food on prescription. All of these strategies are compatible with either low calorie or low carbohydrate approaches.

Conclusions

T2DM can be reversed to normal by substantial weight loss in the early years after diagnosis, and the pathophysiological basis of this is now clear. This is independent of dietary approach in both European and non-European populations. Long term maintenance of weight loss brings about lasting remission of T2DM, but this is more difficult to achieve than weight loss itself. However, the nutritional principles guiding avoidance of weight regain can now be described and will be better enabled with strategies to facilitate healthier food choices.

Conflict of Interests

RT and NGF are members (unpaid) of the Joint SACN/NHS-England/Diabetes-UK Working Group to review the evidence on lower carbohydrate diets compared to current government advice for adults with type 2 diabetes. Views expressed are their own and not that of the Group. RT has received fees for educational lectures from Lilly and Janssen and is author of Life Without Diabetes (Short Books). NGF was an ex-member of ILSI-Europe Qualitative Fat Intake Task Force Expert Group on update on health effects of different saturated fats. This was a non-financial academic advisory role and she received no fees or honoraria. WY is a member of the medical review board for dietdoctor.com and has contributed to guidelines for American Diabetes Association and Guideline Central regarding nutrition and health. Views expressed are his own and not that of these entities. Funding: RT has research funding from Diabetes UK (17/0005645 and 13/0004691). NGF is supported by Medical Research Council Epidemiology Unit (MC_UU_12015/5) and NIHR Biomedical Research Centre Cambridge: Nutrition, Diet, and Lifestyle Research Theme (IS-BRC-1215-20014).
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### Areas of agreement

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<th>Good for CV health</th>
<th>Low or very low carb diets (ie Low: 50-130g/d or between 10-26% total energy; Very low: 20-50g/d or under 10% total energy)</th>
<th>Markedly improves QRISK up to 2 years 44.</th>
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<tr>
<td>Long term outcome data</td>
<td>Low or very low calorie diets (ie 700-1,000 kcal/day, or 35-50% of a 2000kcal/day intake, for a defined weight loss period then weight maintaining diet)</td>
<td>No long term outcome data.</td>
</tr>
<tr>
<td>Long term weight management</td>
<td>This is the major issue. Need for continuing support and rescue management of weight regain.</td>
<td>This is the major issue. Need for continuing support and rescue management of weight regain.</td>
</tr>
</tbody>
</table>

### Areas of disagreement

| Acceptability | Single centre reports acceptability 27. | RCT data to 2 years demonstrates ongoing compliance in the majority 44. Psychological study reports good acceptability up to 6 months 49. |
| Weight loss - RCT evidence | Significant difference from controls at 6 months only. Reduction in the low carb group of 2.6-11.1 kg at 6 months, 3.1-9.8 kg at 1 year and 2.0-6.8 kg at 2 yrs., 22, 48, 50. | Significantly different vs. controls up to 2 years. 39, 44, 51. DIRECT and DROPLET both reported weight loss around 10 kg in the active arm at 12 months and, in DIRECT, 7.6kg at 2 year. 51, 52. |
| Weight loss - non-randomised observational information | Selected paying participants achieved 10kg weight loss at 2 years 23*. A 1 year study reported 4.3kg weight loss in a 1% sample (1,000/105,950 initially signed up) 53. | Mean weight loss of 13.7 at 6 months 2 and 7.6kg at 2 years. 52. |
| Improvement in glucose control – RCT evidence | RCT evidence shows significant decrease in HbA1c of 0.3-1.5% -at 6 months. Decreases of 0.3-1.0% at 1 year and 0-0.6% at 2 years were not significantly different vs. active controls 22, 48. | RCT evidence using intention-to-treat analyses shows clinically important decrease in HbA1c at 6, 12 and 24 months with 36% Remission at 2 years 44. |
| Improvement in glucose control - non-randomised observational information | Observational data on private clinic participants undertaking a very low carb diet during continued hypoglycaemic agent use achieve 0.9% decrease in HbA1c 33. A 1 year study reported 0.3% decrease in Hba1c in a 1% sample (1,000/105,950 of those recruited) 53. | Observational data with withdrawal of all hypoglycaemic agents achieved a 1.1% fall in short duration diabetes and 0.6% fall in long duration diabetes over 6 months. 2 |
| Remission of type 2 diabetes | A Primary Care series reports 46% of completers on continued metformin were in remission at an average of 2 years. 24 Non-randomised cohort reports 17.6% at 2 years 23. *L | RCT evidence of remission in 46% by intention to treat off all diabetes drugs at 12 months and 36% at 24 months from DIRECT 44. Diadem-1 in a Middle Eastern population achieved 61% remission. Observational studies of remission confirm these effects. 1, 2, 40 44 |

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*This study used <30 grams/day of carbohydrate initially.
† Oral hypoglycaemic agents not stopped on commencing the diet.
‡ All oral hypoglycaemic agents were stopped on commencing the diet in all studies.

**Table 1: Comparison of low carbohydrate and low calorie approaches to remission of Type 2 diabetes**
**Text box 1: Definition of remission**

The consensus guideline from UK Primary Care Diabetes Society and Association of British Clinical Diabetologists lays out 3 criteria for remission of type 2 diabetes:  

(i) Weight loss;  
(ii) Fasting plasma glucose or HbA1c below the WHO diagnostic threshold (<7mmol/l or <48mmol/mol, respectively) on two occasions separated by at least 6 months;  
(iii) Attainment of these glycaemic parameters following the complete cessation of all glucose-lowering therapies.

The term ‘remission’ is sometimes used to describe meeting glycaemic targets even though hypoglycaemic drugs have not been stopped, and care must be taken in the interpretation of stated rates of ‘remission’.

**Text box 2: Definition of Low carbohydrate diets**

The term ‘low carbohydrate’ is used in a variety of ways. Recommendations for consistency of approach have been made, the most widely used being that of Feinman et al:  

<table>
<thead>
<tr>
<th>Description</th>
<th>Grams/day of carbohydrate</th>
<th>Amount of carbohydrate (% energy) (based on 2000 kcal/day)</th>
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<tbody>
<tr>
<td>Very low carbohydrate</td>
<td>20 to 50</td>
<td>≤10</td>
</tr>
<tr>
<td>Low carbohydrate</td>
<td>&gt;50 to &lt;130</td>
<td>&gt;10 to &lt;26</td>
</tr>
<tr>
<td>Moderate carbohydrate</td>
<td>130 to 230</td>
<td>26 to 45</td>
</tr>
<tr>
<td>High carbohydrate</td>
<td>&gt;230</td>
<td>&gt;45</td>
</tr>
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**Text box 3: Key points**

- T2DM develops when personal tolerance for level of fat in liver and pancreas is exceeded.  
- Weight loss sufficient to reverse this will permit return to non-diabetic blood glucose in the early years after diagnosis in both European and non-European populations.  
- Remission of T2DM is durable provided weight regain is avoided.  
- Avoidance of weight regain can be achieved by a number of strategies including moderate carbohydrate restriction, low fat, timed or intermittent fasting or Mediterranean diet. The average effect of each diet is similar and individuals must find which method suits them personally. A food-based approach is important alongside consideration of nutrients.  
- Although it is important not to start a new exercise programme during the weight loss phase, increased physical activity is very important for long term weight maintenance.
For the individual, support from family and friends is important to achieve and maintain weight loss. To enable healthful dietary intakes in populations, policy interventions are necessary. These include but are not limited to strategies such as taxation of sugar sweetened beverages, restriction on food size portions, restriction of fast food outlets near schools and selective food incentives including food prescription.

Text box 4: Future Directions

- Strategies to optimise the avoidance of weight regain in the long term require to be developed and to be rigorously tested in both European and other populations.
- Population strategies are required to prevent the current excessive weight gain during childhood, and separately during adult life. Strategies require to be introduced in order to reverse the trend to develop T2DM at younger ages.
- Long term surveillance of people with T2DM in remission is required to extend the preliminary findings of DiRECT that both vascular event rates and rates of weight-related cancers are decreased.
- Population level surveillance is required to document the effectiveness of limiting supply of energy dense and high carbohydrate processed foods.
Figure 1

Type 2 diabetes develops as long term intake of excess food energy (carbohydrate or fat) leads to accumulation of liver fat, driven on by a vicious cycle of hepatic insulin resistance and hyperinsulinaemia. The raised liver fat level causes increased hepatic export of VLDL-triglyceride. If the subcutaneous fat depot cannot accommodate this, ectopic fat will build up, including in the pancreas. In people with susceptible beta cells, the acute insulin response to food becomes diminished, post-prandial hyperglycaemia is prolonged and \textit{de novo} lipogenesis from glucose is enhanced. The further increase in triglyceride supply further compromises insulin secretory function and ultimately causes de-differentiation of beta cells. Weight loss of 10-15kg achieved by any means allows normalisation of liver fat level and all subsequent steps with remission of type 2 diabetes. Figure is reproduced with permission from Cell Metabolism.