# Type 2 diabetes reversal

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TYPE 2 DIABETES REVERSAL

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**Standfirst Statement**

*Type 2 diabetes is a state of excess fat in liver and pancreas and can be reversed to normal in both European and non-European populations by weight loss and avoidance of weight gain using sound nutritional principles.*

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 If so, you are out of date!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 reversal 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.

**Understanding the simplicity**

A series of hypothesis-driven clinical studies over the last 12 years has clarified the mechanisms which switch on T2DM. These processes can be put into reverse by restriction of food energy to achieve weight loss of around 15kg.¹ 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. The elusive aetiology of T2DM is now understood.²

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.³ 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. The Counterpoint study tested this and demonstrated these processes, leading to a normalisation of fasting plasma glucose within 7 days.¹

In a nutshell, T2DM is characterised by non-alcoholic fatty liver disease, and fat within liver cells causes insulin resistance. The hepatic insulin resistance returns entirely to normal if liver fat levels fall to low normal.⁴ ⁵ In the fasting state plasma insulin levels in T2DM are high – and suddenly the hormone can act, restraining the previous outpouring of glucose from the liver into the blood. Hence the very rapid normalisation of fasting blood glucose.

And one of the other major roles of the liver rapidly returns to normal. The liver supplies triglyceride to the rest of the body, and the sudden fall in liver fat causes the rate of triglyceride export to fall to normal⁶. As a result, the fat content decreases to normal in all sites of ectopic fat accumulation, including the pancreas. Counterpoint also showed that pancreas fat levels were high in T2DM and that very gradual decrease over the 8 weeks of the study led to restoration of near normal insulin responses to eating.¹ ⁵ ⁶

The initial study was conducted in people with T2DM diagnosed within only up to 4 years prior to recruitment, while the next study demonstrated that the longer T2DM had been present, the lower was the chance of return to non-diabetic blood glucose control. For people within the first 10 years of diagnosis of T2DM, around 1 in 2 people can stop diabetes medication and return to non-diabetic glucose control.⁴

That set the scene for a randomised trial in primary care of a low calorie diet compared with conventional management according to best practice guidelines. The DiRECT study jointly run by Newcastle and Glasgow Universities, demonstrated that non-medical primary care staff could achieve remission of T2DM for 2 years in 36% of those enrolled by intention to treat. ⁷ Although other dietary approaches such as low carbohydrate have been suggest to achieve
remission, glycaemic improvement is only seen up to 12 months, with medications not always withdrawn. Remission is now defined as HbA1c <48mmol/mol after weight loss, off all oral agents, on two occasions six months apart.

How complete is the return to normal?

One of the most striking findings of Counterpoint was the acceptability of a low calorie liquid diet for short, planned period in achieving a weight loss of around 15kg in the majority of people. DiRECT confirmed widespread acceptability. It also showed that after rapid weight loss then 2 years of structured weight maintenance, those people in remission showed a complete return to normal maximal insulin secretion rates. This return to normal of the 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 the ability to respond rapidly to meals is lost most likely via downregulation of the genes controlling insulin production. This demonstration of return to normal in a large group of people lays to rest the notion of irreversible beta cell loss.

The recovery of the acute surge in insulin production after a glucose stimulus is sufficient to maintain non-diabetic blood glucose control, although not normal, in contrast to the maximal recovery of beta cell capacity. Provided weight regain is avoided, DiRECT has shown that the recovery of beta cell function remains constant for at least up to 24 months. Some individuals are known to remain non-diabetic for many years provided weight regain is avoided.

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. LookAHEAD is an exception, including ~38% non-white (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 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 on 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%. Further information on South Asians from the on-going large prospective STANDby study, using the same low calorie liquid diet as DIRECT will soon be available. It is notable that the high level of acceptance and effectiveness of liquid formula diets to achieve rapid weight loss was found in both non-Europeans and Europeans.

Although levels of intra-pancreatic fat are lower in African Americans those with T2DM still have higher levels than those without. A recent study in Barbados on a predominantly African-Caribbean population observed comparable rates of weight-loss induced reversal 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, remission of prediabetes by weight loss and exercise was shown not to be affected by ethnicity, with significant improvements in insulin resistance and beta cell function.

From achieving remission to long term maintenance

Achieving remission of T2DM is the first critical step in the goal to gain normal health. Then there follows the important challenge of maintaining a state of remission. It is clear that weight loss is a pivotal factor for diabetes remission, but sustaining weight loss is one of the great difficulties in human health. A multibillion dollar industry exists offering solutions, many with overstretched claims of success, yet, challenges remain.

The US national registry of free-living weight-loss maintainers over 10y has provided important insights. 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. This provides reasons for optimism. 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 were in remission.

Dietary advice – key components

Macronutrients

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 intake provides the highest amount of calories, 9 kcal per gram, while carbohydrate and protein provide much less, 4 kcal per gram, coupled with beliefs about cardiovascular risks. There is increasing interest in low- or very low-carbohydrate diets popularised with named programmes like the Atkins diet. Individual RCTs yielded varying results declaring the superiority of one or the other diet type, but when the totality of the evidence was appraised, two patterns emerged. One, that either type of diet, low-fat or low-carbohydrate, can be equally effective as long as participants can adhere to the diet. Second, that greater long-term weight loss at >1y was achieved with a low-carbohydrate diet than with a low-fat diet, but the magnitude of this difference was very modest at around 1kg body weight. Low-fat but high-protein diets may increase weight loss owing partly to greater satiety and energy expenditure, but most RCTs investigating this have been short-term (<6 months) and long-term effects are unclear.

A challenge is the difficulty of dietary adherence, with substantial differences in prescribed and attained intakes. Also, there is confusion on the definition of what constitutes low-carbohydrate, varying widely across studies from <45% of total energy to ketogenic levels of intake of under 50g/day (<10% of energy). Similarly definitions vary for ‘low fat’. The take-home message is that adherence is more important than macronutrient compositions, but the best diet for longer-term success will be one that is tailored to individuals on their personal preferences and circumstances.

Dietary restriction through eating strategies

Portion control is an age-old strategy to reduce caloric intake. The concept of fasting is also not new: short-term dietary self-restraint was traditionally associated with religious faith. Several intermittent fasting options are now promoted for weight control, but three have been more researched. Daily or alternate day fasting aims for ~25% 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 say 12 noon till 6pm. Intermittent fasting may also have longer term impacts for health and longevity. Further research is needed to evaluate the effectiveness of such regimes for long-term weight maintenance and whether different fasting approaches may be combined effectively. Challenges such as hunger and cravings on fasting days could be too great for many despite evidence that these diminish over time. However, as with other dietary approaches such as a low-carbohydrate or low-fat diet, fasting may not be suitable for all, and flexibility and a choice of options are needed for success.

**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 diet-induced thermogenesis, appetite, satiety, hunger and brain reward. Also, weight is a critical contributor to cardiometabolic disease, but not the sole one. Thus, rather than a focus on total fat, limiting saturated fat intake while increasing intake of unsaturated fat is relevant. Similarly, reducing all carbohydrates indiscriminately takes away the benefits from the consumption of fibre and wholegrain for weight, glycaemia, lipids and gut and cardiometabolic health. Whether protein is derived from plant or animal sources matters, given the increased understanding that limiting the habitual consumption of red and processed meat may have health benefits. But, note that not all plant-based diets are automatically healthy, because here too quality matters.

We should acknowledge dietary complexity, for we now know that even a sub-classification of a macronutrient (e.g. saturated fat) based on chemistry is not sufficiently discriminatory for health effects. Both dairy and meat are typically high in saturated fat and protein but some types of dairy such as fermented dairy (yoghurt) is associated inversely with cardiometabolic disease risk, while processed meat is associated positively, highlighting the need to consider food sources of the nutrients.

Advice on foods consumed within an overall dietary pattern is most likely to 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. Other dietary patterns are also effective, such as the DASH diet, the healthy eating index, Nordic diet, and vegetarian or other meal plans. Avoidance of ultraprocessed foods and a move to the consumption of fresh, whole foods has health benefits including for weight and glycaemic control.

**Influences on long-term dietary intakes – lending a helping hand?**

Many personal factors influence what we eat: 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 include food availability, accessibility, cost, and many enticements: advertising, ready availability of fast-food take-aways and home delivery options and ever increasing price promotions for highly processed foods.

Continued support from healthcare professionals is one strategy to increase the avoidance of long-term weight re-gain 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 there is observational evidence that
successful weight-loss maintenance over 10y requires sustained behaviour change including maintaining physical activity, low calorie and fat intake, high levels of dietary restraint, low levels of disinhibition, and frequent self-weighing.\textsuperscript{31}

Education, dietary guidelines, and strategies that enable people to make healthy food choices such as clear food labelling, are necessary but not yet universally available. Clear evidence supports the case for 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.\textsuperscript{32} 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.\textsuperscript{33}

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 has been demonstrated in both European and non-European populations and is independent of initial body mass index, an important point for South Asian 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 with confidence.

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.

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References


Type 2 diabetes develops as long term intake of excess food energy 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 de novo lipogenesis from glucose is enhanced. The further increase in triglyceride supply further compromises insulin secretory function. Weight loss of 10-15kg allows normalisation of liver fat level and all subsequent steps with remission of type 2 diabetes. Figure is reproduced with permission from Cell Metabolism.

Text box: 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 moderate carbohydrate restriction, Mediterranean diet, timed or intermittent fasting or low fat. The average effect of each diet is similar and individuals must find which method suits them personally.
- 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: 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, 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 true health economic effects of the above measures.