Nutritional basis of type 2 diabetes remission

Roy Taylor and colleagues explain how type 2 diabetes can be reversed by weight loss and avoidance of weight regain

Type 2 diabetes mellitus was once thought to be irreversible and progressive, but a series of clinical studies over the past 12 years have clarified the mechanisms that cause the disease. We now know that the processes that cause type 2 diabetes can be returned to normal functioning by restriction of food energy to achieve weight loss of around 15 kg.[1] Around half of people who are within the first 10 years of diagnosis and manage to follow food energy restriction can stop all diabetes medication and return to non-diabetic glucose control.[2 3] Remission is achieved when haemoglobin A_{1c} concentrations of 48 mmol/mol are recorded after weight loss and at least six months later without any anti-diabetic medications (box 1).[4] Here we summarise the new understanding of type 2 diabetes and consider how different changes to food intake can achieve the necessary weight loss and maintenance required for remission of diabetes.

What causes type 2 diabetes and remission?

In 2008 the twin cycle hypothesis postulated that there were vicious cycles of fat accumulation in the liver and pancreas that lead to the development of type 2 diabetes over at least a decade (fig 1).[6] The hypothesis was developed from emerging knowledge on the relation between liver fat and control of the constant flow of glucose into the blood as well as observation that normal insulin secretion returned after substantial weight loss in people with type 2 diabetes. It predicted that major calorie restriction would lead to a rapid fall in liver fat, normalisation of liver insulin sensitivity, and decrease to normal levels of glucose production by the liver.

Testing the hypothesis required a surefire way of achieving around 15 kg weight loss, and one of the most striking findings of the 2011 Counterpoint study was the acceptability of a low calorie liquid diet for a short planned period.[1] People with type 2 diabetes in the study achieved an average of over 15 kg weight loss in eight weeks during normal living.[1] Participants' initially high levels of liver and pancreas fat fell to normal ranges, with decreased hepatic glucose output and improved β cell function. The study included only people who had had diabetes diagnosed within four years, but a subsequent study found that remission was much less likely after 10 years of diabetes.[2]

These studies set the scene for Direct (Diabetes Remission Clinical Trial), a randomised controlled trial in primary care of a low calorie diet with structured follow-up compared with conventional management according to best practice guidelines. This study confirmed widespread acceptability, with almost 30% of those invited accepting to participate and an average weight loss of 14.5 kg.[7] Primary care nurses or dietitians worked with patients in the intervention group, and 36% (53/149) achieved remission for two years.[8]

Direct also showed that people in remission could return to normal maximal insulin secretion rates if they maintained their weight after initial rapid weight loss.[9] This complete return to normal functional β cell mass is remarkable. Previously, both clinical and histological studies on the pancreas found that β cell capacity declined to around 50% by the time of diagnosis, and death or apoptosis of the β cells had been assumed. But we now know that excess fat exposure causes β cells to de-differentiate, losing ability to secrete insulin[10]—most likely through downregulation of the genes controlling insulin production. The return to normal for a large group of people who used to have type 2 diabetes shows the potential for β cell recovery. Some individuals remain in remission for many years provided weight is not regained.[11]

Type 2 diabetes is characterised by accumulation of more fat in the liver and pancreas than an individual can tolerate. Different people have different fat thresholds, and this explains why only around half of people diagnosed with type 2 diabetes are obese and some have a healthy body mass index.[12 13] The excess fat within liver cells causes insulin resistance, and this entirely resolves if liver fat falls to low-normal levels.[12 14] Once this happens insulin can act normally again, restraining the outpouring of glucose from the liver into the blood and rapidly normalising fasting blood glucose concentrations.

Because the liver supplies triglyceride to the rest of the body, the sudden fall in liver fat causes the high rate of triglyceride supply to fall to normal.[14] As a result, fat levels inside the pancreas gradually decrease, along with all ectopic fat depots. Gradually, normal insulin response to eating is restored.[12 14 15]

Any sustained decrease in calorie intake is able to remove the excess intra-organ fat. For example, the enforced sudden decrease

KEY MESSAGES

- Type 2 diabetes develops when personal tolerance for fat levels in the liver and pancreas are exceeded
- Weight loss sufficient to reverse this will permit return to non-diabetic blood glucose in the early years after diagnosis
- Remission is durable provided weight regain is avoided
- Avoidance of weight regain can be achieved by various strategies and individuals must find the dietary strategies most suited to them alongside increased physical activity
- To enable healthful dietary intakes in populations, policy interventions such as taxation on calorie dense foods and restrictions on portion size are needed.

Box 1: Definition of remission*

The consensus guideline from UK Primary Care Diabetes Society and Association of British Clinical Diabetologists lays out three criteria for remission of type 2 diabetes[4]:

- Weight loss
- Fasting plasma glucose <7 mmol/L or HbA_{1c} <48 mmol/mol (WHO diagnostic thresholds) on two occasions separated by at least six months
- Attainment of these glycaemic parameters after complete cessation of all glucose lowering therapies

*Remission is sometimes used to describe meeting glycaemic targets even though hypoglycaemic drugs have not been stopped. Care must be taken in the interpretation of stated rates of remission.

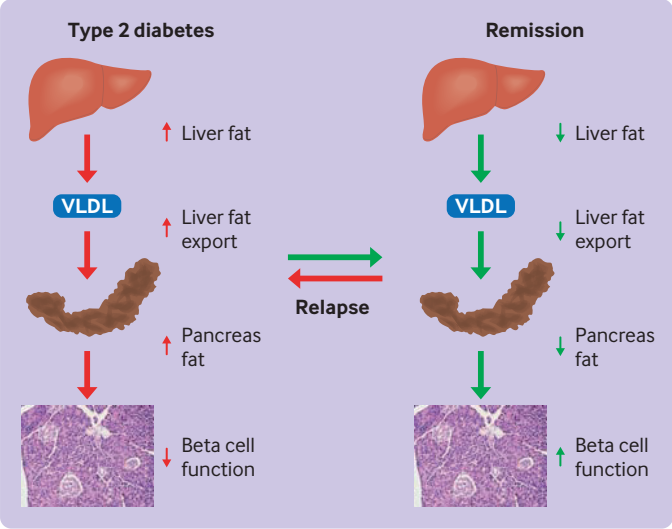

Fig 1 | Type 2 diabetes develops as long term intake of excess food energy leads to accumulation of liver fat, driven by a vicious cycle of hepatic insulin resistance and hyperinsulinaemia. The raised liver fat level causes increased hepatic export of very low density lipoprotein (VLDL) triglycerides. If the subcutaneous fat depot cannot accommodate this, ectopic fat will build up, including in the pancreas. In people with susceptible β cells, the acute insulin response to food becomes diminished and de novo lipogenesis from glucose is enhanced. β Cell function can be restored if liver fat is reduced through weight loss. Figure is modified from Al-Mrabeh et al with permission[5]

in food intake after bariatric surgery brings about remission by the same underlying mechanisms as voluntary dieting.[15 16] Bariatric surgery necessitates nil by mouth for a period followed by much reduced food intake and achieves around 64% remission of diabetes at two years.[17]

In the UK Prospective Diabetes Study, normalisation of fasting glucose levels was reported in 15% of participants following an initial dietary weight loss phase.[18] The Look-Ahead randomised trial compared intensive physical activity advice plus dietary restriction with conventional management of type 2 diabetes.[11] Although diabetes remission was not an outcome measure, the modest weight loss achieved led to remission in 11.5% of participants in the intensive lifestyle intervention group. Merely providing the information on the degree of weight loss required for remission can allow motivated people to achieve this for themselves using their preferred method.[19]

Key components of dietary advice

Low carbohydrate versus low calorie diets

Much noise and confusion surround the "best" macronutrient composition in dietary advice for weight loss. Low fat diets used to be favoured. This was because fat contains a higher density of calories (9 kcal/g) than carbohydrate and protein (4 kcal/g), coupled with concerns about the cardiovascular risks of higher fat diets. On the other hand, interest is increasing in low or very low carbohydrate diets for weight loss because carbohydrate is the primary contributor to post-prandial glycaemia. Table 1 summarises the main evidence comparing low calorie and low carbohydrate diets.

Randomised trials in general populations (not specific for diabetes) show that both low calorie and low carbohydrate diets can be effective for weight loss as long as participants can adhere to the diet.[33] Studies show slightly greater weight loss up to one year with low carbohydrate diets than low fat diets, with a modest difference of around 1 kg body weight,[34 35] but the scanty randomised trial evidence at two years shows no difference between diets.[20 36]

A non-randomised study with intensive follow-up reported that a very low carbohydrate approach in people with type 2 diabetes can achieve and sustain weight loss of 12 kg at two years.[28] Moreover, a two year follow-up of a cohort (not selected for diabetes) in a single British general practice reported a decrease in median weight of 8.3 kg at two years on a low carbohydrate diet (50-130 g/day).[30] For glycaemic control, a non-randomised study of a diet with less than 30 g/day of carbohydrate reported 58% of participants achieving HbA_{1c} <48 mmol/mol, but metformin was not discontinued.[37] However, non-randomised or uncontrolled studies report data on completers and are therefore not directly comparable with randomised trials, which analyse by intention to treat and outcomes. Randomised trials are generally considered to provide the highest quality of evidence when they are feasible.

To our knowledge only one randomised trial has reported diabetes remission rates after a low carbohydrate diet intervention in patients with poorly controlled glycaemia. However, as metformin was continued the participants did not meet the current definition of remission (box 1). Participants in the intervention group lost 3.7 kg more than those in the comparator group and 11% (12/109) achieved HbA_{1c} <48 mmol/mol compared with 0/117 in the comparator group.[31]

Heterogeneity in definitions also makes interpretation difficult. What constitutes a low carbohydrate diet varies widely across studies from <45% of total energy[22] to ketogenic levels of intake of under 50 g/day (<10% of energy).[28] Box 2 gives a standardised definition.

Dietary restriction through eating strategies

Portion control is an established strategy for weight loss, as is the concept of fasting: short term dietary self-restraint was traditionally associated with religious practices. Intermittent fasting has become popular more recently. Daily or alternate day fasting aims for roughly 25% lower intake of food energy: the 5:2 diet reduces intake to 500 to 700 calories a day for two days each week, while time restricted feeding limits eating to within a 6 to 8 hour window each day (for instance, omit breakfast and eat only between 12 pm and 6 pm). Systematic reviews show that each of these eating strategies can be effective, with reports of weight loss of up to 13% of baseline weight,[39] and that different intermitting fasting approaches achieve similar weight losses as the traditional continuous energy restriction approach.[40 41] However, the existing randomised trials are of short duration with small sample size and heterogeneity across studies, and further research is warranted to test whether these approaches can be effective for the remission of type 2 diabetes.[39 42] Beyond weight loss, intermittent fasting may have longer term effects on health and longevity.[43] Challenges such as hunger and cravings on fasting days could be too great for some despite evidence that these diminish over time.[43]

Dietary quality

Food is eaten within overall sociocultural contexts, and focusing solely on the

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Table 1 | The controversy about low carbohydrate or low calorie approaches to remission of type 2 diabetes: Areas of agreement and disagreement

	Low or very low carbohydrate diets	Low or very low calorie diets†
Good for cardiovascular health	Improves indices of cardio-vascular risk for up to 2 years[20 21]	Improves QRISK score up to 2 years[8]
Long term outcome data	Not available	Not available
Long term weight management	The major problem. Need for continuing support and rescue management of weight regain	The major issue. Need for continuing support and rescue management of weight regain
Acceptability	Single centre reports acceptability[22]	RCT data to 2 years shows ongoing compliance in the majority.[8] Psychological study reports good acceptability up to 6 months[23]
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 years[20 21 24]	Significantly different from controls up to 2 years.[8 25 26] Weight loss around 10 kg in the active arm at 12 months in Direct and Droplet and 7.6 kg at 2 year in Direct[26 27]
Observational studies	Selected paying participants achieved 10 kg weight loss at 2 years.‡[28] A 1 year study reported 4.3 kg weight loss in a 1% sample completing follow-up (1000/105 950 initially signed up)[29]	Mean weight loss of 13.7 kg at 6 months[2]
Improvement in glucose control:		
RCT evidence	Meta-analyses of multiple trials show significant decrease in HbA_{1c} 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 from active controls[20 21]	One multisite trial found clinically important decrease in HbA_{1c} at 6, 12, and 24 months with 36% remission at 2 years[8]
Observational studies	Private clinic participants undertaking a very low carb diet while continuing hypoglycaemic agents achieved 0.9% decrease in HbA_{1c}[28] A 1 year study reported 0.3% decrease in HbA_{1c} in 1000 people[29]	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[30] Non-randomised cohort reports 17.6% at 2 years[28] RCT evidence of remission following weight management based on low carbohydrate diet in 11% at 1 year‡¶[31]	RCT evidence of remission in 46% by intention to treat off all diabetes drugs at 12 months and 36% at 24 months from Direct.[8] Diadem-1 in a Middle Eastern population achieved 61% remission. Observational studies of remission confirm these effects.[12 32§]

*Low: 50-130 g/day or between 10-26% total energy; Very low: 20-50 g/day or under 10% total energy
†700-1000 kcal/day (or 35-50% of a 2000 kcal/day intake) for a defined period then weight maintaining diet
‡This study used <30 g/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.

quantity or type of macronutrients may be over simplistic. Different food sources affect physiological pathways differently, including appetite, satiety, hunger, and diet induced thermogenesis. Reducing all carbohydrates indiscriminately may take away the benefits from the consumption of fibre and wholegrain. Decades of research have clarified the importance of distinguishing between saturated, unsaturated, and trans fats for cardiometabolic disease.[44-46] Furthermore, even considering saturated fats as a group is not sufficiently discriminatory to understand health effects because individual saturated fatty acids differ in their association with type 2 diabetes.[47]

The importance of food sources rather than macronutrient type is highlighted by the associations of meat and dairy, which are both typically high in saturated fat and protein, with cardiometabolic risk. Some types of dairy such as fermented dairy (yoghurt or cheese) are associated inversely with type 2 diabetes and cardiovascular disease, whereas red and processed meat are positively associated.[45 48 49]

Advice on foods consumed within an overall dietary pattern may facilitate better longer term adherence. Evidence supports the benefits of Mediterranean-type diets for several health outcomes, although this dietary pattern is not singularly superior or easier to adhere to. Other effective dietary patterns include DASH (dietary approaches to stop hypertension), the healthy eating index, Nordic diet, and vegetarian or other meal plans, but more research is needed.[50] Consensus is also emerging that avoidance of ultraprocessed foods and increased consumption of fresh, whole foods has health benefits, including for weight and glycaemic control. 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 its effect on type 2 diabetes more comprehensively.

Box 2: What is a low carbohydrate diet?

The term "low carbohydrate" is used in various ways. Recommendations for consistency of approach have been made, the most widely used being that of Feinman and colleagues[38]:

- Very low carbohydrate: 20 to 50 g/day (≤10% of energy, based on 2000 kcal/day)
- Low carbohydrate: >50 to <130 (>10% to <26%)
- Moderate carbohydrate: 130 to 230 (26% to 45%)
- High carbohydrate >230 (>45%)

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

Remission in ethnically diverse and global populations

Most participants in studies on remission of type 2 diabetes carried out in western countries have been white, and background nutritional patterns of other ethnicities have to be considered.[7 51] The Look-Ahead study included around 38% ethnic minority participants (mainly Hispanic and African American). Although not a primary aim of the study, remission of type 2 diabetes was observed in proportion to weight loss (11.5% (248/2157) at year 1 and 7.3% (150/2056) at year 4, with weight loss of 8.6% and 4.7%, respectively); no association of ethnicity with remission was observed.[11] A large community based analysis from the Kaiser Permanente Northern California Registry showed a higher likelihood of remission in African Americans than in the white population, with overall

seven year remission of 4.6% among people with type 2 diabetes for less than two years.[52] A similar retrospective survey of people aged over 65 years observed higher rates of non-surgical remission after eight years in Asian and Hispanic people than in white and African American groups.[53]

South Asians achieve remission after a low calorie liquid diet similarly to white Europeans.[54] A two year prospective study of a low calorie diet and advice to walk daily in a young South Asian population with recent onset type 2 diabetes found 75% remission at three months and 69% at two years. HbA_{1c} was <39 mmol/mol in 53% of participants at three months and in 47% at two years; 22% had HbA_{1c} 39-47 mmol/mol at both time points.[55] Similar observations were made in a Thai population: 79% had achieved remission at 12 weeks (with an average weight loss of 10 kg) and 30% had maintained remission at 12 months.[56] A trial in a Middle Eastern population observed remission in 61% of those allocated to total diet replacement and lifestyle intervention.[25]

A recent study in Barbados on a predominantly African Caribbean population observed rates of weight loss induced remission similar to those documented in Direct.[32] This was achieved over eight weeks by using a hypocaloric liquid diet (760 kcal) with withdrawal of diabetes medication on day 1 of the diet. Nine of the 11 (82%) participants who lost at least 10 kg achieved non-diabetic fasting blood glucose levels compared with six of 14 (43%) who lost <10 kg. Remission of prediabetes by weight loss and physical activity has also been shown in Indian populations, with significant improvements in insulin resistance and β cell function.[57 58]

Evidence on ways to improve long term remission

The US national registry has documented the feasibility of people maintaining substantial weight loss over 10 years and has provided important insights into nutritional and other factors.[59] Weight regain was fastest for participants in the early years of follow-up, with decreasing rates over each of the first five years followed by stable maintenance over the subsequent five years, suggesting that maintenance requires less effort over time. Many personal factors influence what we eat and therefore how well weight loss is maintained, including age, sex, genetics, ethnicity, body fat status, level of physical activity, and family and social culture. But there are also profound wider influences on food intake. These include food availability, accessibility, cost, advertising, ready availability of fast food takeaways and home delivery options, and price promotions for processed energy dense foods.

Psychological study of participants in weight loss studies of remission has shown support from family and friends has a critical role in both achieving weight loss and avoiding regain.[23 60] Eating is a social activity, with individuals tending to eat similarly to their family and friendship groups. The psychological term "behaviour contagion" is descriptive, and it is notable that spouses or partners often report weight loss. Given that type 2 diabetes runs in families, all, including children, are likely to benefit.

Continued support from healthcare professionals, irrespective of composition of food advised, is one strategy to avoid weight regain and sustain diabetes remission. In Direct a "rescue plan" of partial or total meal replacement was offered to participants who regained 2 kg or 4 kg, respectively.[8] More research is needed, but observational evidence indicates that maintaining weight loss over 10 years requires sustained dietary change, regular physical activity, and frequent self-weighing.[59 61]

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. 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 food portions, packages, and tableware to influence the quantities of food and beverages consumed.[62] Another potentially clinically and economically effective strategy is food prescription to promote healthier eating. Pilot data from the US on people with uncontrolled type 2 diabetes and food insecurity shows substantial reductions in HbA_{1c} in those who received fresh food on prescription.[63]

Future directions

Type 2 diabetes can be reversed by substantial weight loss in the early years after diagnosis, and the pathophysiological basis of this is now clear. Long term maintenance of weight loss brings about lasting remission, but this is more difficult to achieve than weight loss. Strategies to optimise the avoidance of weight regain in the long term need to be developed and rigorously tested in all populations. Population strategies are also required to enable healthier food choices and prevent the current excessive weight gain during childhood and adult life. Long term surveillance of people with type 2 diabetes in remission is needed to determine whether it also decreases the rates of vascular events and weight related cancers.

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