

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 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 sure-fire 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 insulin¹⁰—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 diabetes⁴:

- 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.

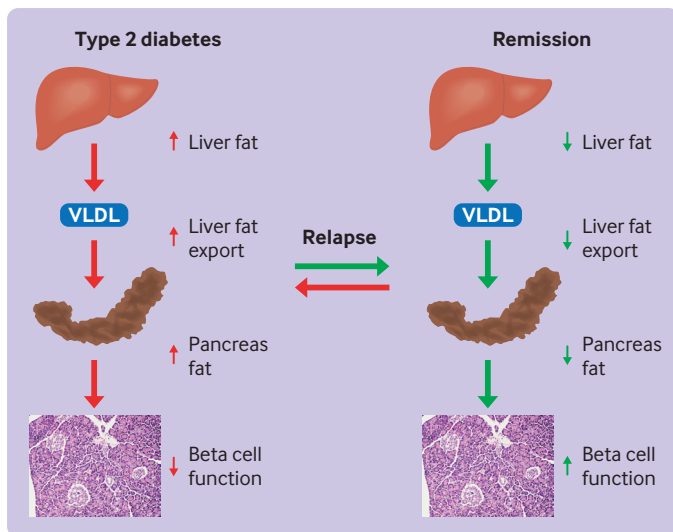


Fig 1 | Type 2 diabetes develops as long term intake of excess food energy leads to accumulation of liver fat, driven by a vicious cycle of hepatic insulin resistance and hyperinsulinaemia. The raised liver fat level causes increased hepatic export of very low density lipoprotein (VLDL) triglycerides. 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 permission⁵

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 energy²² 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 intermittent 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

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.

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

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 colleagues³⁸:

- 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.

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.

Competing interests: RT and NGF are unpaid members of the Joint SACN/NHS-England/Diabetes-UK Working Group to review the evidence on lower carbohydrate diets compared with current government advice for adults with type 2 diabetes. RT has received fees for educational lectures from Lilly and Janssen and is author of *Life Without Diabetes* (Short Books). 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. The views expressed are the authors' own. RT has research funding from Diabetes UK (17/0005645 and 13/0004691). NGF was supported by Medical Research Council Epidemiology Unit (MC_UU_00006/3) and NIHR Biomedical Research Centre Cambridge: Nutrition, Diet, and Lifestyle Research Theme (IS-BRC-1215-20014) and NGF is a NIHR Senior Investigator. The views expressed are those of the authors and not necessarily those of the NIHR, the Department of Health and Social Care, or any other organisations they are associated with.

Provenance and peer review: Commissioned; externally peer reviewed.

This article is one of a series commissioned by The BMJ. Open access fees for the series were funded by Swiss Re, which had no input into the commissioning or peer review of the articles. The BMJ thanks the series advisers, Nita Forouhi, Dariush Mozaffarian, and Anna Larrey for valuable advice and guiding selection of topics in the series.

Roy Taylor, professor¹

Ambady Ramachandran, professor^{2,3}

William S Yancy Jr, physician⁴

Nita G Forouhi, professor⁵

¹Magnetic Resonance Centre, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

²India Diabetes Research Foundation, Chennai, India

³Dr A Ramachandran's Diabetes Hospitals, Chennai, India

⁴Duke Lifestyle and Weight Management Center, Duke University Health System and Department of Medicine, Duke University Medical School, Durham, NC, USA

⁵MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Cambridge, UK

Correspondence to: R Taylor
Roy.Taylor@ncl.ac.uk



OPEN ACCESS

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.



- 1 Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 2011;54:2506-14. doi:10.1007/s00125-011-2204-7
- 2 Steven S, Hollingsworth KG, Al-Mrabeh A, et al. Very low-calorie diet and 6 months of weight stability in type 2 diabetes: pathophysiological changes in responders and nonresponders. *Diabetes Care* 2016;39:808-15. doi:10.2337/dc15-1942
- 3 Taylor R, Al-Mrabeh A, Zhyzhneuskaya S, et al. Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for β cell recovery. *Cell Metab* 2018;28:547-556.e3. doi:10.1016/j.cmet.2018.07.003
- 4 Nagi D, Hambling C, Taylor R. Remission of type 2 diabetes: a position statement from the Association of British Clinical Diabetologists (ABCD) and the Primary Care Diabetes Society (PCDS). *British Journal of Diabetes*. 2019;19:73-6. doi:10.15277/bjd.2019.221
- 5 Al-Mrabeh A, Zhyzhneuskaya SV, Peters C, et al. Hepatic lipoprotein export and remission of human type 2 diabetes after weight loss. *Cell Metab* 2020;31:233-249.e4. doi:10.1016/j.cmet.2019.11.018
- 6 Taylor R. Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause. *Diabetologia* 2008;51:1781-9. doi:10.1007/s00125-008-1116-7
- 7 Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2018;391:541-51. doi:10.1016/S0140-6736(17)33102-1
- 8 Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019;7:344-55. doi:10.1016/S2213-8587(19)30068-3
- 9 Zhyzhneuskaya SV, Al-Mrabeh A, Peters C, et al. Time course of normalization of functional β -cell capacity in the diabetes remission clinical trial after weight loss in type 2 diabetes. *Diabetes Care* 2020;43:813-20. doi:10.2337/dc19-0371
- 10 Cinti F, Bouchi R, Kim-Muller JY, et al. Evidence of β -cell dedifferentiation in human type 2 diabetes. *J Clin Endocrinol Metab* 2016;101:1044-54. doi:10.1210/jc.2015-2860
- 11 Gregg EW, Chen H, Wagenknecht LE, et al. Look AHEAD Research Group. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA* 2012;308:2489-96. doi:10.1001/jama.2012.67929
- 12 Taylor R, Holman RR. Normal weight individuals who develop type 2 diabetes: the personal fat threshold. *Clin Sci (Lond)* 2015;128:405-10. doi:10.1042/CS20140553
- 13 Logue J, Walker JJ, Leese G, et al. Scottish Diabetes Research Network Epidemiology Group. Association between BMI measured within a year after diagnosis of type 2 diabetes and mortality. *Diabetes Care* 2013;36:887-93. doi:10.2337/dc12-0944
- 14 Taylor R, Al-Mrabeh A, Zhyzhneuskaya S, et al. Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for β cell recovery. *Cell Metab* 2018;28:667. doi:10.1016/j.cmet.2018.08.010
- 15 Steven S, Hollingsworth KG, Small PK, et al. Weight loss decreases excess pancreatic triacylglycerol specifically in type 2 diabetes. *Diabetes Care* 2016;39:158-65. doi:10.2337/dc15-0750
- 16 Lingvay I, Guth E, Islam A, Livingston E. Rapid improvement in diabetes after gastric bypass surgery: is it the diet or surgery? *Diabetes Care* 2013;36:2741-7. doi:10.2337/dc12-2316
- 17 Panunzi S, Carlsson L, De Gaetano A, et al. Determinants of Diabetes Remission and Glycemic Control After Bariatric Surgery. *Diabetes Care* 2016;39:166-74. doi:10.2337/dc15-0575
- 18 UKPDS. UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients, UKPDS Group. *Metabolism* 1990;39:905-12. doi:10.1016/0026-0495(90)90299-R
- 19 Steven S, Lim EL, Taylor R. Population response to information on reversibility of Type 2 diabetes. *Diabet Med* 2013;30:e135-8. doi:10.1111/dme.12116
- 20 Sainsbury E, Kizirian NV, Partridge SR, Gill T, Colagiuri S, Gibson AA. Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: A systematic review and meta-analysis. *Diabetes Res Clin Pract* 2018;139:239-52. doi:10.1016/j.diabres.2018.02.026
- 21 Korsmo-Haugen HK, Brurberg KG, Mann J, Aas AM. Carbohydrate quantity in the dietary management of type 2 diabetes: A systematic review and meta-analysis. *Diabetes Obes Metab* 2019;21:15-27. doi:10.1111/dom.13499
- 22 Unwin DJ, Tobin SD, Murray SW, Delon C, Brady AJ. Substantial and sustained improvements in blood pressure, weight and lipid profiles from a carbohydrate restricted diet: an observational study of insulin resistant patients in primary care. *Int J Environ Res Public Health* 2019;16:E2680. doi:10.3390/ijerph16152680
- 23 Rehackova L, Araujo-Soares V, Adamson AJ, Steven S, Taylor R, Sniehotta FF. Acceptability of a very-low-energy diet in Type 2 diabetes: patient experiences and behaviour regulation. *Diabet Med* 2017;34:1554-67. doi:10.1111/dme.13426
- 24 Sato J, Kanazawa A, Hatae C, et al. One year follow-up after a randomized controlled trial of a 130 g/day low-carbohydrate diet in patients with type 2 diabetes mellitus and poor glycemic control. *PLoS One* 2017;12:e0188892. doi:10.1371/journal.pone.0188892
- 25 Taheri S, Zaghoul H, Chagoury O, et al. Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial. *Lancet Diabetes Endocrinol* 2020;8:477-89. doi:10.1016/S2213-8587(20)30117-0
- 26 Astbury NM, Aveyard P, Nickless A, et al. Doctor referral of overweight people to low energy total diet replacement treatment (DROPLET): pragmatic randomised controlled trial. *BMJ* 2018;362:k3760. doi:10.1136/bmj.k3760
- 27 Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019;7:344-55. doi:10.1016/S2213-8587(19)30068-3
- 28 Athinarayanan SJ, Adams RN, Hallberg SJ, et al. Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: a 2-year non-randomized clinical trial. *Front Endocrinol (Lausanne)* 2019;10:348-65. doi:10.3389/fendo.2019.00348
- 29 Saslow LR, Summers C, Aikens JE, Unwin DJ. Outcomes of a digitally delivered low-carbohydrate type 2 diabetes self-management program: 1-year results of a single-arm longitudinal study. *JMIR Diabetes* 2018;3:e12. doi:10.2196/diabetes.9333
- 30 Unwin D, Khalid AA, Unwin J, et al. Insights from a general practice service evaluation supporting a lower carbohydrate diet in patients with type 2 diabetes mellitus and prediabetes: a secondary analysis of routine clinic data including HbA1c, weight and prescribing over 6 years. *BMJ Nutr Prev Health* 2020;3:285-94. doi:10.1136/bmjnp-2020-000072
- 31 Yancy WS Jr, Crowley MJ, Dar MS, et al. Comparison of group medical visits combined with intensive weight management vs group medical visits alone for glycaemia in patients with type 2 diabetes: a noninferiority randomized clinical trial. *JAMA Intern Med* 2020;180:70-9. doi:10.1001/jamainternmed.2019.4802
- 32 Bynoe K, Unwin N, Taylor C, et al. Inducing remission of Type 2 diabetes in the Caribbean: findings from a mixed methods feasibility study of a low-calorie liquid diet-based intervention in Barbados. *Diabet Med* 2020;37:1816-24. doi:10.1111/dme.14096
- 33 Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA* 2014;312:923-33. doi:10.1001/jama.2014.10397
- 34 Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. *Br J Nutr* 2013;110:1178-87. doi:10.1017/S0007114513000548
- 35 Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB. Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2015;3:968-79. doi:10.1016/S2213-8587(15)00367-8
- 36 van Zuuren EJ, Fedorowicz Z, Kuijpers T, Pijl H. Effects of low-carbohydrate- compared with low-fat-diet interventions on metabolic control in people with type 2 diabetes: a systematic review including GRADE assessments. *Am J Clin Nutr* 2018;108:300-31. doi:10.1093/ajcn/nqy096
- 37 Hallberg SJ, McKenzie AL, Williams PT, et al. Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 year: an open-label, non-randomized, controlled study. *Diabetes Ther* 2018;9:583-612. doi:10.1007/s13300-018-0373-9
- 38 Feinman RD, Pogozelski WK, Astrup A, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. *Nutrition* 2015;31:1-13. doi:10.1016/j.nut.2014.06.011
- 39 Welton S, Minty R, O'Driscoll T, et al. Intermittent fasting and weight loss: Systematic review. *Can Fam Physician* 2020;66:117-25.
- 40 Davis CS, Clarke RE, Coulter SN. Intermittent energy restriction and weight loss: a systematic review. *Eur J Clin Nutr* 2016;70:292-9. doi:10.1038/ejcn.2015.195
- 41 Rynders CA, Thomas EA, Zaman A, Pan Z, Catenacci VA, Melanson EL, et al. Effectiveness of intermittent fasting and time-restricted feeding compared to continuous energy restriction for weight loss. *Nutrients* 2019;11:2442-64. doi:10.3390/nu11102442
- 42 Headland M, Clifton PM, Carter S, Keogh JB. Weight-loss outcomes: a systematic review and meta-analysis of intermittent energy restriction trials lasting a minimum of 6 months. *Nutrients* 2016;8:354-65. doi:10.3390/nu8060354
- 43 de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. *N Engl J Med* 2019;381:2541-51. doi:10.1056/NEJMr1905136
- 44 Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. *Circulation* 2016;133:187-225. doi:10.1161/CIRCULATIONAHA.115.018585
- 45 Feroz NG, Krauss RM, Taubes G, Willett W. Dietary fat and cardiometabolic health: evidence, controversies, and consensus for guidance. *BMJ* 2018;361:k2139. doi:10.1136/bmj.k2139
- 46 Feroz NG, Misra A, Mohan V, Taylor R, Yancy W. Dietary and nutritional approaches for prevention and management of type 2 diabetes. *BMJ* 2018;361:k2234. doi:10.1136/bmj.k2234
- 47 Feroz NG, Koulman A, Sharp SJ, et al. Differences in the prospective association between

- individual plasma phospholipid saturated fatty acids and incident type 2 diabetes: the EPIC-InterAct case-cohort study. *Lancet Diabetes Endocrinol* 2014;2:810-8. doi:10.1016/S2213-8587(14)70146-9
- 48 Schwingshackl L, Hoffmann G, Lampousi AM, et al. Food groups and risk of type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. *Eur J Epidemiol* 2017;32:363-75. doi:10.1007/s10654-017-0246-y
- 49 Key TJ, Appleby PN, Bradbury KE, et al. Consumption of meat, fish, dairy products, and eggs and risk of ischemic heart disease. *Circulation* 2019;139:2835-45. doi:10.1161/CIRCULATIONAHA.118.038813
- 50 Schulze MB, Martínez-González MA, Fung TT, Lichtenstein AH, Forouhi NG. Food based dietary patterns and chronic disease prevention. *BMJ* 2018;361:k2396. doi:10.1136/bmj.k2396
- 51 Dambha-Miller H, Day AJ, Strelitz J, Irving G, Griffin SJ. Behaviour change, weight loss and remission of Type 2 diabetes: a community-based prospective cohort study. *Diabet Med* 2019.
- 52 Karter AJ, Nundy S, Parker MM, Moffet HH, Huang ES. Incidence of remission in adults with type 2 diabetes: the diabetes & aging study. *Diabetes Care* 2014;37:3188-95. doi:10.2337/dc14-0874
- 53 Tangeloju S, Little BB, Esterhay RJ, Brock G, Lajoie AS. Type 2 diabetes mellitus (t2dm) "remission" in non-bariatric patients 65 years and older. *Front Public Health* 2019;7:82. doi:10.3389/fpubh.2019.00082
- 54 Bhatt AA, Choudhari PK, Mahajan RR, et al. Effect of a low-calorie diet on restoration of normoglycemia in obese subjects with type 2 diabetes. *Indian J Endocrinol Metab* 2017;21:776-80. doi:10.4103/ijem.IJEM_206_17
- 55 Sarathi V, Kolly A, Chaithanya HB, Dwarakanath CS. High rates of diabetes reversal in newly diagnosed Asian Indian young adults with type 2 diabetes mellitus with intensive lifestyle therapy. *J Nat Sci Biol Med* 2017;8:60-3. doi:10.4103/0976-9668.198343
- 56 Umphonsathien M, Prutanopajai P, Aiam-O-Ran J, et al. Immediate and long-term effects of a very-low-calorie diet on diabetes remission and glycemic control in obese Thai patients with type 2 diabetes mellitus. *Food Sci Nutr* 2019;7:1113-22. doi:10.1002/fsn3.956
- 57 Snehalatha C, Mary S, Selvam S, et al. Changes in insulin secretion and insulin sensitivity in relation to the glycemic outcomes in subjects with impaired glucose tolerance in the Indian Diabetes Prevention Programme-1 (IDPP-1). *Diabetes Care* 2009;32:1796-801. doi:10.2337/dc09-0676
- 58 Nanditha A, Ram J, Snehalatha C, et al. Early improvement predicts reduced risk of incident diabetes and improved cardiovascular risk in prediabetic Asian Indian men participating in a 2-year lifestyle intervention program. *Diabetes Care* 2014;37:3009-15. doi:10.2337/dc14-0407
- 59 Wing RR, Phelan S. Long-term weight loss maintenance. *Am J Clin Nutr* 2005;82(Suppl):222S-5S. doi:10.1093/ajcn/82.1.222S
- 60 Rehackova L, Araujo-Soares V, Steven S, Adamson AJ, Taylor R, Sniehotta FF. Behaviour change during dietary Type 2 diabetes remission: a longitudinal qualitative evaluation of an intervention using a very low energy diet. *Diabet Med* 2020;37:953-62. doi:10.1111/dme.14066
- 61 Thomas JG, Bond DS, Phelan S, Hill JO, Wing RR. Weight-loss maintenance for 10 years in the National Weight Control Registry. *Am J Prev Med* 2014;46:17-23. doi:10.1016/j.amepre.2013.08.019
- 62 Hollands GJ, Shemilt I, Marteau TM, et al. Portion, package or tableware size for changing selection and consumption of food, alcohol and tobacco. *Cochrane Database Syst Rev* 2015;(9):CD011045. doi:10.1002/14651858.CD011045.pub2
- 63 Hess A, Passaretti M, Coolbaugh S. Fresh food farmacy. *Am J Health Promot* 2019;33:830-2. doi:10.1177/0890117119845711d

Cite this as: *BMJ* 2021;373:n1449
<http://dx.doi.org/10.1136/bmj.n1449>