

Treating not managing diabetes

Authors

Dr Elizabeth Morris, BMBCh ^{1,2}

Prof Susan Jebb, FMedSci ^{1,2}

*Prof Paul Aveyard, PhD ^{1,2}

Affiliations

¹ Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, OX2 6GG, UK

² NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, OX2 6GG, Oxford, UK

* Corresponding author. Correspondence to: Professor Paul Aveyard, paul.aveyard@phc.ox.ac.uk

Type 2 diabetes is one of the foremost global threats to improvements in health. One in 12 adults has type 2 diabetes and the prevalence has quadrupled over the past 30 years, fuelled by the rise in the global prevalence of obesity(1). Despite this, healthcare systems worldwide have taken practically no effective action to address the root cause to try and reverse the disease. Will the results from the DiRECT trial change this?

In this issue, Lean and colleagues address one of the main limitations of their original study – durability of outcomes - reporting the two-year results from the DiRECT trial investigating the effect of primary care-based intensive weight management on remission of type 2 diabetes(2). Of the 149 20-65 year olds with type 2 diabetes who started the low energy formula diet intervention, 68 (46%) were in remission at one year and 53 (36%) remained so at two years, compared with 6 (4%) and 3 (2%) in the usual care control group at one and two years. Remission of type 2 diabetes is possible for at least two years, and this has important implications for future management of people with diabetes. Here, all patients had diabetes of <6 y duration, but there was no evidence of an association between duration and the likelihood of remission, raising the possibility that this intervention may be more generally applicable.

However, there is no universally agreed definition of remission. The American Diabetes Association defines remission as achieving normoglycaemia (HbA1c <42mmol/mol) for at least a year, whereas the DiRECT authors used two months and sub-diabetic range glycosylated haemoglobin (HbA1c <48mmol/mol)(3, 4). In practice, the DiRECT treatment protocol stopped all medication for diabetes at inception and most people defined as in remission are likely to have been off medication for the two years of follow-up. Discontinuing all diabetes medications may be a powerful motivator for patients, but raises the question of the role of metformin - a cheap and effective drug, which has been shown to reduce incidence of type 2 diabetes in at-risk groups (including those in the “pre-diabetes” range, HbA1c 42-48mmol/mol)(5), and may also reduce the risk of cardiovascular disease and some cancers(6, 7).

In line with current clinical practice the DiRECT protocol did not test for remission in the control group. Assuming a normal distribution for weight change, around 30% of participants in the control group lost 5kg or more, where remission was observed in 29%, suggesting that perhaps 10% of the control group might have achieved remission, had they been tested for it, though still considerably less than in those supported to lose weight. Gaining agreement on the definition of remission of diabetes and procedures for testing is important for future research and may also help reset clinical thinking.

The findings from DiRECT strongly suggest that the key to diabetes remission is weight loss. The investigators tested a rapid weight loss regimen, aiming to achieve an initial 15kg weight loss, which they considered as a threshold at which remission was more likely. However, the trial results suggest a linear relationship; the greater the weight loss, the greater the chance of remission with no apparent threshold. The key question for any clinician seeking to change their practice is then how to achieve weight loss. Other research shows that similar weight losses, averaging 10kg at one year can be achieved by a similar total diet replacement programme delivered by a commercial provider more cheaply than the cost of the DiRECT programme(8). Alternatively, mean weight losses of around 7kg at one year can be achieved by referral to community weight-loss groups that advise on, but do not supply, food to participants. This is considerably less expensive, and around 30% achieve at least 10kg weight loss at a year(9). Whatever method is used, the key for clinicians is to move beyond simply advising patients to lose weight and implement active referral to behavioural weight loss programmes(10).

Participants in the DiRECT trial were offered, and most accepted, continuing 30-minute monthly appointments with a nurse or dietitian through the second year to monitor their progress after a more intensive initial support programme. Multiple visits bring significant additional costs to the health system, to patients, and the wider economy since such appointments will often require time off work. Regardless of cost-effectiveness, providing this programme at scale would challenge primary care provision worldwide. For example, in the UK, people see a primary care nurse for 1·28 10-minute appointments per year on average(11). If 25% of people with diabetes decided to follow a DiRECT programme, this would necessitate a 50% increase in total nurse consultations and therefore workforce. Is such intensive support crucial? A systematic review of 45 trials found no evidence that behavioural support reduced weight regain following an intensive weight loss programme(12). That said, the DiRECT programme offered more advice and support to prevent weight regain than tested in previous trials, including the prompt offer of a further diet period or treatment with orlistat. This is a plausible approach, albeit with no clear evidence it is effective in this context; about half those in the programme resumed their total diet replacement on at least one occasion, but even so, there was a mean of 2·6kg weight regain between 12- and 24-month follow-ups, so further evidence is required.

Despite these questions, DiRECT should change the paradigm – remission from diabetes is possible with support from generalist clinicians. The NHS in England has announced a plan to test total diet replacements as a treatment to induce diabetes remission as part of a broader agenda to treat weight-related diseases with active weight loss support. It's time to move beyond *managing* diabetes to *treating* diabetes.

Competing interests

Susan Jebb and Paul Aveyard lead an investigator-initiated trial of total diet replacement funded by Cambridge Weight Plan and receive no personal payments from this. Paul Aveyard has done half a day of consultancy for Weight Watchers that led to no payments to him personally.

Funding

Elizabeth Morris is funded by an NIHR in-practice fellowship. Susan Jebb and Paul Aveyard are NIHR senior investigators and funded by NIHR Oxford Biomedical Research Centre and CLAHRC.

References:

1. WHO. World Health Organisation global report on diabetes. https://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_engpdf?sequence=1 accessed February 2019. 2016.
2. Lean MEJ, Leslie WS, Barnes A, Brosnahan N, Thom G, McCombie L, et al. Two-year results of the randomised Diabetes Remission Clinical Trial (DiRECT). *The Lancet*. 2019.
3. Buse JB, Caprio S, Cefalu WT, Ceriello A, Del Prato S, Inzucchi SE, et al. How Do We Define Cure of Diabetes? *Diabetes care*. 2009;32(11):2133-5.
4. McCombie L, Leslie W, Taylor R, Kennon B, Sattar N, Lean MEJ. Beating type 2 diabetes into remission. *BMJ*. 2017;358:j4030.
5. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England journal of medicine*. 2002;346(6):393-403.
6. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *The Lancet*. 2017;389(10085):2239-51.
7. Chan AT. Metformin for cancer prevention: a reason for optimism. *The Lancet Oncology*. 2016;17(4):407-9.
8. Kent S, Aveyard P, Astbury NM, Mihaylova B, Jebb SA. Is doctor referral to a low energy total diet replacement programme cost-effective for the routine treatment of obesity? *Obesity*. 2019.
9. Ahern AL, Wheeler GM, Aveyard P, Boyland EJ, Halford JCG, Mander AP, et al. Extended and standard duration weight-loss programme referrals for adults in primary care (WRAP): a randomised controlled trial. *The Lancet*. 2017;389(10085):2214-25.
10. Aveyard P, Lewis A, Tearne S, Hood K, Christian-Brown A, Adab P, et al. Screening and brief intervention for obesity in primary care: a parallel, two-arm, randomised trial. *The Lancet*. 2016;388(10059):2492-500.
11. Hobbs FDR, Bankhead C, Mukhtar T, Stevens S, Perera-Salazar R, Holt T, et al. Clinical workload in UK primary care: a retrospective analysis of 100 million consultations in England, 2007–14. *The Lancet*. 2016;387(10035):2323-30.
12. Dombrowski SU, Knittle K, Avenell A, Araújo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. *BMJ : British Medical Journal*. 2014;348:g2646.