

Type 2 diabetes: treating not managing

Type 2 diabetes is one of the foremost global threats to improvements in health. One in 12 adults has type 2 diabetes worldwide and the prevalence has quadrupled in the past 30 years, fuelled by the global rise in the prevalence of obesity.¹ However, health-care systems worldwide have taken little effective action to address the root causes of type 2 diabetes and to try to reverse the disease among those in whom it develops. Will the results from the DiRECT trial change this situation?

Previously, the results of DiRECT at 1 year showed the effectiveness of a primary care-based intensive weight-management programme on remission of type 2 diabetes.² Now, in *The Lancet Diabetes & Endocrinology*, Michael Lean and colleagues address one of the main limitations of the original report—durability of outcomes—by reporting the 2-year results from the trial.³ The intervention programme (Counterweight-Plus) consisted of total diet replacement with a low-calorie formula (825–853 kcal per day) for 3–5 months followed by stepped food reintroduction (2–8 weeks) and then structured support for weight-loss maintenance. Of the 149 adults aged 20–65 years with type 2 diabetes (duration <6 years) who started the intervention, 68 (46%) were in remission at 1 year and 53 (36%) were in remission at 2 years, compared with six (4%) and five (3%) of 149 in the control group (best-practice care in accordance with guidelines) at 1 and 2 years, respectively (adjusted odds ratio at 2 years 25.8, 95% CI 8.3–80.8; $p < 0.0001$). Remission of type 2 diabetes is thus possible for at least 2 years—a finding with important implications for future management of people with the disease. Notably, although all patients in DiRECT had diabetes of less than 6 years' duration, there was no evidence of an association between duration and the likelihood of remission, raising the possibility that this intervention might be more generally applicable.

However, there is no universally agreed definition of remission. The American Diabetes Association defines remission as achieving normoglycaemia ($HbA_{1c} < 42 \text{ mmol/mol}$ [6.0%]) for at least a year off medication.⁴ In DiRECT, in the primary analysis at 12 months the investigators used 2 months off medication and sub-diabetic range of HbA_{1c} ($< 48 \text{ mmol/mol}$ [6.5%]).^{2,5} 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 2 years of follow-up; for the new analysis at 24 months, the investigators have defined remission based on participants having been off medication since baseline.³ Discontinuing all diabetes medications could be a powerful motivator for patients, but this approach 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 prediabetes range [HbA_{1c} 42–47 mmol/mol (6.0 – 6.4%))]⁶ and might also reduce the risk of cardiovascular disease and some cancers.^{7,8}

In line with current clinical practice, the DiRECT protocol did not ask clinicians to take participants in the control group off medication to test whether they were in remission or not. Assuming a normal distribution for weight change in the control group, about 30% of people in the control group lost 5 kg or more and 29% of participants in the overall trial population who lost between 5 and 10 kg achieved remission, suggesting that perhaps 10% of the control group might have achieved remission, had they been tested for it by being taken off medication, although still considerably less than in the intervention group. Gaining agreement on the definition of remission of diabetes and procedures for testing is important for future research and might also help to 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 15 kg weight loss, which they regarded as a threshold at which remission was more likely. However, the trial results suggest a linear relation: 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 10 kg at 1 year, can be achieved by a similar total diet replacement programme delivered by a commercial provider more cheaply than the cost of the DiRECT intervention.⁹ Alternatively, mean weight losses of about 7 kg at 1 year can be achieved by referral to community weight-loss groups that advise on, but do not supply, food to participants. This approach is considerably less expensive and about



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30% of participants achieve at least 10 kg weight loss at 1 year.¹⁰ 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.¹¹

Participants in the DiRECT trial were offered, and most accepted, continuing 30 min 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 substantial additional costs to the health system, patients, and the wider economy (since such appointments will often require time off work). Irrespective 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-min appointments per year on average.¹² If 25% of people with type 2 diabetes were to follow the DiRECT programme, this would necessitate a roughly 50% increase in total nurse consultation time and therefore workforce. Is such intensive support crucial? A systematic review of 45 trials showed no evidence that behavioural support reduced weight regain following an intensive weight-loss programme.¹³ However, the DiRECT programme offered more than the advice and support to prevent weight regain that has been tested in previous trials, including the prompt offer of a further diet-replacement period or treatment with orlistat. This approach is plausible, albeit with no clear evidence it is effective in this context; about half of the intervention participants resumed their total diet replacement on at least one occasion, but even so, there was a mean of 2·6 kg weight regain between the 12-month and 24-month assessments, so further evidence is needed.

Despite these questions, DiRECT should change the paradigm—remission from type 2 diabetes is possible with support from generalist clinicians. In keeping with these findings, 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.¹⁴

It is time to move beyond managing and towards truly treating type 2 diabetes.

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