Remission of type 2 diabetes: mission not impossible

Type 2 diabetes is a heterogeneous disease with a rapidly increasing prevalence worldwide. The main risk factors are weight gain and obesity, sedentary lifestyle, and unhealthy dietary pattern—all of which are modifiable.1 Well controlled lifestyle interventions in individuals with impaired glucose tolerance can prevent or postpone the development of type 2 diabetes through weight loss, physical activity, and healthy dietary choices.1,3 Moreover, diabetes risk is decreased for many years after the active intervention period, suggesting a legacy effect.1,3 However, no findings from large-scale randomised trials are available for the effects of non-pharmacological treatment on the remission rate of diabetes in patients with type 2 diabetes who are receiving antidiabetic drug therapy.

In *The Lancet*, Michael Lean and colleagues4 report 1 year results from their cluster-randomised DiRECT trial investigating the effect of primary care-based weight management on diabetes remission in patients with type 2 diabetes of up to 6 years in duration. With the primary care general practice as the unit of randomisation, 298 patients (aged 20–65 years) with hyperglycaemia were allocated to receive a weight management programme delivered by practice dietitians or trained nurses (n=149) or best practice care by guidelines (control group; n=149). The weight management programme began with a diet replacement phase, consisting of a low calorie formula diet, followed by structured food reintroduction and weight loss maintenance phases. Antidiabetic and antihypertensive medicines were discontinued in the intervention group at the onset of the study. The co-primary outcomes were weight loss of 15 kg or more and remission of diabetes, defined as glycated haemoglobin (HbA1c) of less than 6·5% (<48 mmol/mol) at 12 months. 36 (24%) patients in the intervention group achieved weight loss of 15 kg or more, compared with no patients in the control group (p<0·0001). Diabetes remission (off antidiabetic drugs) was achieved in 68 (46%) patients in the intervention group and six (4%) patients in the control group (odds ratio 19·7, 95% CI 7·8–49·8; p<0·0001). Remission was closely associated with degree of weight loss and occurred in 31 (86%) of the 36 patients who lost 15 kg or more.

These results are impressive and strongly support the view that type 2 diabetes is tightly associated with excessive fat mass in the body. Interest to take part in the study was high, and 128 (86%) participants in the intervention group and 147 (99%) participants in the control group attended the 12 month study assessment. Nine serious adverse events were reported by seven participants in the intervention group and two were reported by two participants in the control group. These events were mostly mild and possibly unrelated to the programme, except for two adverse events (biliary colic and abdominal pain) in one patient in the intervention group. Furthermore, the investigators recorded a clinically meaningful reduction in mean serum triglyceride of 0·31 mmol/L (SD 1·33) in the intervention group, and at 12 months the proportion of participants taking medication for hypertension was lower in the intervention group than in the control group (32% vs 61%). The main limitation of this study is the duration, but long-term follow-up will continue to 4 years. Additionally, the cluster-randomised design might raise criticism because individual-based randomisation is usually applied in studies of this type. Blinded studies with any diet are not possible to do in outpatient settings.

Lean and colleagues’ results, in addition to those from other studies of type 2 diabetes prevention2,3,5 and some smaller interventions in this setting,6 indicate that weight loss should be the primary goal in the treatment of type 2 diabetes. Weight loss results in improved insulin sensitivity in muscles and liver, decreases intra-organ fat content,7 and might improve insulin secretion.5,9 In the long term, weight loss might help to preserve β-cell mass.7 One of the putative mechanisms could be decreased fat content of the pancreas,7 but more mechanistic studies are needed. The role of physical activity and quality of diet, such as dietary fibre and fatty acid composition, should not be forgotten when considering the long-term success of prevention and treatment of type 2 diabetes.1,2,3,8

Some important questions need to be addressed. Should the results of DiRECT lead to changes in the treatment options for type 2 diabetes? Long-term results from the study would be extremely important because post-intervention weight regain has been reported...
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in most weight management studies in non-diabetic patients and in patients with type 2 diabetes. A key question regards the optimal time to start prevention or treatment of type 2 diabetes by non-pharmacological measures. Treatment is currently based on different algorithms for the selection of antidiabetic drugs and insulin and, in severely obese patients, treatment with bariatric surgery if available. In view of the results of the DIRECT trial, a non-pharmacological approach should be revived. In clinical practice, antidiabetic drugs seldom result in normalisation of glucose metabolism if patients’ lifestyles remain unchanged. Mechanisms of action of some drugs for type 2 diabetes might not be in line with current knowledge of pathophysiology of disease, whereas intensive weight management along with physical activity and healthy diet is targeted therapy for type 2 diabetes. Importantly, successful weight reduction when combined with increased physical activity might reduce cardiovascular morbidity, as shown in post-hoc analyses of the Look AHEAD study.

The DIRECT study indicates that the time of diabetes diagnosis is the best point to start weight reduction and lifestyle changes because motivation of a patient is usually high and can be enhanced by the professional health-care providers. However, disease prevention should be maintained as the primary goal that requires both individual-level and population-based strategies, including taxation of unhealthy food items to tackle the epidemic of obesity and type 2 diabetes.

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I declare no competing interests.


Tradition and innovation in development of a Zika virus vaccine

In response to the urgent need for a vaccine to prevent congenital syndromes associated with Zika virus, the scientific community has responded swiftly. Several vaccine technologies are in development. In The Lancet, Kayvon Modjarrad and colleagues and Martin R Gaudinski and colleagues report results of phase 1 clinical trials of candidate Zika vaccines. It has been less than 2 years since the association between Zika virus infection and microcephaly was established in Recife, Brazil, and to have multiple promising vaccine candidates in so short a time is impressive.

Modjarrad and colleagues report the safety and immunogenicity results of a clinical study with a purified formalin-inactivated Zika virus vaccine and aluminium hydroxide adjuvant. Formalin-inactivated virus formulation is a proven technology, with a classic example being the polio vaccine developed by Salk and colleagues in the 1950s. In Modjarrad and colleagues’ trial, 55 healthy volunteers received two intramuscular injections of 5 μg vaccine, and safety and immunogenicity outcomes were compared with those in 12 people who received vaccinations of placebo. The vaccine was immunogenic in 48 (92%) of 52 vaccine recipients with data available at 57 days after first vaccination, and 40 (77%) of 52 produced neutralising antibody titres that were protective in...