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# Type 2 Diabetes Remission: Achieving Calorie Restriction and Weight Loss by Any Which Way?

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Type 2 diabetes affects more than 400 million people and generates ghastly morbidity, premature mortality, and colossal health expenditure. For people with type 2 diabetes to be able to achieve remission, that is, freedom from diabetes as diagnosed clinically, would have obvious medical and social benefits. It may be potentially lifesaving for some. It is now an exciting reality thanks to consistent evidence from 3 landmark randomized controlled trials that feature structured low-energy meal replacement for the weight loss phase. Three distinct populations have been studied: DiRECT among predominately white Europeans; DIADEM-1 in Middle Eastern people, and STANDby in South Asians (1-3). In each of these trials, the intervention was acceptable to most participants and all yielded striking results in terms of weight loss and type 2 diabetes remissions. Other dietary interventions, such as low-carb diets, have yet to be reported in randomized trials, but other than short-term effects of acute carbohydrate restriction, the remission rates appear to be broadly in line with the amount of weight loss achieved (4).

In this issue of the journal, Yang and colleagues (5) build upon this work and report the results of a well-conducted, parallel design, open-label 1:1 randomized controlled trial of intermittent caloric restriction vs control, in 72 participants of body mass index range 19.1 to 30.4 kg/m<sup>2</sup>, and a mean duration of diabetes of just over 6 years (range, 1-11 years). Participants in the intervention group entered into 6 15-day cycles, each comprising 5 days of hypocaloric real food (as opposed to meal replacement) (840 kcal/day) and 10 days of an ad libitum diet titled *Chinese Medical Nutrition Therapy* (CMNT), compared with the unrestricted usual food diet of the control group. Energy intake during CMNT was spread across 3 2-hour eating windows, with a fasting period of around 12 hours. The authors describe CMNT as a form of *intermittent fasting*, a slightly harsh term for *intermittent low-energy dieting*.

Upon completing the 3-month intervention plus 3-month follow-up period, 47.2% of participants achieved diabetes remission in the intervention group, whereas only 2.8% of participants achieved remission in the control group. The mean body weight of participants in the intervention group was reduced by 5.9 kg compared with 0.3 kg in the control group. Importantly, after the 12-month follow-up, 44.4% of the participants achieved sustained remission, with a glycated hemoglobin (HbA1c) level of 6.3%. Medication costs of the CMNT group were 77.2% lower than those of the control group, valuable in offsetting the cost of weight management intervention (6).

The difference in weight losses between groups was large, but the results are better than expected for the mean weight loss, when compared with previous randomized controlled trials (see Fig. 2 in (3)). It is theoretically possible that there is some as yet unexplained effect, independent of weight loss, in time-restricted eating, but racial/ethnic effects are possible, and the participants were in general older and leaner, with a greater proportion of men (66%), factors which might generate better remission rates for the same weight loss (7), but had

longer duration of type 2 diabetes, which would usually make remission less likely. Indeed, 65% of the participants who achieved remission had a duration of type 2 diabetes longer than 6 years. Baseline HbA1c was similar in the responders and nonresponders, but with more glucose-lowering medications, including sulfonylureas, at baseline.

These findings add to existing evidence across all trials that the likelihood of remission is broadly proportional to degree of weight loss achieved. It supports the hypothesis that type 2 diabetes is a disease mediated by ectopic fat excess, which is reversible with sufficient loss, regardless of how that is achieved. Chinese and Asian people in general appear to be more prone to ectopic (hepatic) fat accumulation, thus more metabolically sensitive to weight gain, and a little more responsive to weight loss than Europeans.

We believe that the results of this study also reinforce the view that long-term randomized controlled trials are no longer going to be possible to examine clinical outcomes from weight loss and remission, because the intervention is not blind, it is desirable to patients, and it is likely to improve prognosis for most. Furthermore, the size of trials to determine effects on mortality or other hard endpoints puts dietary interventions a long way beyond what is possible in non-commercial investigator-led research. So vital clinical “hard” outcomes from weight management and remission can only realistically be researched in well-designed “pragmatic” (real-life) long-term observational studies.

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