



Type 2 Diabetes Remission: A New Mission in Diabetes Care

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Diabetes Care 2024;47:47–49 | <https://doi.org/10.2337/dci23-0062>

Type 2 diabetes mellitus (T2DM) remains a devastating disease with significant global prevalence (1). The disease is challenging for the individual and for health care services. Traditional T2DM management, based on the belief that T2DM is irreversible, has concentrated on glycemic control through diabetes education and glucose-lowering medication intensification. With this approach, however, adequate glycemic control is not achieved in a significant proportion of patients (2–4). T2DM is intimately linked to obesity and excessive liver and pancreas fat deposition (5,6). Thus, weight management is increasingly taking center stage in T2DM, and there is accumulating evidence that T2DM remission can be achieved through weight loss interventions.

Without specific intervention, T2DM remission is infrequent. A U.S. study of 122,781 adults reported a 7-year cumulative incidence of remission as 1.60%, but it was higher (4.6%) in those with early T2DM (<2 years from diagnosis) (7). Data from England, including 2,297,700 people with T2DM, showed that only 1.7% met the criteria for T2DM remission (8). Those with a T2DM diagnosis of <1 year had greater odds of remission (2.87) than those with a diagnosis of 3–5 years. BMI reduction of $\geq 10\%$ garnered a 3.57 odds of remission compared with that at <5% reduction.

T2DM reversibility has been highlighted by metabolic/bariatric surgery (MBS), where significant weight loss is enhanced by a favorable hormonal milieu to maintain glycemia (9,10). Predictors of diabetes

remission after MBS include younger age, better glycemic control, fewer glucose-lowering medications, no insulin treatment, and greater degree of weight loss. Three-year data from the Alliance of Randomized Trials of Medicine Versus Metabolic Surgery in Type 2 Diabetes (ARMMS-T2D) showed that diabetes remission occurred in 37.5% of participants after MBS (11). Clinical trials of T2DM remission with MBS have not used a consistent definition of remission and have employed medical comparator groups aiming for glycemic control rather than weight loss and glucose-lowering medication deescalation. MBS achieves durable weight loss and remission but is not universally accepted, accessed, or available.

Recently, focus has shifted to intensive lifestyle interventions (ILI) to achieve weight loss and T2DM remission. The Look AHEAD (Action for Health in Diabetes) study achieved greater weight loss in the group with T2DM randomized to ILI compared with the control group receiving diabetes education (difference of -7.9% at 1 year and -3.9% at 4 years) (12). Only 2% of the control group achieved remission, but 11.5% and 7.3% of ILI participants achieved remission at 1 and 4 years, respectively. Look AHEAD participants were ~ 60 years old, were mainly White, and had a mean diabetes duration of 5 years. The U.K. Diabetes Remission Clinical Trial (DiRECT) study was a cluster randomized controlled primary care trial that examined whether weight loss through use of a low-energy (~ 850 kcal/day) total

diet replacement phase (using nutritionally complete meal replacement products) followed by gradual food reintroduction could achieve T2DM remission compared with conventional diabetes care (13). DiRECT participants were also mainly White but were younger by ~ 5 years and had a shorter diabetes duration (~ 3 years) than Look AHEAD participants. The DiRECT intervention resulted in $\sim 10\%$ weight loss, with 46% achieving T2DM remission at 1 year. Remission occurred in only 4% of the control group. The Diabetes Intervention Accentuating Diet and Enhancing Metabolism (DIADEM-I) study recruited participants originating from the Middle East and North Africa region who were randomized to a dietary intervention similar to that of DiRECT, with support for unsupervised physical activity or standard T2DM management (control) (14,15). The weight loss for individuals in DIADEM-I was $\sim 12\%$. Diabetes remission was observed at 1 year in 61% of the intervention group compared with 12% of the control group. With the intervention, 33% of participants achieved normoglycemia. DIADEM-I participants were about a decade younger than DiRECT participants and had diabetes duration of ≤ 3 years.

Hocking et al. (16) now report a non-randomized open-label primary care study from Australia (DiRECT-Aus) that used an intervention similar to those of DiRECT and DIADEM-I. DiRECT-Aus participants were of similar age to participants in DiRECT and had a mean diabetes duration of 2.8 years. The intention-to-treat population achieved weight loss of 11.2%.

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With the same definition of T2DM remission as that for DIADEM-I, 55% of the 155 participants in the intention-to-treat analysis achieved remission at 1 year. There was some weight regain after 6 months that was not seen in DiRECT and DIADEM-I. DiRECT-Aus was conducted during the coronavirus disease 2019 pandemic, which may have hampered weight maintenance. Rescue plans for weight gain (return to use of meal replacement products for a few weeks) were used in both DiRECT and DiRECT-Aus. In DiRECT-Aus, rescue plans were offered to a significant number of participants (44%) and used a median of four times by those offered. DiRECT, DIADEM-I, and DiRECT-Aus safely stopped all diabetes medications at the start of intervention. While DiRECT-Aus was non-randomized, it demonstrates the generalizability and safety of the dietary and lifestyle intervention used by previous studies. A recent small randomized clinical trial (South Asian Diabetes Remission Feasibility Trial [STANDby]) of 25 U.K.-based South Asians reported T2DM remission in 43% at 4 months, adding further support (17). Across all studies to date, there is a close relationship between degree of weight loss and percentage achieving remission. Interestingly, the DiRECT study demonstrated recovery of pancreatic volume and morphology via MRI with the dietary intervention (18).

The definition of T2DM remission has differed among various studies. The recent consensus statement recommends a simplified criterion for diabetes remission ($\text{HbA}_{1c} < 6.5\%$ [48 mmol/mol] and at least 3 months off glucose-lowering medications), which helps standardize future studies (19,20). The consensus definition excludes those achieving remission through medications. Newer diabetes and weight loss medications that target the glucagon-like peptide 1 (GLP-1) receptor, GLP-1/glucose-dependent insulinotropic polypeptide receptors (dual agonists), and GLP-1/glucose-dependent insulinotropic polypeptide/glucagon receptors (tragonists), as well as combination therapy targeting GLP-1 and amylin receptors, are promising in achieving significant weight loss and HbA_{1c} levels within the T2DM remission range (21). It may be argued that like other chronic diseases, the T2DM remission designation should extend to those achieving remission on medication, blurring the lines between T2DM treatment and remission.

The DiRECT-Aus study adds to the evidence that T2DM remission is possible through weight loss via interventions that incorporate total diet replacement across several populations. T2DM remission is also increasingly recognized in international clinical practice guidelines. Those with early T2DM who are willing to undertake this intervention and achieve $\geq 10\%$ weight loss are most likely to achieve T2DM remission. This degree of weight loss at 1 year was associated with a 21% mortality risk reduction in Look AHEAD (22). A >10 -kg weight loss was associated with 19.1% and 33.4% reduction in predicted cardiovascular risk in DiRECT and DIADEM-I, respectively, using plasma proteomic panels (23).

The two-year follow-up of the DiRECT study saw the percentage in remission drop to 36% (24). The proportion in remission is likely to diminish further with time, given the challenges of weight loss maintenance. Nevertheless, a longer time spent in remission and delaying the disease is likely to reduce the risk of complications. Linking T2DM remission to screening will permit a greater number to benefit at an earlier stage with a greater likelihood for pancreatic islet β -cell recovery. While the definition of T2DM remission is glucocentric, it is important that blood pressure and lipid management as well as T2DM complication screening should continue. Future efforts should focus on enhancing the evidence-based, and increasingly generalizable, lifestyle intervention by including frequent follow-up and provider contact (supported by digital technologies), use of rescue plans, a greater role for regular physical activity and sleep optimization (25), and, if required, potentially combining the lifestyle intervention with weight loss medications that also have glycemic and cardiovascular benefits. It is time to embrace T2DM remission as a key therapeutic goal in T2DM and to offer ILI to the increasing number of people with T2DM.

Funding. S.T.'s research has been funded by the Qatar National Research Fund through National Priorities Research Program grants (NPRP 8-912-3-192 and NPRP 10-0213-170456).

The statements made in this commentary are solely the responsibility of the author.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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