



Weighing in on Type 2 Diabetes Remission

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Type 2 diabetes (T2D) is a growing public health challenge that affects 422 million people and increases morbidity and mortality (1). Obesity is a major driver of the T2D pandemic (2). T2D is frequently associated with progressive decline in β -cell function in the setting of insulin resistance, necessitating escalation of pharmacotherapy that often culminates in insulin treatment (3). Weight loss can potentially reverse this trajectory and induce remission of T2D (3,4). Metabolic surgery (MS) is the most efficacious treatment for T2D remission, with its initial effects largely mediated by reduced caloric intake and weight loss (5,6). Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the two most common MS procedures worldwide, with the latter being the most common MS in the U.S. (7,8). In a randomized controlled trial, RYGB achieved T2D remission in 75% of patients at 2 years (defined as $HbA_{1c} < 6.5\%$ and fasting glucose < 100 mg/dL in the absence of glucose-lowering medication), which declined to 25% at 10 years (4). The HbA_{1c} cutoff of $< 6.5\%$, off glucose-lowering medications, for T2D remission is concordant with the recent American Diabetes Association consensus definition of remission (9). Using a stricter HbA_{1c} cutoff of $< 6\%$ for T2D remission, 42% of patients undergoing RYGB and 37% of patients undergoing SG achieve remission 1 year after surgery, which declines to 29% (RYGB) and 23% (SG) at 5 years (10). Weight regain is associated with relapse of T2D (4,10,11). Indicators of more advanced T2D, including increasing age, duration of

T2D, number of glucose-lowering medications, baseline HbA_{1c} , and insulin use, predict T2D nonremission and are incorporated into predictive tools such as the diabetes remission (DiaRem) score and advanced DiaRem score (12).

How much weight loss is needed to induce initial T2D remission after MS? In this issue of *Diabetes Care*, Barthold et al. (13) report on the association between percent total weight loss (%TWL) and T2D remission ($HbA_{1c} < 6.5\%$, off glucose-lowering therapy for at least 3 months) in a multiethnic cohort of 5,982 patients 1 year after RYGB (57% of patients) or SG. Seventy-one percent of patients achieved T2D remission at 1 year. Patients were categorized based on 1-year %TWL: 0–5% (the comparator group), 5–10%, 10–15%, 15–20%, 20–25%, 25–30%, and 30–35%. After adjusting for covariates (including age, ethnicity, sex, BMI, DiaRem score, comorbidities, and medication use), increased %TWL was associated with increased odds of T2D remission, starting with the 10–15% group. However, this increase was nonlinear, and T2D remission rates plateaued at 20–25% TWL; $> 25\%$ TWL did not confer additional benefits. Intriguingly, for patients on insulin and those with DiaRem scores of ≥ 8 , increased odds of T2D remission were only seen after 20–25% TWL. These data indicate that more modest weight loss can induce T2D remission, but only early in the course of T2D. All ethnicities had similar odds of T2D remission with $> 20\%$ TWL. How-

ever, non-Hispanic Black individuals were more likely to experience T2D remission starting at $> 5\%$ TWL, and Hispanic individuals had a slightly increased likelihood for remission at $> 10\%$ TWL compared with White individuals. These findings can aid decision-making by patients and their health care providers. Particularly noteworthy was the finding that even patients with more advanced T2D can achieve remission with $> 20\%$ TWL. RYGB likely causes greater TWL and T2D remission than SG and may be more preferable for those with more advanced T2D (14). Biliopancreatic diversion is even more efficacious for weight loss and T2D but is associated with more adverse effects (15).

Strengths of this study include the large sample size derived from multiple sites and inclusion of data from patients undergoing both RYGB and SG. A further strength of the study was the inclusion of diverse ethnicities, although some ethnicities, such as Middle Eastern, South Asian, and East Asian, were underrepresented.

Limitations include the retrospective observational nature of the study and the short duration of follow-up after MS. Information on duration of T2D, a predictor of remission, was unavailable (12). Long-term data on the durability of T2D remission and the influence of weight regain are awaited. The attrition rate of 17%, although comparable to that of other observational studies in this field (11), is a limitation, especially as

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See accompanying article, p. 92.

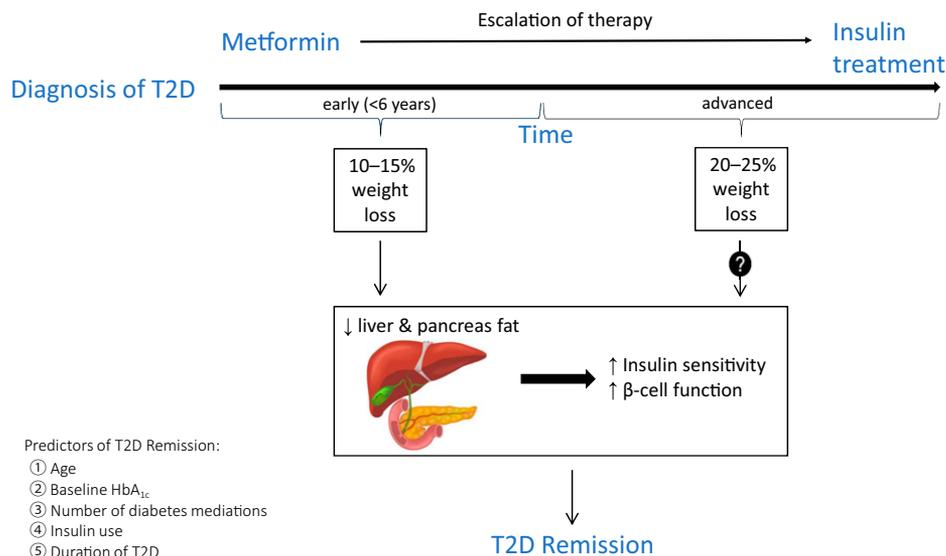


Figure 1—Overview of amount of weight loss needed for T2D remission. Weight loss–induced T2D remission may be modulated by the time course of the disease. Pharmacotherapy for patients in the early stages of T2D is usually with metformin monotherapy. Over time, escalation of pharmacotherapy, due to declining β -cell function, frequently culminates in insulin treatment. Weight loss of 10–15% with very-low-calorie intervention in early stages of T2D can remit T2D, likely by reversal of ectopic lipid deposition in liver and muscle and restoration of insulin sensitivity and β -cell function. Barthold et al. (13) show increased odds of T2D remission after metabolic surgery in the early stages of T2D starting at a weight loss of 10–15%, which plateaus with weight loss of 20–25%. For those with more advanced T2D, including those on insulin, T2D remission was only seen with 20–25% weight loss.

these patients are less likely to achieve T2D remission.

How do these data compare with T2D remission with dietary weight loss (Fig. 1)? In the DiRECT trial, T2D remission at 1 and 2 years was 46% and 37%, respectively (3). This was achieved with a very-low-calorie dietary intervention. Subsequent analysis revealed that in those who achieved remission, TWL was \sim 15% (16). The majority of patients with 10–15% TWL (57%) and $>$ 15% TWL (86%) achieved remission at 1 year compared with 34% with 5–10% TWL (3). Importantly, the participants in the DiRECT trial had T2D for fewer than 6 years (mean, 3 years) and were on oral antihyperglycemic agents only (3). In the DIADEM-I trial (mean %TWL, \sim 12%), conducted in the Middle East, 61% T2D remission was seen 1 year after low-calorie dietary intervention in conjunction with increased physical activity. The patient population was younger, with a T2D duration of $<$ 3 years (17). These data appear to be concordant with the data from Barthold et al. (13), who report increased odds of T2D remission starting with weight loss of 10–15% in patients with lower DiaRem scores and those not on insulin. Those with higher DiaRem scores and on insulin had increased odds of T2D remission with

20–25% weight loss but not 10–15% and 15–20% weight loss. These data again indicate that more modest weight loss can induce T2D remission early in the course of T2D. In the DiRECT study, T2D remission was associated with reversal of ectopic lipid in liver (with improvement in insulin sensitivity) and pancreas (with improvement in insulin secretion) (16). Do patients with more advanced T2D have greater ectopic lipid deposition, necessitating greater weight loss? Both insulin and sulfonylurea use are associated with weight gain (18). More detailed mechanistic studies will help clarify whether this is the case.

While these thresholds predict initial T2D remission after MS, more modest weight loss can still improve glycemic control, hypertension, dyslipidemia, obstructive sleep apnea, and functional capability (19). Further, MS may have long-term glycemic effects independent of weight loss (20). In those who do not achieve the desired TWL and T2D remission and/or in those with weight regain and T2D relapse, treatment with the glucagon-like peptide 1 (GLP-1) receptor agonist can achieve further weight loss and improve glycemia (21). Newer agents such as the GLP-1 receptor agonist semaglutide and the dual GLP-1 receptor/glucose-dependent insulinotropic peptide

receptor agonist tirzepatide can cause 10–15% TWL (22,23). Further, these medications likely have weight loss–independent glycemic efficacy. Semaglutide can lower HbA_{1c} by \sim 1.8% and tirzepatide by \sim 2.3% (22). Although we have effective therapies for T2D, including MS and pharmacotherapy, access to treatment remains a significant barrier (24,25).

In summary, Barthold et al. (13) provide important information on the amount of weight loss needed to induce initial T2D remission. Although early intervention is very likely important for T2D remission, those with more advanced T2D can achieve remission with $>$ 20% weight loss. This information can guide clinical decision-making by patients and health care providers. Longer-term studies assessing the association between %TWL and durability of T2D remission, along with exploration of underlying mechanisms, will be important.

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