

## Remission of type 2 diabetes mellitus

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### Abstract

The surge in type 2 diabetes mellitus (T2DM) is tightly linked to obesity, leading to ectopic fat accumulation in internal organs. Weight management has become a cornerstone of T2DM treatment, with evidence suggesting that significant weight loss can induce remission. Remission, defined as sustained hemoglobin (HbA1c) below 6.5% for at least 3 months without medication, can be achieved through various approaches, including lifestyle, medical, and surgical interventions. Metabolic bariatric surgery offers significant remission rates, particularly for patients with severe obesity. Intensive lifestyle modifications, including low-calorie diets and exercise, have also demonstrated significant potential. Medications like incretin-based agents show robust results in improving beta-cell function, achieving glycemic control, and promoting weight loss. While complete remission without medication may not be attainable for everyone, especially those with severe insulin resistance or deficiency, early and aggressive glycemic control remains a crucial strategy. Maintaining HbA1c below 6.5% from the time of diagnosis reduces the risk of long-term complications and mortality. Moreover, considering a broader definition of remission, encompassing individuals with sustained control on medication, could offer a more comprehensive and inclusive approach to managing this chronic disease.

**Key Words:** Type 2 diabetes mellitus; Remission; Lifestyle intervention; Metabolic bariatric surgery; Glucose-lowering medications; Weight management medications

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**Core Tip:** The rise in type 2 diabetes mellitus (T2DM) parallels the obesity epidemic. Notably, significant weight loss can induce remission, with hemoglobin levels below 6.5% for three months without medication. Herein we present the recent data on a variety of approaches, including lifestyle interventions, glucose-lowering and weight management medications and metabolic surgery that hold promise for inducing T2DM remission.

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## INTRODUCTION

The surge in type 2 diabetes mellitus (T2DM) is undeniably linked to the alarming rise in obesity. While mammalian physiology utilizes subcutaneous adipose tissue as a natural reservoir for energy storage, obesity disrupts this equilibrium. It triggers ectopic fat deposition, where adipose tissue infiltrates internal organs such as the liver, pancreas, heart, kidneys, and muscles[1]. Therefore, in most cases of newly diagnosed T2DM, weight management has moved to the forefront of treatment approach, as growing evidence suggests that weight loss interventions can lead to T2DM remission[2].

The recent consensus statement defines T2DM remission as a sustained return of glycated hemoglobin (HbA1c) levels to below 6.5% (or 48 mmol/mol) for at least 3 months, without the use of glucose-lowering medications[3]. This improvement can occur spontaneously or through intervention, but crucially, it must be achieved and maintained without medications. In situations where HbA1c is not a reliable indicator of long-term blood sugar control, alternative criteria can be employed. These include a fasting plasma glucose level below 126 mg/dL (7.0 mmol/L) or an estimated HbA1c value of less than 6.5%, calculated using continuous glucose monitoring data. This consensus definition will help standardize future studies. However, the current definition does not include individuals who achieve remission (HbA1c < 6.5%) while maintaining glucose-lowering medications.

Several therapeutic modalities can be employed to achieve T2DM remission, including intensive lifestyle modifications, pharmacological agents, and surgical interventions targeting glycemic control and weight management.

## INTENSIVE LIFESTYLE INTERVENTIONS FOR T2DM REMISSION

Studies employing intensive lifestyle modification programs have demonstrated that substantial weight loss in patients with T2DM is successful in reversing hyperglycemia and lowering risk factors.

The DiRECT trial, which assessed a very low-calorie diet using meal replacements, demonstrated remission rates of 46% at 1 year and 36% at 2 years versus 4.0% and 3.4% in control groups, respectively[4]. Another similar trial, DIADEM-I, achieved even a higher remission rate of 61% at 1 year by using short-term, very low-calorie diets and facilitating a significant weight loss of 12 kg[5].

The recently published DiRECT-Aus found that over half (56%) of newly diagnosed patients with T2DM achieved remission after 1 year of intensive lifestyle intervention using low-energy total diet replacement[6]. Remission rates were similar to previous studies in other parts of the world, suggesting the effectiveness of this approach across ethnicities and cultures. DiRECT-Aus suggests prioritizing intensive lifestyle interventions, especially within 6 years of diagnosis, to maximize remission chances[6].

While the LOOK AHEAD trial's intensive diet and exercise program achieved remission in only 11.5% of participants after 1 year and 7.3% after 4 years[7], a follow-up study revealed a crucial link between weight loss and long-term health benefits[8].

This study found that participants who maintained remission for a longer period had a greater decrease in systolic blood pressure and a larger increase in high-density lipoprotein cholesterol. However, there was only a small reduction in low-density lipoprotein cholesterol[9].

The LOOK AHEAD study found that the greater the weight loss, the lower the risk of developing cardiovascular disease over 10 years. Specifically, a 10% weight loss was associated with a 21% reduction in cardiovascular disease risk [8].

We can speculate that the low rates of diabetes remission in the LOOK AHEAD trial as compared to the DiRECT trial may be related to the longer T2DM duration of participants in the LOOK AHEAD trial (mean of 5 years) versus 3 years in the DiRECT trial.

A recent post-hoc analysis of the DiRECT study offers compelling evidence that weight loss-induced remission can lead to a remarkable reversal of abnormal pancreas structure in individuals with T2D. After 2 years of remission, the study found a significant increase in pancreas volume and a decrease in its shape irregularity[10]. This remarkable finding suggests that gradual morphological and functional recovery of the entire pancreas is possible during remission, highlighting the potential for T2DM reversal.

Other approaches, including time-restricted eating[11] and even high-protein diets[12], have successfully induced remission.

Emerging evidence suggests that incorporating exercise into diabetes management plans can effectively enhance beta cell function in a dose-dependent manner, which is crucial for better glycemic control and induction of diabetes remission. For adults with newly diagnosed T2DM, adding regular exercise to a weight-loss program significantly improved their beta cell function over a 16-wk period. The most significant benefits were seen in those who exercised six times per week[13].

Lean individuals [body mass index (BMI) < 25 kg/m<sup>2</sup>] with T2DM can also benefit from an intensive physical activity and dietary program to achieve diabetes remission. A recent study in China showed that with a program combining a low-carbohydrate diet, exercise, and diabetes management support, approximately 60% of lean individuals with T2DM achieved diabetes remission (HbA1c < 6.5%) after 6 months without the need for any anti-diabetic medications[14].

Overall, these trials demonstrate that well-supported lifestyle changes can achieve T2DM remission in a substantial proportion of individuals, with benefits extending beyond remission to weight loss and likely improved overall health. However, the current evidence underscores the importance of early intervention, coinciding with the putative timeframe of preserved beta-cell function.

## MEDICAL INTERVENTIONS-GLUCOSE-LOWERING AND WEIGHT MANAGEMENT MEDICATIONS FOR T2DM REMISSION

T2DM is characterized by a progressive decline in beta-cell function, which is already reduced to approximately 50% of normal function at diagnosis[15]. Short-term intensive insulin therapy has been investigated for potential to reverse this decline and achieve diabetes remission. This approach involves actively titrating insulin for 2 wk to attain beta-cell rest and glycemic control. This can improve beta-cell function and enhance insulin sensitivity. Studies have shown that intensive insulin therapy can lead to drug-free T2DM remission in 42% of participants after 2 years, with higher success rates observed in those who initiate treatment earlier[16]. However, potential drawbacks like the complexity of treatment and risk of hypoglycemia limit its use[17].

Studies suggest that initial insulin therapy followed by non-insulin antidiabetic drugs (NIAD) can preserve beta-cell function as compared to NIADs alone, potentially leading to better long-term glycemic control. Studies like REMIT and REMIT-dapa exemplify this approach[18,19]. In REMIT, the intervention group received a combination of metformin, acarbose, and insulin glargine[18]. REMIT-dapa used a similar approach with insulin glargine, metformin, and dapagliflozin[19]. Both studies demonstrated the potential of intensive combined therapy with NIADs and insulin. Up to 25% of patients in REMIT and 14% in REMIT-dapa achieved remission after 1 year, with the likelihood of success increasing with a longer treatment duration[18,19].

Incretin-based medications like glucagon-like peptide 1 receptor agonists (GLP-1 RAs), GLP-1/glucose-dependent insulinotropic polypeptide (GIP) dual agonists, and GLP-1/GIP/glucagon tri-agonists can improve glycemic control, preserve beta-cell function, and promote weight loss in patients with T2DM[2,20]. This suggests they may offer less-invasive diabetes remission potential as compared to more aggressive interventions like metabolic bariatric surgery (MBS).

Semaglutide significantly reduced HbA1c to ≤ 6.5% in 60% to 68% of T2DM patients with overweight or obesity over 68 wk[21].

GLP-1/GIP dual agonists are even more effective for glycemic control and weight loss. Furthermore, they are associated with greater beta-cell function and improvements in insulin sensitivity as compared to GLP-1 RAs alone. In the SURPASS-4 trial, 66% to 81% of T2DM patients on tirzepatide achieved an HbA1c ≤ 6.5% after 1 year[22]. In SURMOUNT-1, a remarkable 95.3% of participants with prediabetes and obesity in the tirzepatide groups achieved normoglycemia by week 72[23]. In a recent study of overweight or obese T2DM patients, the GLP-1/GIP/glucagon tri-agonist retatrutide successfully lowered HbA1c levels, with up to 82% of participants reaching ≤ 6.5% after 24 wk[24].

Cases of T2DM “remission” achieved through incretin-based medications do not technically meet the proposed definition of remission and only persist while patients are keeping their weight loss achievement mostly by actively taking the medication. However, achieving medication-free remission may not be feasible for all T2DM patients. This is due to the diverse nature of T2DM, including factors like severe insulin resistance (particularly in non-obese individuals) or marked insulin deficiency, as identified in the recent adult-onset diabetes subclassification by Ahlqvist *et al*[25].

Although complete remission without glucose-lowering medication may not be achievable for all patients, we firmly advocate for early and proactive glycemic control as a crucial aspect of long-term diabetes management. Maintaining good control early on can prevent future complications and improve outcomes. The legacy effect supports this approach. A large cohort study with a 13-year follow-up period emphasized the importance of achieving good glycemic control (HbA1c < 6.5%) within the first year of diagnosis. The study clearly demonstrates that the longer HbA1c levels remain below 6.5%, the greater the protection against both microvascular and macrovascular complications, and the lower the mortality risk. Conversely, sustained exposure to higher HbA1c levels significantly increases these risks. Therefore, taking prompt action to achieve early glycemic control can significantly enhance long-term outcomes and prevent debilitating complications.

## SURGICAL INTERVENTIONS FOR T2DM REMISSION

MBS can reverse T2DM in many patients, especially those with severe obesity (BMI  $\geq$  35). Weight reduction can result in better glycemic control, reduced medication use, improved quality of life, and improved cardiovascular outcomes[26]. Among MBS procedures, malabsorptive techniques like Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BPD) and the newly used mini-gastric bypass surgery achieve higher remission rates compared to purely restrictive methods like gastric banding. It's worth noting, however, that the utilization of BPD has waned in recent years[27]. Sleeve gastrectomy (SG) is a restrictive procedure that offers promising results; its mechanism primarily reduces stomach volume, ultimately falling behind the efficacy of malabsorptive approaches that alter the digestive pathway.

For severe obesity (BMI  $\geq$  35) with T2DM, RYGB offers a 67% remission rate at 3 years that is double that of SG (33%) [28]. At 5 years of follow-up, RYGB demonstrates superior and sustained glycemic control as compared to SG, with a 25% lower rate of T2DM relapse[29]. However, remission rates typically decrease over time, with relapse rates reaching around 50% after 5 years for both RYGB and SG[28]. The likelihood of T2DM remission after MBS surgery increases with greater weight loss, younger age, shorter duration of diabetes, reasonable pre-operative glycemic control, fewer diabetes medications, and not using insulin[30]. Careful patient selection, risk/benefit assessment, and lifelong monitoring are crucial for successful MBS implementation. More research is needed on long-term outcomes and expanding access to MBS for eligible patients. Studies exploring the potential for remission of T2DM with MBS lack a standardized definition of "remission", making comparisons and conclusions challenging. Furthermore, these studies often relied on comparator groups focused on glycemic control rather than weight loss. While MBS has demonstrated promising results in achieving sustained weight loss and potentially inducing T2DM remission, its broader availability remains limited.

## CONCLUSION

Current evidence suggests that T2DM can be effectively managed and potentially put into remission through various lifestyle, medical, and surgical interventions. In these interventions, weight loss remains the primary driver of remission. Significant weight loss (greater than 10%) and early intervention after T2DM diagnosis enhance the likelihood of achieving long-term remission. Taking into consideration the approval of new effective and safe medications for weight reduction, we propose a broader definition of T2DM remission, including individuals who achieve sustained glycemic control using glucose-lowering and weight management medications. For newly diagnosed T2DM patients, achieving an HbA1c below 6.5% should be the primary objective. Therefore, an aggressive, comprehensive approach is recommended, with patients fully informed about all available remission options, including potential medication combinations, right from the beginning of their diagnosis.

## FOOTNOTES

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