

## About the Author



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Dr. Akshay Jain is the first Canadian physician to be triple board-certified by the American Boards in Endocrinology, Internal Medicine and Obesity Medicine. He is the only Canadian to have won the AACE Rising Star in Endocrinology Award (2022) and to feature on Medscape's list of 25 Top Rising Stars of Medicine (2020). He practices in Surrey, BC and is a Clinical Instructor in the Division of Endocrinology at the University of British Columbia. He is fluent in 6 languages: English, Hindi, Gujarati, Marathi, Marwari, and Urdu. In 2022, he won the Top 25 Canadian Immigrant Award.

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# Diabetes Remission: Where are We Now?

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## Introduction

Type 2 diabetes (T2D) poses a substantial global health burden. In 2023, we published an overview on the remission of T2D. Since then, additional long-term data has emerged regarding the outcomes associated with T2D remission, highlighting the importance of revisiting this topic. This article synthesizes findings from the landmark Diabetes Remission Clinical Trial (DiRECT), its 5-year follow-up, and recent studies exploring the enduring benefits of both short-term and sustained remission.

## Overview of the DiRECT Trial<sup>1</sup>

The DiRECT trial, a randomized controlled trial conducted in the UK, investigated the efficacy of intensive weight management in achieving T2D remission. The study enrolled 298 participants who had been diagnosed with T2D within the preceding 6 years and had a body mass index between 27 and 45 kg/m<sup>2</sup>. Participants were randomly assigned to either an intervention group, receiving

a very low-calorie diet followed by structured dietary support for 1 year, or a control group, receiving standard diabetes care. All patients were managed in a primary care setting.

## Results of the DiRECT Trial

The initial 12-month results, published in 2017, demonstrated a significant remission rate of 46% (68 participants) in the intervention group, defined as an HbA1c below 6.5% without the use of glucose-lowering medication. In contrast, only 4% (6 participants) in the control group achieved remission.

## Five-Year Follow-Up Findings<sup>2</sup>

After sharing the 2-year results with all participants, UK National Health Service data were collected annually until year five. This included data from the remaining intervention participants who received low-intensity dietary support, intervention withdrawals, and the original randomly allocated groups. The primary outcome

was remission of T2D. Based on the findings established in the DiRECT trial, which showed that sustained weight loss was the dominant driver of remission, this assumption was carried forward into the extension study.

After 2 years, all intervention participants still in the trial (101 [68%] of 149) were approached to receive low-intensity support for a further 3 years. Of these, 95 (94%) had consented to continue and were allocated to the DiRECT extension group, while 54 participants were allocated to the non-extension group, where the intervention was withdrawn (**Figure 1**). At the 5-year time point, DiRECT extension participants (n=85) lost an average of 6.1 kg, with 11 (13%) in remission (**Figure 2**). Compared with the non-extension group, DiRECT extension participants had more visits with HbA1c <6.5% (36% vs 17%,  $p=0.0004$ ), without glucose-lowering medication (62% vs 30%,  $p<0.0001$ ), and in remission (34% vs 12%,  $p<0.0001$ ).

The 5-year follow-up, as reported in the *Lancet Diabetes & Endocrinology* publication, presents a nuanced picture of sustained remission. Notably, the original intervention group demonstrated a higher remission rate compared to the original control group. Specifically, 27% of the original intervention group were in remission at 5 years, compared to 4% of the original control group ( $p<0.0001$ ). Of those in remission at year 2, 26% remained in remission at year 5.

### Long-Term Benefits of Remission: Insights from Recent Research

In addition to the DiRECT trial, 2 additional studies<sup>3,4</sup> have evaluated the long-term outcomes observed in individuals who achieve remission, even if only for a brief period of time. Key findings from these studies highlight several significant advantages. Short-term remission was correlated with significant reductions in cardiovascular risk factors, including blood pressure and improved lipid profiles, suggesting lasting cardioprotective effects. Additionally, transient remission led to sustained improvements in glucose metabolism and insulin sensitivity, extending beyond the remission period. Participants who experienced remission reported an enhanced quality of life, improved mental health, reduced diabetes-related distress, and higher levels of physical activity. Evidence also suggests that even a brief remission

may promote beneficial changes in pancreatic beta-cell function, contributing to improved long-term metabolic health. Furthermore, the potential for reduced healthcare costs associated with managing diabetes complications during and after remission underscores the economic benefits of investing in effective weight management programs.

### Challenges Associated with Achieving and Maintaining Remission

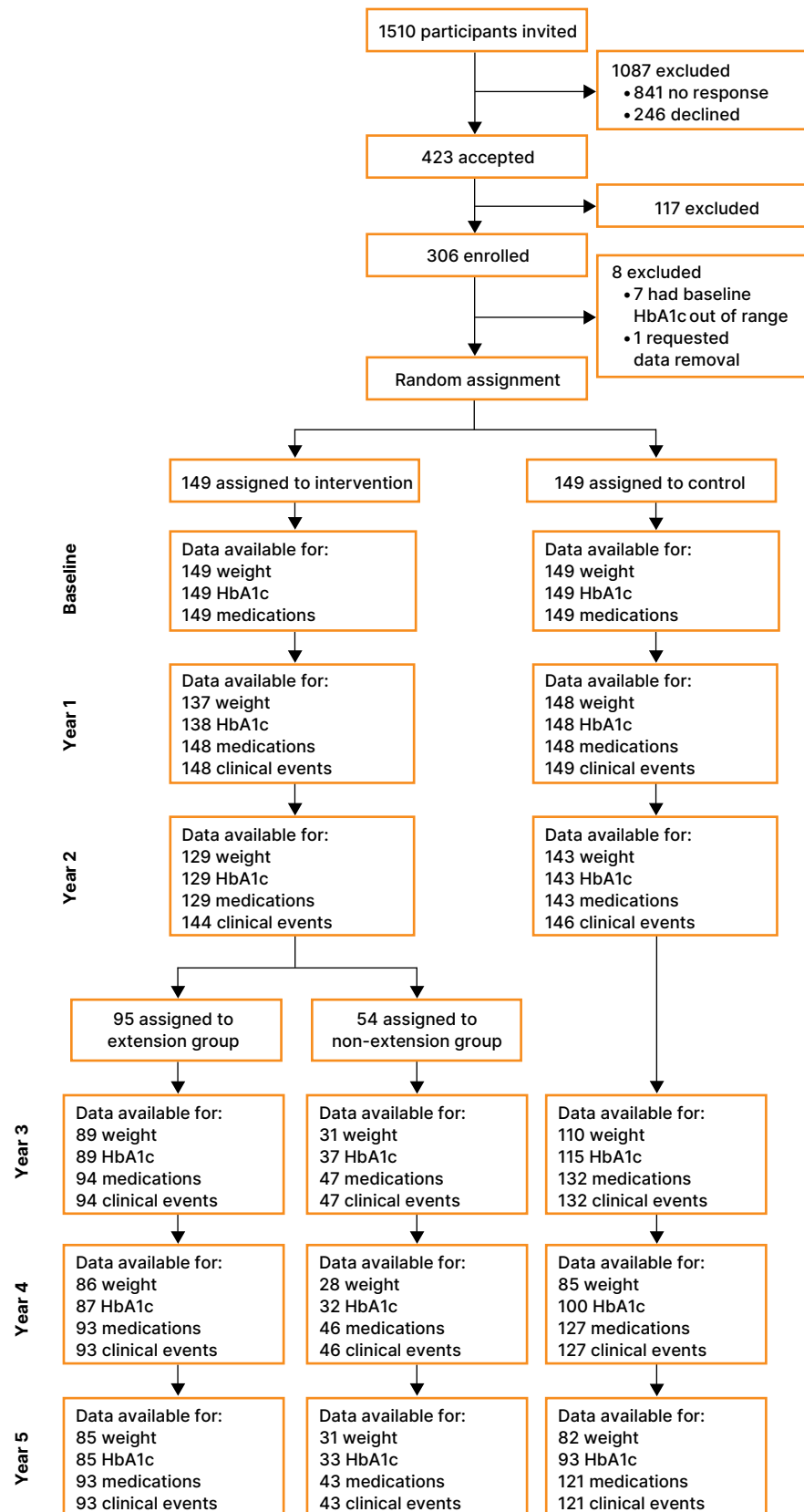
Although the benefits of T2D remission are well-known, achieving remission is difficult for many individuals and maintaining ongoing remission is even more difficult (**Figure 3**). Key factors associated with the recurrence of T2D include the following.

#### 1. Weight Regain

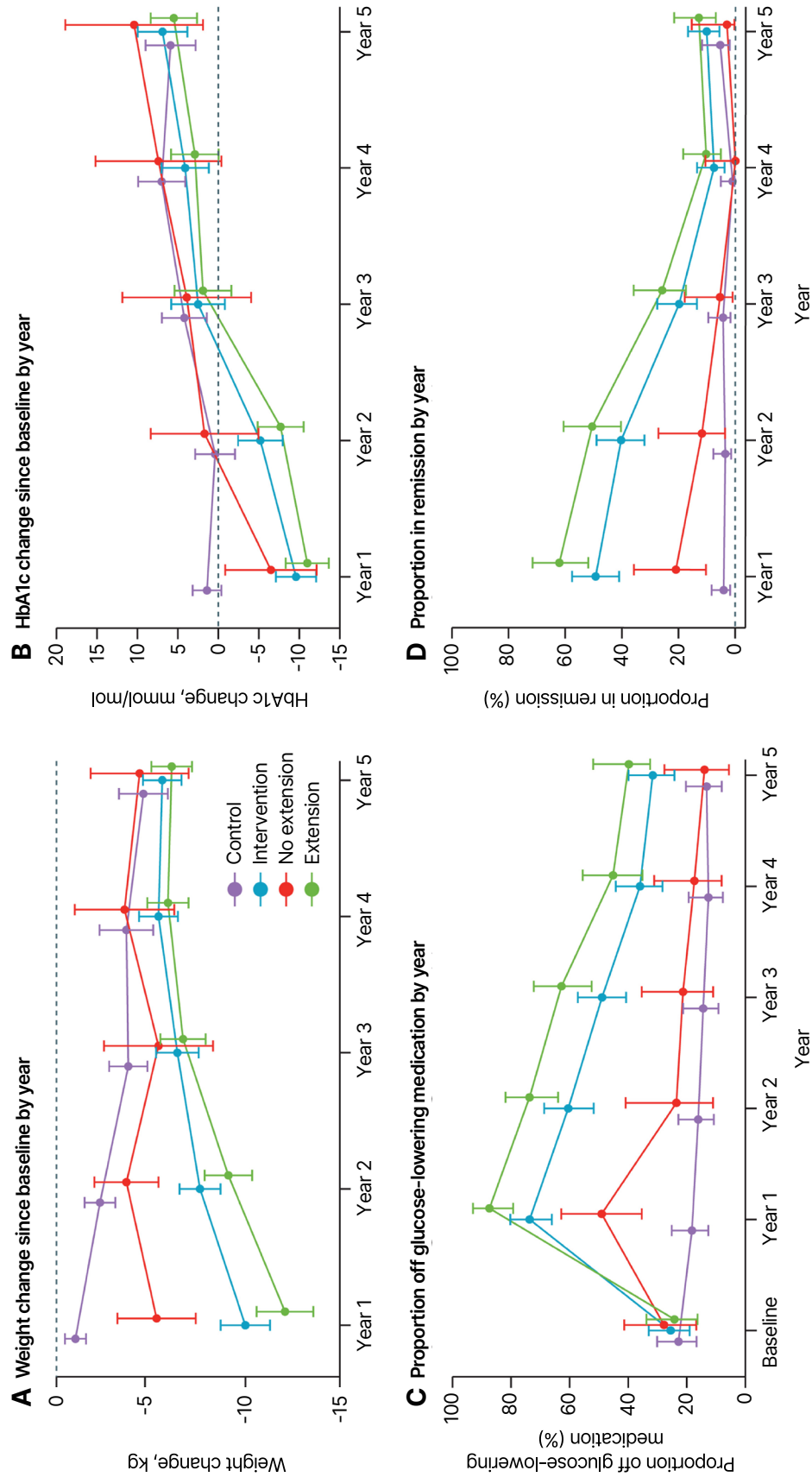
Weight regain is influenced by several factors. Physiological adaptations play a significant role, as the body's natural tendency to defend against weight loss can lead to metabolic adaptations that promote weight regain. These adaptations include alterations in appetite-regulating hormones and a reduction in the basal metabolic rate. This factor was notable, as observed in the DiRECT trial follow ups. Additionally, sustaining long-term lifestyle changes, such as dietary modifications and increased physical activity, is difficult for many individuals. Social, economic, and psychological factors can also contribute to weight regain. Furthermore, very low-calorie diets such as those used in the DiRECT study are extremely restrictive, making it challenging for most individuals to adhere to nutritionally depletive diets.

#### 2. Beta-Cell Function

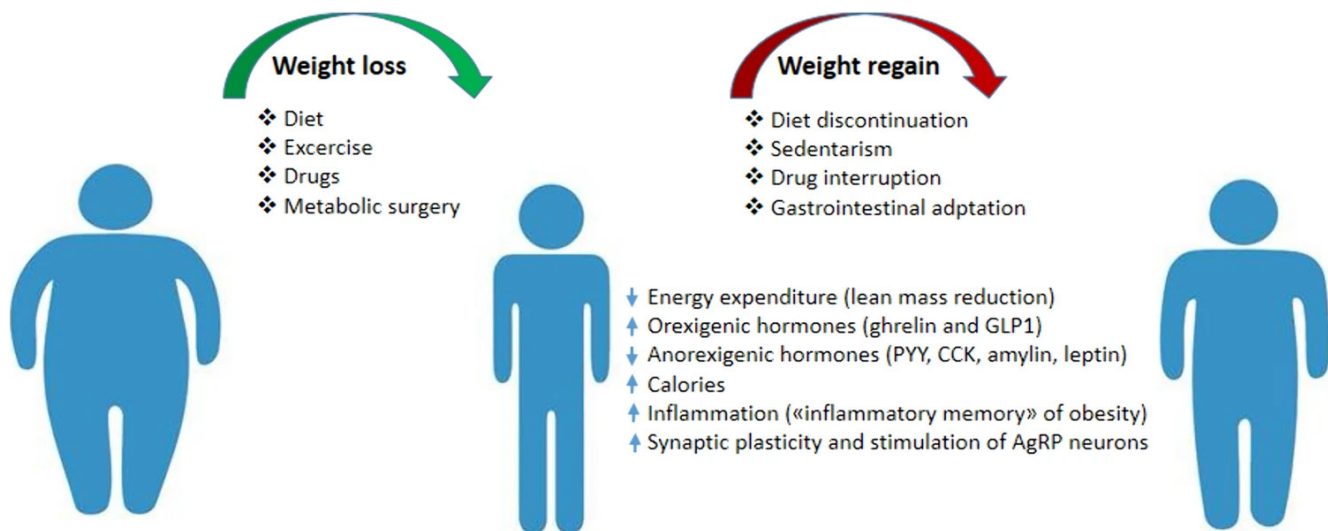
Beta-cell function can progressively decline.<sup>5</sup> Even with remission, underlying beta-cell dysfunction may persist. Over time, this can lead to a gradual decline in beta-cell function and subsequent relapse. The degree to which beta-cell function can be recovered is still under investigation. However, it is known that the longer the duration following a T2D diagnosis, the higher the likelihood of beta-cell dysfunction.



**Figure 1.** Overview of the DiRECT trial; *adapted from Lean ME et al., 2024.*



**Figure 2.** Mean weight in kg (A) HbA1c in mmol/mol (B) changes since baseline, proportions of those off all glucose-lowering medications (C) and in remission each year (D); adapted from Lean ME et al., 2024.



**Figure 3.** Pathophysiology of weight regain; *adapted from Capoccia D, et al., 2024.*

### 3. Psychological and Behavioural Factors<sup>6</sup>

Psychological and behavioural factors play an important role in maintaining long-term adherence to lifestyle changes. Sustained motivation and support are essential for individuals to continue with healthy habits. However, psychological factors, such as stress, depression, and anxiety, can hinder adherence. Over time, individuals may gradually revert to previous behaviours, leading to weight gain, thereby contributing to recurrence of diabetes.

### 4. Lack of Long-Term Support

Healthcare systems may not always provide adequate long-term support for individuals in remission. This can include limited access to dietary counselling, behavioural therapy, and ongoing monitoring. In the current Canadian healthcare system, this is particularly important as there are no provincial-funded programs that

offer long-term support with registered dietitians, behavioural health coaches, kinesiologists, and other key healthcare team members to assist with ongoing, targeted maintenance of remission using an individualized approach. Additionally, a lack of social support from family and friends can also make it difficult to maintain lifestyle changes.

### 5. Individual Variability

T2D is a heterogeneous disease, and individuals respond differently to interventions. Factors such as the duration of diabetes, the severity of insulin resistance, and genetic predisposition can influence the likelihood of achieving long-term remission.

By understanding these challenges, healthcare professionals can develop more effective strategies to support individuals in achieving and maintaining T2D remission.

## Implications for Diabetes Management

The findings from the DiRECT trial and its 5-year follow-up, along with the long-term data from the LOOK AHEAD study, have significant implications for T2D management.

- **Emphasis on Intensive Lifestyle Interventions.**

These studies reinforce the efficacy of intensive lifestyle interventions, particularly those involving significant weight loss, in achieving diabetes remission for those who are willing and able to incorporate these interventions. The 5-year follow-up data reinforces the need for long-term support to maintain remission.

- **Importance of Ongoing Support.**

Sustaining remission necessitates continuous support and reinforcement of healthy lifestyle behaviours. The 5-year data shows the importance of long-term support and demonstrates how a lack of long-term support negatively impacts remission rates. Healthcare systems must provide accessible resources and counselling.

- **Personalized Care Plans.**

Tailoring interventions to suit individual preferences and challenges is crucial for optimizing outcomes, given the heterogeneity in responses to treatment.

- **Integration of Mental Health Support.**

Recognizing the psychological benefits of remission and integrating mental health support into diabetes management programs can enhance adherence and overall well-being.

- **Addressing Insurance and Clinical Practice Gaps.**

There is a pressing need for insurance companies to develop policies regarding the impact of remission on premiums. Additionally, clear clinical guidelines are required to define appropriate blood pressure and lipid targets for individuals in remission, which address uncertainties about their cardiovascular risk.

## Key Considerations

- Remission is not a cure, and ongoing monitoring is essential.
- A multidisciplinary approach, involving healthcare professionals, dietitians, and behavioural therapists, is crucial for long-term success.
- Further research is needed to identify predictors of long-term remission and develop effective maintenance strategies.

## Conclusion

The findings from the DiRECT trial indicate that, despite a disappointing decline in remission rates over five years, the intervention group achieved a mean weight loss of 6.1 kg, which is significantly better than typical outcomes in conventional T2D care. In comparison, the LOOK AHEAD trial reported only 11% of participants had achieved remission at year one and 7% achieved remission at year four, highlighting the relative success of the DiRECT trial in maintaining weight loss and achieving remission compared to other interventions.

Achieving and maintaining T2D remission presents a significant challenge. However, the benefits are substantial, including enhanced quality of life, improved cardiovascular health, and potential economic advantages. Ongoing research and the implementation of evidence-based strategies are essential for optimizing diabetes management and improving patient outcomes.



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