

Type 2 diabetes remission: An overview

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About the Author



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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Introduction

In my practice, one of the most common questions I encounter with my type 2 diabetes (T2D) patients is, "How can I get rid of this disease?" The primary focus of practitioners' discussion regarding T2D is the chronicity and irreversibility of the condition. Recently, however, new hope is emerging concerning remission of diabetes with the increasing amount of evidence-based data available.

The need for remission

Diabetes is one of the most expensive conditions to manage in the medical arena. The global burden of diabetes-associated medical costs is predicted to be \$1,028 billion by 2030 and \$1,054 billion by 2045.¹

Diabetes is currently the 15th most common cause of decreased life expectancy;² socioeconomically disadvantaged and high-risk populations are more adversely affected than the general population.³

Diabetes occurs in millions of Canadians; according to the most recent data, approximately 10% of Canadian adults live with diagnosed diabetes. Furthermore, when combined with undiagnosed diabetes and prediabetes, prevalence increases to approximately 30%.⁴ The cost of managing diabetes includes both direct costs (including cost of medications, testing supplies, visits to healthcare providers) and indirect costs (including loss of workdays; diminished productivity at work; reduced

productivity among the unemployed, diabetes-related disability causing unemployment; and premature deaths attributed to diabetes as a result of workforce loss). The above does not even include the ramifications to mental health that arise as a result of the diagnosis, as well as the ongoing management of a chronic condition such as diabetes. Clearly, therefore, remission of diabetes can have profound benefits from a bio-psycho-socio-economic perspective.

Definition of remission

According to the most recent Diabetes Canada Clinical Practice Guidelines (CPG) type 2 diabetes remission is defined as achieving specified glycated hemoglobin (A1c) thresholds without the use of any antihyperglycemic medication for a minimum of 3 months. Remission to prediabetes is defined as A1C between 6.0% and 6.4%; remission to normal glucose concentrations is defined as A1C <6.0%.⁵

It is important to note that, although there are modalities such as islet cell transplant for type 1 diabetes, this article will focus on remission of type 2 diabetes, which is more clearly established within a growing body of scientific evidence.

Who can achieve remission?

The United Kingdom Prospective Diabetes Study (UKPDS) suggested that at the time of T2D diagnosis,

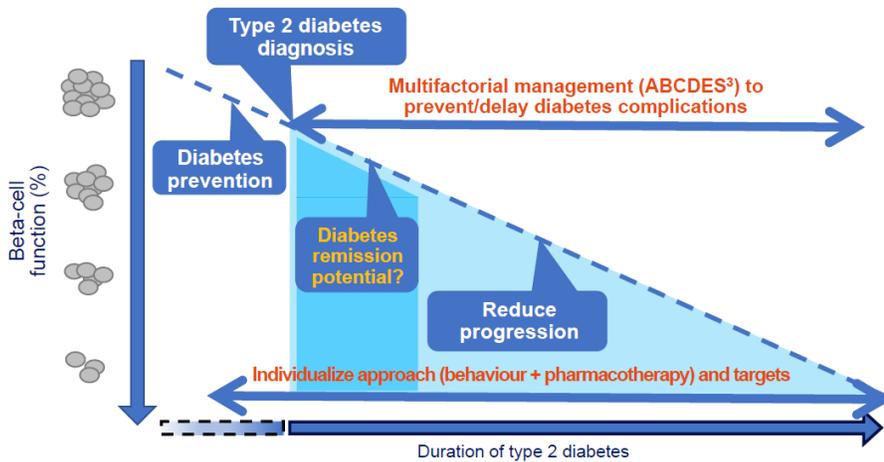


Figure 1: Potential goals and approaches for Type 2 Diabetes

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the β -cell function of an individual has diminished to approximately 50%.⁶ Subsequently, decline of β -cell function occurs at the rate of about 4% to 7% per year.⁷ The likelihood of achieving remission is highest in individuals who have received a recent diagnosis of diabetes, and is inversely proportionate to the number of years since diagnosis. Similarly, those individuals on few antihyperglycemic agents, at low doses, achieving good glycemic control are more likely to experience remission than individuals on very high doses of insulin/multiple antihyperglycemic agents. The CPG states that remission may be considered for individuals with T2D who are interested in attempting remission; do not have significant eating or mental health disorders; do not have a compelling indication for antihyperglycemic agent(s) for renal or cardiovascular benefit; and are able to participate in health-related behavioural interventions (caloric restriction leading to weight loss, exercise training) with or without bariatric surgery.⁵

How remission is achieved

The succinct response to the vital question, "How is remission

achieved?" is, primarily through healthy weight loss. However, this may not be easily accomplished. Of the various CPG recommendations for diabetes remission, only 2 achieve Grade A Level 1A status, both of which entail weight loss: bariatric surgery for those in whom it is appropriate, and a low-calorie diet leading to weight loss with or without large increase in physical activity.⁵

Bariatric surgery

An abundance of data supports the fact that bariatric surgery leads to significant improvement in glycemic control, with favourable results in both ensuing weight loss following surgery and weight-independent effects including: activation of gastrointestinal hormones that influence insulin secretion; altering the rate and site of nutrient delivery; augmentation of gut-brain crosstalk concerning food preferences and behaviour; and modification of bile acids and bacteria that influence peripheral insulin sensitivity and glycemic control.⁸

The CPG recommend bariatric surgery for individuals with diabetes and a BMI ≥ 35 . However, the current bariatric surgery guidelines by the American Society for Metabolic

and Bariatric Surgery (ASMBS) recommend surgery for individuals with metabolic disease and a BMI of 30–34.9 kg/m². More importantly, the guidelines recommend reconsideration of BMI thresholds in individuals of Asian origin, such that individuals with a BMI of 27.5 kg/m² should be offered metabolic and bariatric surgery.⁹

Low calorie diets

The majority of the data examining calorie-restrictive nutritional intake by behavioural intervention has been limited as there has been a paucity of robust, randomized control trials (RCTs) specifically investigating diabetes remission as a predefined primary outcome.

However, the results of four key RCTs (DiRECT, DIADEM-I, U-TURN and LookAHEAD) have been instrumental in proposing the following: low-calorie (800 to 850 kcal/day) diets with meal replacement products for a period of three to five months, aimed at achieving >15 kg body weight loss; followed by structured food reintroduction and increased physical activity for weight loss maintenance. This applies to nonpregnant adults with a BMI between 27 and 45 kg/m²; T2D duration of <6 years, A1C <12% and not using insulin.⁵ A recent position statement from Diabetes Canada recognizes that low-carbohydrate food patterns support weight loss, improve the ability to reach glycemic targets and/or attenuate the potential use of anti-hyperglycemic therapies.

In order to limit the risk of weight relapse, it is recommended that a personalized dietary plan is formulated for each T2D patient with the help of a registered dietitian. The likelihood of diabetes remission is directly proportionate to the degree of weight loss. The data on weight loss in excess of 15 kg is particularly robust. The DiRECT trial, in particular, was very practical

in its design, with intervention occurring at a primary care level. Patients adhered to an approximately 850 kcal/day meal replacement plan for up to 20 weeks, followed by a 2- to 8-week food reintroduction phase and then a weight loss maintenance phase that included instructions to increase physical activity. Nearly 46% of individuals were able to achieve and maintain remission at the one-year mark; 35.6% maintained remission at the two-year mark. Among those who achieved remission, followed by relapse, there was a strong correlation with weight regain.¹⁰

Clinical investigations to establish remission of type 2 diabetes

In light of the fact that the definition of remission is based predominantly on A1c parameters, monitoring A1c is critical to establish remission. If A1c is deemed unreliable, experts suggest using secondary criteria, which may include: meeting fasting plasma glucose (FPG) thresholds on two separate occasions (FPG \leq 6 mmol/L for remission to normal glucose levels; or 6.1 to 6.9 mmol/L for remission to prediabetes). The alternative is meeting both oral glucose tolerance test (OGTT) thresholds (both FPG [as above] and 2hPG \leq 7.7 mmol/L for remission to normal glucose levels or 7.8 to 11.0 mmol/L for remission to prediabetes). It is recommended that remission laboratory testing (A1c or, if A1c is deemed unreliable, FPG/2-hour OGTT) be performed at three and six months following cessation of any antihyperglycemic therapy.

After remission criteria have been met, testing to evaluate for persistence of remission vs relapse should be performed at least every six months.⁵

Remission vs reversal

From my perspective, it is crucial to impress upon individuals with diabetes that remission is not synonymous with diabetes reversal. The latter often implies finality, suggesting that recurrence cannot take place. However, if there is worsening of metabolic health, a relapse of T2D can potentially take place. Therefore, emphasizing this fact will help motivate individuals to continue with maintenance of the lifestyle changes that led to the occurrence of remission.

Additional diabetes management approaches

Clearly, weight loss is one of the most fundamental aspects of diabetes remission. Based on epidemiological data, it is estimated that virtually 80% of people with diabetes are living with obesity or overweight.¹¹ Practitioners' evolving understanding of obesity has

contributed to the realization that, in addition to the foundational lifestyle modifications required (nutrition modification and physical activity), three pillars of obesity management exist: psychological, bariatric surgery and pharmacotherapy.¹² Pharmacotherapy is particularly important in the context of diabetes remission. Considering the fact that obesity is a chronic disease, most individuals with obesity who are on pharmacotherapy for weight management will require it over the long term. Discontinuation of these medications is often associated with weight regain.

Many of the approved therapies for the management of obesity (including lipase inhibitors, GLP-1 receptor agonists) are also approved for the management of T2D; however, the doses may be different from each other in some instances.

At the time of this article's development, the U.S. FDA is evaluating the possible approval of GIP/GLP-1 receptor co-agonist therapy (already approved for the management of T2D) for the management of obesity. As the treatment for obesity is long-term, individuals on these agents may not meet the definition of diabetes remission, despite their A1C being well within the range of normoglycemia, and their target weight having been achieved. Additional guidance is needed concerning how to characterize patients who previously had T2D, are receiving obesity pharmacotherapy with adequate weight loss, and have normoglycemia. At this point, it is not a certainty that these patients can be considered as having undergone diabetes remission.

Conclusion

The previously unimaginable concept of T2D remission is now within reach for at least some individuals with the condition. It is extremely important that this therapeutic objective be considered in order to reduce the bio-psycho-socio-economic ramifications of this increasingly prevalent condition. Current data suggests that remission of diabetes might be a distinct possibility in individuals with relatively recent onset of diagnosis; with A1C $<$ 12%; and in those who are able to participate in either surgical and/or health behavioural modification to achieve sustained weight loss of $>$ 15 kg.

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