

# A Review of Understanding Remission in Diabetes Mellitus

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## ABSTRACT

This article reviews the current state of research on remission in Diabetes Mellitus (DM), explores the mechanisms, potential interventions, and clinical implications of achieving remission in both Type 1 and Type 2 Diabetes Mellitus. DM is a chronic metabolic disease characterized by elevated blood sugar levels due to insulin inadequacy or cell response, leading to high morbidity and mortality rates. Remission in diabetes, a condition where blood glucose levels return to normal or near-normal levels without medication, has gained significant attention in recent years. Diabetes remission may be defined by achieving a glycated hemoglobin (HbA1c) level below 6.5% (48 mmol/mol). These glycemic targets must be sustained for at least 3 months, and the individual should not be receiving any glucose-lowering medications during this time. Diabetes remission is to improve all aspects of the metabolic syndrome with significant (A reduction of 5-10% of baseline body weight, having a BMI less than or equal to 25 kg/m<sup>2</sup>) intentional weight loss. The concept of type 2 diabetes mellitus (T2DM) remission is rapidly evolving, drawing significant public and care. The traditional treatment goal was an HbA1c concentration of 53 mmol/mol (7%), indicating that diabetes was still present and permitting disease progression. Pursuing standard glycemic control with older medications was risky due to the prospect of adverse effects and hypoglycemia. It was shown that the functional  $\beta$ -cell mass was normalized, while other trials treating T2DM patients with metabolic surgery, a necessary therapeutic intervention, or severe lifestyle modifications achieved sustained normal glycemic status. In summary, some people can reach and maintain normal blood glucose levels without therapeutic intervention, and with newly developed medications, this semi-permanent improvement in diabetes is becoming more common. We discuss recent advances, challenges, and future directions in the quest for diabetes remission.

**Keywords:** *Diabetes Mellitus, remission, glycemic control, therapeutic intervention, lifestyle modification.*

## INTRODUCTION

The main characteristic of DM is persistent hyperglycemia caused by deficiencies in insulin action, secretion, or both. T2DM mainly involves insulin resistance and  $\beta$ -cell dysfunction, while T1DM is an autoimmune disorder that leads to the degeneration of beta cells that produce insulin. However, until recently, diabetes was thought to be a chronic condition with treatment consisting of maintaining general health, preventing complications, and controlling blood sugar levels [1-3]. The concept of remission in diabetes is an emerging phenomenon, particularly in T2DM. Remission is a state in which a person's blood glucose levels fall within normal ranges without the need for pharmacological interventions. Achieving remission in diabetes has significant implications for patients, as it can reduce medication burden, enhance quality of life, and decrease the long-term risks of diabetes-related complications [4-6].

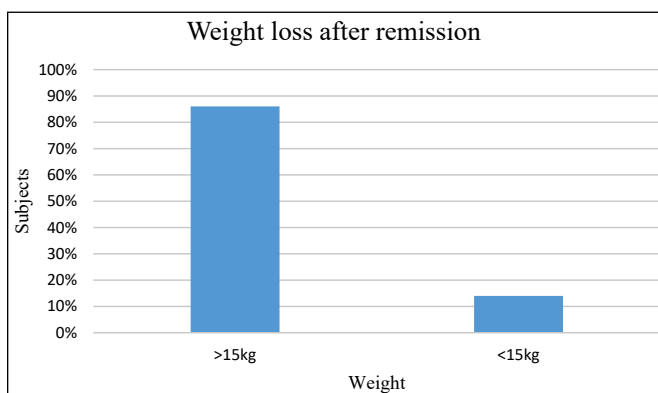
## TYPES OF DIABETES AND REMISSION

DM has various types, including T1DM, T2DM, gestational DM, maturity onset diabetes of the young (MODY), Neonatal diabetes, and latent autoimmune diabetes in adults.

## Remission in T2DM

T2DM is largely preventable and often reversible, especially when diagnosed early. The primary drivers of T2DM are insulin resistance and  $\beta$ -cell dysfunction. Although T2DM was once thought to be irreversible, increasing evidence suggests that remission is achievable through intensive lifestyle changes, pharmacological interventions, and surgical treatments [7, 8]. According to the most recent consensus statement, glycated hemoglobin (HbA1c) levels must be consistently below 6.5% for at least 3 months, without the use of glucose-lowering drugs, for T2DM to be in remission [9, 10]. Furthermore, this improvement must be achieved and sustained without the use of drugs, whether it occurs naturally or as a result of intervention. Other criteria can be used when HbA1c is not an accurate indicator of long-term blood sugar control. These include an HbA1c value of less than 6.5% (determined from continuous glucose monitoring) or a fasting plasma glucose level below 126 mg/dL (7.0 mmol/L). Future research will be standardized according to this standard definition. However, those who achieve remission (HbA1c < 6.5%) while using glucose-lowering medicines are not included in the current criteria. Partial remission means improvement, but not entirely normal blood glucose levels, maintained without medication for at least 1 year. Complete remission occurs when normal glycemic levels are achieved without treatment for one year, though diabetes is not cured. Prolonged remission

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**Fig. (1):** Comparison of weight loss after remission.

refers to complete remission lasting five years or more, reflecting sustained glycemic control but still requiring lifelong monitoring.

## Mechanisms of Remission in T2DM

### Weight Loss

Weight reduction is essential for achieving T2DM remission. Significant weight reduction, especially by bariatric surgery or calorie restriction, has been shown in studies to restore  $\beta$ -cell function and enhance insulin sensitivity, both of which are necessary for adequate glucose metabolism [11]. The primary interrelated variables that determine diabetes remission are beta-cell functioning. In the DiRECT randomized study, which enrolled 298 individuals with T2DM for up to 6 years, the dietary intervention group achieved 46% remission at year 1, mainly due to weight loss [12]. Fig. (1) shows that the majority of DiRECT participants who lost more than 15 kg of body weight experienced remission for two years, whereas only 14% of those who did not lose more than 15 kg achieved remission.

Type 2 diabetes has been associated with obesity, and managing weight is essential for treatment. Surgery, medication, and lifestyle changes can all cause remission. A sustained HbA1c below 6.5% for at least three months without taking medication is considered remission. Weight loss (by food items such as leafy greens, lentils, chickpeas, fish, apples, and nuts. Remission-focused weight loss can be further helped by restricting fried foods, white rice, sugary drinks, and sweets. In the long term, they usually result in poor nutrition, slower metabolism, and weight gain, and beta-cell function can be improved with medications, lifestyle modifications, and metabolic bariatric surgery, including incretin-based therapies. To reduce mortality and long-term complications, early and aggressive glucose control is required [12-14]. The research shows that weight-loss methods can lead to T2DM remission, and weight management has therefore become the primary treatment for the majority of newly diagnosed cases of T2DM [15].

### Improved Insulin Sensitivity

Individuals without diabetes maintain blood glucose levels between 70 and 150 mg/dl, a relatively modest

range. Despite significant variations in insulin sensitivity and secretion, this incredible balance is maintained. Insulin sensitivity varies by more than ten times, which is substantial [16]. Beta-cells are designed to store an enormous amount of insulin, which can be released in a matter of minutes to adapt to a wide range of diets. Even with a usual three-meal-a-day routine, the proper amount of insulin is released for different types of food items, like chicken, lentil soup, and spaghetti at a late dinner, and bacon, oats, fruits, and eggs in the morning. The beta-cell quickly synthesizes more insulin after each meal, which may be stored and released as needed [17].

In the early stages of T2DM, insulin resistance is the predominant pathology, and Weight loss and increased physical activity have been shown to reduce this resistance and improve glucose uptake in muscle and adipose tissues.

Insulin resistance is the most common pathophysiology in the early stages of T2DM. It has been shown that reducing body weight and increasing physical activity can enhance glucose uptake in adipose and muscle tissues.

### $\beta$ -Cell Preservation and Function

Treatment of both type 1 and type 2 diabetes depends on maintaining pancreatic islet  $\beta$ -cells. Leukotriene antagonists, immunosuppressive therapies, and anti-inflammatory medications are being investigated in type 1 diabetes. Islet transplantation, stem cell therapy, and xenogeneic transplantation are promising treatments. In T2DM, lifestyle changes, pharmacological interventions, and bariatric surgery can improve insulin sensitivity, gut hormones, and  $\beta$ -cell mass, leading to diabetes remission and improved glycemic control [18].

### Incretin Hormones

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), medications that stimulate incretin hormone and other receptors, may increase their capacity to regulate blood glucose levels and promote weight loss [19]. Postprandial release of GLP-1 inhibits appetite and stimulates insulin production in response to glucose. Any diet rich in beans, lentils, vegetables, fruits, fish, and/or chicken that enhances the synthesis of GLP-1 or other incretins, such as GIP, may help prevent the progression of type 2 diabetes and/or achieve remission of prediabetes [20].

### Reduction of Chronic Inflammation

Glycaemia is associated with the main micro- and macrovascular effects of diabetes. The level at which diabetes-specific microvascular problems develop is the diagnostic threshold for the disease; as these issues are extremely uncommon at HbA1c <48 mmol/mol (<6.5%), remission should reduce the risk of developing them. Although a single observational study cannot establish causation, the preliminary data now available all point to remission as a means of preventing or delaying the

clinical effects of type 2 diabetes. Follow-up over 30 years revealed sustained protection against diabetes and suggested a slight decrease in cardiac events in the Da Qing study, which involved a lifestyle intervention for 500 individuals with prediabetes [21]. Compared to people who did not achieve remission, those with type 2 diabetes who showed signs of remission had significantly decreased incidences of chronic kidney disease and cardiovascular disease, respectively. Post-baseline improvements in weight, fitness, HbA1c, and low-density lipoprotein cholesterol may affect this association [22]. Diabetes is associated with chronic low-grade inflammation, which increases insulin resistance and complications. Pro-inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 contribute to poor metabolic control. Effective diabetes treatment reduces inflammation by improving glycemic control, lowering blood glucose levels, and thereby decreasing oxidative stress and inflammatory signaling. This improvement correlates with reduced levels of inflammatory markers, such as C-reactive protein and HbA1c. Certain antidiabetic medications, including metformin and GLP-1 receptor agonists, also have direct anti-inflammatory effects, enhancing metabolic outcomes and minimizing complication risks [23, 24].

### **Interventions Leading to Remission in T2DM**

#### ***Caloric Restriction and Low-Calorie Diets***

Low-calorie diets and calorie restriction can cause remission in as many as 50% of subjects with early-stage T2DM, according to studies such as the DiRECT experiment. Remission rates in the DiRECT experiment, which evaluated a very low-calorie diet using meal replacements, were 46% at one year and 36% at two years, compared with 4.0% and 3.4% in the control groups, respectively. DIADEM-I, another similar experiment, used short-term, extremely low-calorie diets and helped participants lose 12 kg, resulting in an even greater remission rate of 61% at 1 year [25]. After a year of thorough lifestyle intervention utilizing low-energy complete food replacement, more than half (56%) of newly diagnosed patients with type 2 diabetes achieved remission, according to the recently published DiRECT-Aus study [26]. Remission rates were comparable to those reported in earlier research from other regions of the world, indicating that this strategy works well for people of many races and cultural backgrounds. To increase the probability of remission, DiRECT-Aus advises giving priority to demanding lifestyle changes, particularly within 6 years of diagnosis [27].

#### ***Bariatric Surgery***

Bariatric surgery has been related to significant improvements in insulin sensitivity and, in some cases, complete remission of T2DM. Procedures like gastric bypass and sleeve gastrectomy not only reduce weight but also induce metabolic changes that improve glucose control. By physically decreasing the pathway through which food is absorbed, surgery improves fullness and

reduces absorption. This method has positive benefits for glycemic management in addition to weight loss, such as raising the threshold for incretin hormones through structural changes in the intestines [28]. There are several types of metabolic surgery, including Roux-en-Y gastric bypass, vertical sleeve gastrectomy, and adjustable gastric bands. Depending on the surgical technique, the result may differ [29]. Postoperative weight loss was related to diabetic remission; however, even after controlling for weight change, patients undergoing Roux-en-Y gastric bypass had an increased chance of achieving diabetes remission relative to those undergoing laparoscopic adjustable gastric banding. Bariatric surgery is more likely to achieve diabetic remission and improve blood glucose control than nonsurgical therapy in individuals with T2DM whose body mass index is less than 35 kg/m<sup>2</sup> [30].

#### ***Exercise and Physical Activity***

Frequent exercise has been reported to enhance insulin sensitivity, reduce blood glucose, and promote weight loss, heart and mental health, all of which are factors in the remission of diabetes. Along with dietary changes, regular exercise enhances metabolic health and supports weight loss [12]—a confirmed relationship between diabetic remission and a healthy lifestyle in people with newly diagnosed type 2 diabetes. According to the study's findings, modifying one's lifestyle following a diabetes diagnosis may help the condition achieve remission.

Remarkable improvements in quality of life, weight loss, and diabetes remission were associated with lifestyle changes. Food and exercise, which are essential elements of lifestyle therapies, have a significant impact on blood glucose and weight control in individuals with type 2 diabetes. Therefore, it is recommended that the main lifestyle issues be addressed through diet and exercise [31, 32].

#### ***Pharmacological Therapies***

Drugs such as GLP-1 receptor agonists and SGLT2 inhibitors have shown promise in treating T2DM and may help achieve remission, especially in those who cannot achieve sufficient control with lifestyle modifications alone. New diabetic medications have a particular mechanism for causing patients to lose significant amounts of weight. In this case, sodium-glucose cotransporter-2 (SGLT2) inhibitors decrease glucose levels independent of insulin production or insulin sensitivity by acting on the kidney's proximal convoluted tubule to reduce glucose resorption, leading to glycosuria [33].

#### ***Remission in T1DM***

Although the gradual loss of insulin-producing  $\beta$ -cells is more difficult in remission in T1DM, there is evidence that newly diagnosed patients experience an initial period of happiness. Blood glucose control improves, and insulin needs decrease at this time; however, this remission is

usually temporary. The third stage, also referred to as the “honeymoon phase,” is particularly significant due to its complex pathophysiology. The ideal time to use targeted therapy with different immunomodulatory drugs appears to be during the honeymoon phase of type 1 diabetes, which may lead to the elusive “diabetes reversal” in T1DM. Therefore, identifying this phase is essential, and many different criteria have been proposed [34].

## Factors Influencing Remission in T1DM

### **Early Diagnosis and Tight Glycemic Control**

The honeymoon period, when insulin production and glucose metabolism are comparatively well-maintained, may be prolonged by early intervention with strict glucose monitoring [35]. Adequate glycemic control, sometimes with little to no insulin therapy, is an indication of remission in type 1 diabetes. Complete remission is rare in T1DM, although partial remission is more common [36].

### **Immunomodulatory Treatments**

The goal of immunomodulatory therapy for T1DM is to alter the immune response to protect, and possibly repair, pancreatic  $\beta$ -cells. These therapies are essential because they provide alternatives to conventional insulin therapy, which focuses more on symptom management than on the underlying autoimmune etiology. The potential of stem cell therapy to replace damaged  $\beta$ -cells and restore insulin production is attracting more interest. Research into immunotherapy, such as anti-CD3 monoclonal antibodies, has shown potential to preserve  $\beta$ -cell function in T1DM. The FDA has approved teplizumab, an anti-CD3 monoclonal antibody that targets T cells, to delay the onset of stage 3 T1DM in individuals with stage 2 illness. It maintains  $\beta$ -cell activity by regulating the immunological response [37]. Although its benefits are often temporary, rituximab is well known for its ability to preserve  $\beta$ -cell function. It targets B lymphocytes, which contribute to  $\beta$ -cell autoimmune death [38]. However, these treatments are still experimental and are not yet widely available.

### **Stem Cell Therapy**

According to developments in stem cell research, T1DM patients may be able to achieve remission through the transplantation of insulin-producing cells or stem cells that can regenerate  $\beta$ -cells. The ability of mesenchymal stem cells to differentiate into insulin-producing cells, as well as their immunomodulatory capabilities, is being investigated. It allows pancreatic cells to regain insulin secretory capacity after glucotoxic and lipotoxic stress is reduced. Partial preservation or temporary recovery of residual  $\beta$ -cell function after the initiation of exogenous insulin therapy reduces glucotoxicity and allows some recovery of surviving  $\beta$ -cells. Concerns nevertheless exist regarding immunological reactions after transplantation or differentiation [39]. The goal of stem cell therapy is to prevent autoimmunity and support the maintenance and

regeneration of  $\beta$ -cells, both of which are essential for reducing the burden of long-term diabetes [40].

### **Challenges in Achieving Remission**

Long-term remission maintenance is a significant challenge. After an initial period of remission, many individuals return to hyperglycemia, especially if they lose weight or fail to follow through on lifestyle improvements. Long-term safety concerns and the need for specific treatment remain significant barriers. The effectiveness of stem cell therapies is limited by the development of autoantibodies and the requirement for continuous immunosuppression [41]. Partial remission is considerably more common in T1DM than complete remission. However, the conditions controlling its onset and persistence are comparable between the two. Better residual pancreatic B-cell secretory activity and earlier detection are associated with the majority of these. Whether remission is full, partial, or absent depends on quantitative differences in these variables (e.g., lower HbA1c and higher C-peptide levels). To achieve both partial and complete remission, it is crucial to diagnose T1DM as early as possible. This further confirms the idea that T1DM screening can detect the illness in its early stages [42].

## CONCLUSION

In diabetes, especially T2DM, remission is a promising new potential. Weight loss, increased insulin sensitivity, and novel pharmacologic treatments are among the significant advancements in identifying the components that lead to remission. Although T1DM remission is still challenging to achieve, developments in immunomodulation and stem cell therapy may open new therapeutic options in the future. Remission involves more than just improving glycemic control; it also consists of enhancing quality of life and reducing the disease's long-term consequences. The longevity of remission remains a significant obstacle, though, and further study is required to refine the tactics and determine which patient groups stand to gain the most from them. T2DM remission is predominantly metabolic and reversible, whereas T1DM remission is immune-mediated and short-term.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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