

Remission of diabetes

Type 2 diabetes mellitus (T2DM) is regarded as a chronic condition that needs lifelong management with lifestyle modifications and medications. The natural history of T2DM starts with normal glucose tolerance, followed by pre-diabetic condition, and eventually, diabetes. However, this trajectory can get reversed, following the sequence of diabetes to pre-diabetes, and ultimately to normal glucose levels. This is referred to as ‘Remission of diabetes’. ‘Remission’ in the context of diabetes refers to a sustained period where the blood glucose levels become normal in a person who earlier had blood sugar values in the ‘diabetes’ range. According to the American Diabetes Association, Remission is defined as maintaining a glycated hemoglobin (HbA1c) level below 6.5% for at least three months without the use of any antidiabetic medication in individuals who were earlier on medication (Riddle, M. C. *et al.*, *Diabetes Care*, 2021, **44**(10), 2438–2444; doi:10.2337/dci21-0034). The possibility of achieving remission provides hope to people with T2DM diabetes. Therefore, it is essential for physicians to explore and promote interventions that facilitate the attainment of remission.

Remission can manifest in various ways within the realm of diabetes. For instance, drug-induced diabetes may get resolved once the administration of steroids is discontinued; gestational diabetes often returns to normal following childbirth. Remission can also be achieved through interventions such as bariatric surgery, intensive insulin treatment, or the resolution of acute mental stress. Each of these avenues offers a potential path towards remission, highlighting the multifaceted nature of T2DM.

In 2008, the twin cycle hypothesis was introduced, which suggests that the root cause of diabetes is the excessive, yet reversible, accumulation of fat in the liver and pancreas (Taylor, R., *Diabetologia*, 2008, **51**(10), 1781–1789; doi:10.1007/s00125-008-1116-7). This excess fat accumulation in the liver leads to hepatic insulin resistance and increased glucose production, ultimately resulting in hyperglycemia. However, significant weight loss, resulting in the removal of excess fat from these organs, can lead to restored hepatic insulin sensitivity and potential recovery of beta cells.

How is remission of diabetes achieved? In 2011, the physiological mechanisms underlying diabetes remission following weight loss through dietary interventions were elucidated, and this discovery piqued global interest in the

concept of remission (Lim, E. L. *et al.*, *Diabetologia*, 2011, **54**(10), 2506–2514; doi:10.1007/s00125-011-2204-7). Lifestyle interventions such as low-calorie diets, weight management, pharmacological treatments, and metabolic surgical interventions have all been shown to contribute to remission of diabetes.

A very low-calorie diet, containing just 800 calories per day, has been found to be effective in promoting significant weight loss in people with diabetes. This approach triggers notable physiological changes in the body, leading to improvements in glycemic control. Research has shown that after just one week of calorie restriction, fasting plasma glucose levels can normalize, and hepatic insulin sensitivity can improve due to a reduction in liver fat content. Over an eight-week period, insulin secretion rates can return to normal levels, coinciding with a decrease in pancreatic fat content. However, it is important to note that a very low carbohydrate diet can increase fat intake, potentially leading to elevated LDL cholesterol levels and an increased risk of coronary heart disease. Furthermore, these diets can be challenging to adhere to over the long term, particularly in India, where dietary habits may be difficult to modify.

In the UK, the DiRECT trial was conducted to investigate whether effective weight management could lead to sustained remission of diabetes in a primary care setting. The trial recruited 298 individuals aged between 20 and 65 who had been diagnosed with diabetes in the preceding 6 years. They had a body mass index between 27 and 45 kg/m² and were not receiving insulin. The intervention involved withdrawing antidiabetic and antihypertensive medications, total diet replacement, stepped food reintroduction, and structured support for long-term weight loss maintenance. The study showed that nearly half (46%) of participants in the intervention group achieved remission compared to 4% in the control group, highlighting the potential benefits of weight management interventions in achieving remission of diabetes (Lean, M. E. J. *et al.*, *Lancet Diabetes Endocrinol.*, 2019, **7**(5), 344–355; doi:10.1016/S2213-8587(19)30068-3).

Several recent studies have demonstrated the effectiveness of lifestyle interventions in achieving remission of diabetes. For example, a meta-analysis of 28 randomized controlled trials involving over 6,000 participants found that caloric restriction coupled with intensive lifestyle modification programmes was effective in achieving remission (Jayedi, A.

et al., Am. J. Clin. Nutr., 2023, **117**(5), 870–882; doi:10.1016/j.ajcnut.2023.03.018). These findings highlight the potential benefits of lifestyle interventions in achieving remission of diabetes.

However, diabetes remission through lifestyle interventions is not applicable to everyone. Eligibility can be determined through the ABCDE approach where A stands for the individual's HbA1c levels, B for body weight, C for peptide/insulin secretion, D for duration of diabetes and E for motivation to succeed.

It is worth noting that understanding of remission of diabetes is mainly restricted to T2DM and not to other types, such as type 1 diabetes or fibro calculous pancreatic diabetes. Long-term evidence for diabetes remission is currently limited, and further research is required, particularly in culturally diverse populations such as in India.

It is also crucial to note that the sustainability of diabetes remission is largely dependent on an individual's ability to maintain lifestyle modifications. Failure to adhere to these changes may result in 're-reversal' or relapse of diabetes.

The sustainability of diabetes remission is closely tied to sustained weight loss, as it is often the driving force behind remission. However, if an individual regains weight (which is not uncommon), diabetes may return with greater intensity. Although there are a few instances where individuals have maintained remission for extended periods, it is more common for diabetes to reoccur, necessitating the resumption of medication. Consequently, the long-term sustainability of diabetes reversal programmes remains a major concern.

In recent times, a range of technologies have emerged to assist diabetes remission efforts. A popular approach involves the use of mobile phones and a designated coach or diabetes educator who provides ongoing support and motivation to individuals, encouraging adherence to lifestyle changes and weight loss goals. Mobile apps that track daily steps taken and caloric intake are also utilized, offering real-time feedback to assist in achieving diabetes remission. However, it is important to note that with the increasing number of these technologies, there is also an influx of false claims and hype that can mislead individuals seeking effective solutions.

The concept of diabetes remission is not new, as it was described by our team, over forty years ago (Ramachandran, A. *et al., J. Med. Assoc. Thai.*, 1987, **70**, 185–189). Our study involved 45 individuals with T2DM who were treated with a strict diet, exercise, and oral medication, resulting in the normalization of their blood sugar levels and remission of diabetes. Surprisingly, the amount of weight loss required for achieving remission was very modest, often as little as 5 kg, and mostly in obese individuals. We also observed some non-obese individuals who achieved remission with only 2 kg of weight loss. We also showed that re-reversal or relapse of diabetes occurred in 5 of the 45 individuals. Poor dietary adherence, weight regain, infections and stress were identified as the main factors leading to the recurrence of diabetes. Our study also showed a considerable reduction in

plasma insulin levels in those who achieved remission after weight loss. We also found that while some individuals were able to maintain remission for several years, others experienced re-reversal of diabetes. The longest period of remission observed in our study was 9 years.

Studies on the remission of diabetes have been primarily discussed at an individual level, but recent data from the Indian Council of Medical Research – India DIABetes (ICMR-INDIAB) national study explores the potential diabetes remission at population level. This study used a data-driven optimization model to determine what changes in the macronutrient composition of the diet could promote remission and prevent diabetes in Indians (Anjana, R. M., *Diabetes Care*, 2022, **45**(12), 2883–2891; doi:10.2337/dc22-0627).

Indians tend to have a high-carbohydrate diet, with carbohydrates accounting for about 65–70% of their diet (Mohan, Br. *J. Nutr.*, 2009, **102**(10), 1498–1506; doi:10.1017/S0007-114509990468) and very low protein intake. We have also shown earlier that excess carbohydrate consumption, especially in the form of rice, is a contributing factor to the onset of diabetes (Bhavadarini, B. *et al., Diabetes Care*, 2020, **43**(11), 2643–2650; doi:10.2337/dc19-2335). By analysing the dietary data of individuals with normal glucose tolerance, prediabetes, and diabetes, the INDIAB study formulated macronutrient recommendations to compute the optimal composition of carbohydrates, protein, and fat in the diet that would promote the remission of diabetes. The results indicated that reducing carbohydrate intake to a level between 49% and 54%, increasing protein to 19–20%, and healthy fats to 21–26%, could lead to remission of diabetes. While these figures were obtained through mathematical modeling, they represent the first population-based recommendation for inducing remission of diabetes in Indians who consume high amounts of carbohydrates. However, further research, such as randomized clinical trials, is necessary to confirm the effectiveness of these recommendations.

As we delve deeper into the possibility of achieving remission in selected individuals with T2DM, it is crucial to understand that while low-calorie and low-carbohydrate diets have both proven to be effective, a reduction in calorie intake is ultimately necessary for weight reduction leading to remission.

Long-term interventions in the diabetes process offer promise for achieving remission. To support individuals towards this goal, structured programmes must be put in place, providing continued regular support, and involving dietitians for long-term success.

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