Remission of Type 2 Diabetes: How, When, and for Whom?

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Abstract

Type 2 diabetes (T2DM) is conventionally considered a progressive disorder, with most patients requiring increasingly intensive therapy to control hyperglycemia over time. Recently, there has been a major paradigm shift towards trying to reverse T2DM. Emerging evidence suggests that remission of T2DM is feasible in a subset of patients. Identification and careful selection of candidates for remission are crucial for the success of these programs. Among various dietary strategies, low-calorie diets (LCDs) and low-carbohydrate diets (LCDDs) have been demonstrated as being effective in facilitating remission of T2DM in a targeted population within a clinical setting. Remission with LCDDs may be maintained in the absence of weight loss, however, long-term evidence is limited and remission may not be maintained without long-term carbohydrate restriction, which poses major challenges. In very low-calorie diets (VLCDs), weight loss of 15 kg or greater and maintenance of weight loss is the main driver and predictor of remission. However, most individuals with T2DM were unable to maintain remission beyond 2 years, despite being on VLCDs. Most data are required on the long-term sustainability of remission in an ethnically diverse population like Asian Indians with T2DM who have less obesity and hence less weight to lose. Moreover, “re-reversal” or “relapse” of diabetes can occur in a large percentage of individuals who discontinue the dietary restrictions. Hence, regular follow-up by a multi-disciplinary team to ensure sustainability of the lifestyle modification is crucial to the maintenance of remission of T2DM.

Introduction

Type 2 diabetes is conventionally considered a progressive disorder, with most patients requiring increasingly intensive therapy to control hyperglycemia over time, with around 50% of individuals requiring insulin therapy within 10 years.¹,²

The global prevalence of diabetes in adults has been increasing over recent decades. The total number of people with diabetes is projected to increase from 537 million in 2021 to 784 million by 2045. India has more than 74 million people living with diabetes, the second highest number worldwide. This number is estimated to reach 92.97 million by 2030 and 124.87 million by 2045.³ India also ranks second in the world with 51.7% people with undiagnosed diabetes.³ In the Indian Council of Medical Research-Indian Diabetes (ICMR-INDIAB) study conducted in 15 states, the overall prevalence of pre-diabetes and diabetes were 10.3% and 7.3%, respectively.⁴

Increased prevalence of diabetes in India can probably be attributed to the higher than recommended consumption of carbohydrates especially simple carbohydrates such as polished white rice, refined wheat, and its products.⁵,⁶

Despite advancements in both pharmaceutical and technological treatments, diabetes management still remains suboptimal. The ICMR-INDIAB study data showed high mean hemoglobin A1C (HbA1C) levels (8.9 ± 2.1%) in subjects with self-reported diabetes. More than 60% of subjects had not had their HbA1C level checked in the past 1 year.⁷ Also, glycomic control tends to deteriorate even in those individuals who initially achieve good control, necessitating the addition of increasing doses of oral antidiabetic agents and ultimately insulin.⁸ This deterioration in control has been interpreted to mean that while T2DM is treatable and controllable, it is not curable or reversible. Indeed, it is fair to state that the major focus thus far has been on control of hyperglycemia and delaying the progression to the stage of complications. Current treatment guidelines for T2DM recognize this aspect of the natural history of disease by advocating stepwise addition of therapeutic agents so as to achieve glycemic targets.⁹

Most individuals having diabetes find taking medications life-long a hassle with worries about the long-term side effects of these medications. They wish to go off medications and be declared as “nondiabetic.”

Recently, the management of T2DM has undergone a sea change wherein, efforts are being focused on “reversing” the disorder completely. New evidence shows that it is possible to achieve remission of T2DM but, long-term data on sustainability are lacking. Reversal of glucose levels back into the normal range may be achieved due to modalities of treatment like bariatric surgery or by drastically changing diet and lifestyle to achieve profound weight loss resulting in drastic reduction in body fat (particularly hepatic fat), thereby improving insulin sensitivity. This article will review the literature available on remission of T2DM using dietary interventions such as low-carbohydrate diets (LCDDs) and low-calorie diets (LCDs).

Definitions

As per the consensus report proposed by the International Expert Group convened by the American Diabetes Association (ADA), the term “remission” is to be preferred to “relapse,” and should be defined as a return of HbA1C to <6.5% (48 mmol/mol) and/or fasting plasma glucose to <126 mg/dL (<7.0 mmol/L) either spontaneously or following an intervention, and that persists for at least 3 months in the absence of glucose-lowering pharmacotherapy.

“Partial remission” is when an individual with T2DM achieves an HbA1C <6.5% and/or fasting glucose 100–125 mg/dL and is off all diabetes medication for more than 1 year.

“Complete remission” is when an individual with T2DM achieves an HbA1C <6.5% and/or fasting glucose <100 mg/dL and is off all diabetes medication for more than 1 year.

“Prolonged remission” is when an individual with T2DM achieves an HbA1C <5.6% and/or fasting glucose <100 mg/dL and is off all diabetes medication for 5 years and more.

The expert group suggested that testing of HbA1C to document a remission should be performed just prior to an intervention and no sooner than 3 months after initiation of the intervention or withdrawal of any

Helpful medically reviewed content, insights, and advice from experts are available on the Diabetes Education Center. Our team of diabetes educators, dieticians, and other healthcare professionals are here to help you with your diabetes.

REFERENCES

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glucose-lowering pharmacotherapy. Subsequent testing to determine long-term maintenance of remission should be done at least yearly.

The group also made suggestions for active observation of individuals experiencing remission and discussed further questions and unmet needs regarding predictors and outcomes of remission. They rightly concluded that “More research is needed to determine the frequency, duration and effects on short- and long-term medical outcomes of remission of T2DM using available interventions.”

The Primary Care Diabetes Society and the Association of British Diabetologists define remission of T2DM as the achievement and maintenance of HbA1c <6.5% (48 mmol/mol) or fasting plasma glucose <126 mg/dL (<7.0 mmol/L) after weight loss and discontinuation of all glucose-lowering therapies over 6 months or longer.

As per the Virta Health trial, reversal of T2DM is defined as achievement and maintenance of HbA1c <6.5% for more than 1 year with no diabetes medication or on metformin alone, and remission as achievement and maintenance of HbA1c <6.5% with no diabetes medication for more than 1 year.

While weight loss is the most significant driver and predictor of remission, euglycemia on a LCBD may occur without weight loss. As it does not meet the criteria of remission, it may be referred to as a “state of mitigation” of T2DM.

“Mitigation” of T2DM refers to euglycemia achieved because of continuous carbohydrate restriction and is not associated with weight loss. This “state of mitigation” will only last as long as the carbohydrate restriction is maintained.

Table 1 summarizes the various definitions of remission/reversal of T2DM.

Thus, it can be seen that there are several definitions of reversal, but the ADA definition seems to be the simplest to use in clinical practice.

### Table 1: Definitions of remission/reversal of T2DM

<table>
<thead>
<tr>
<th>Guidelines for remission</th>
<th>Reversal/remission</th>
<th>Glucose lowering agents</th>
<th>Glycemic parameters</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>Remission</td>
<td>No diabetes medication</td>
<td>HbA1c &lt;6.5% and/or fasting blood glucose &lt;126 mg/dL</td>
<td>&gt;3 months</td>
</tr>
<tr>
<td>Virta Health</td>
<td>Reversal</td>
<td>No medication or metformin alone</td>
<td>HbA1c &lt;6.5%</td>
<td>1 year</td>
</tr>
<tr>
<td>ABCD/PCD</td>
<td>Remission</td>
<td>No medication</td>
<td>HbA1c &lt;6.5%</td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cessation of all diabetes medication</td>
<td>Fasting blood glucose &lt;126 mg/dL, HbA1c &lt;6.5%</td>
<td>&gt;6 months</td>
</tr>
</tbody>
</table>

### Dietary Strategies Involved in the Remission of T2DM are: LCD and LCBD

#### Low-calorie Diets (LCDs)

Dietary calorie restriction approaches for the remission of T2DM have used either LCDs (1000–1500 kcal/day) or very low-calorie diets (VLCDs) (<800 kcal/day) to achieve weight reduction.

A VLCD regime usually involves the replacement of all food with a liquid diet formulation providing approximately 400–800 kcal/day for a period of 12–16 weeks, followed by a reintroduction phase which includes structured solid food tailored for weight loss maintenance. Most of the VLCD liquid formulae comprise approximately 50–60% of energy coming from carbohydrates (maltodextrins and sucrose) in order to prevent ketosis, essential fatty acids to meet the daily requirements, and high-biological-value proteins such (1.2–1.5 gm/kg body weight) to preserve loss of lean body mass. Liquid VLCD formulae typically contain very little fiber, are sweetened with artificial sweeteners, and are fortified with vitamins and minerals to meet the nutritional requirements. However, vitamin and mineral supplements are often suggested to meet the micronutrient needs for obese adults.

#### Low-carbohydrate Diets (LCBDs)

Low-carbohydrate diets primarily work on the hypothesis that when LCBD is initiated, insulin secretion is lowered thereby reducing fat storage, facilitating weight loss, and improving cardio-metabolic function. They are classified as:

- Low-carbohydrate diet—less than 26% of energy coming from carbohydrates or less than 130 gm carbohydrates per day
- Very low-carbohydrate diet—less than 10% energy coming from carbohydrates or 20–50 gm carbohydrates per day

### Evidence for LCD and LCBD

#### LCDs

Evidence has shown a positive correlation between significant loss of weight and T2DM remission. The ADA guidelines recommend short-term (3-month) interventions focusing on lifestyle with the use of VLCDs (≤800 kcal/day) to achieve >5% loss of body weight. To achieve this calorie deficit, meal replacement formulas can be advised by qualified healthcare professionals to selected patients with close monitoring. To sustain weight loss for a longer duration, such lifestyle intervention programs must include long-term weight-maintenance counseling and regular follow-up.

In the COUNTERPOINT study, Lim et al. found improvement in hepatic insulin sensitivity and beta cell function in 11 individuals with T2DM (49.5 ± 2.5 years, body mass index (BMI) 33.6 ± 1.2 kg/m²) on a VLCD liquid diet of 600 kcal/day. A total of 510 kcal/day was contributed by a low-calorie liquid formulae providing carbohydrate 46.4%, fat 20.1%, protein 32.5%, vitamins, minerals, and trace elements, and 90 kcal/day from three portions of non-starchy vegetables daily for 8 weeks. Mean weight loss post dietary intervention was 15.3 ± 1.2 kg of initial body weight. It was observed that there was an increase in the first phase of insulin response. Remission of T2DM was noted in 8 weeks, with blood glucose returning to the normal range in 1 week. Hepatic triacylglycerol levels decreased to 2.9 ± 0.2% (baseline 12.8 ± 2.4%) (p = 0.003) and pancreatic triacylglycerol content reduced to 6.2 ± 1.1% (baseline 8.0 ± 1.6%) (p = 0.03) by week 8. Improvement in hepatic insulin sensitivity and regularization of beta cell function was attained by calorie restriction alone. Positive outcomes were achieved with a decrease in pancreatic and liver triacylglycerol stores. This study showed that the aberrations underlying T2DM are reversible with reduction of body fat, weight, hepatic and pancreatic fat, and can be achieved by restriction of calories alone.
In the COUNTERBALANCE study, 29 people with T2DM, short-duration group (n = 15), having diabetes for <4 years, long-duration group (n = 14) having diabetes for >8 years, consumed VLCD of 624–700 calories comprising liquid replacements, vegetables, and 2 L water per day for a period of 8 weeks. Weight loss achieved in the short- and long-duration groups was found to be similar (14.8 ± 0.8% and 14.4 ± 0.7%, respectively; p = 0.662). About 87% of the individuals in the short-duration group and 50% of the individuals in the long-duration group achieved fasting plasma glucose levels in the nondiabetic range at 8 weeks.18

The COUNTERBALANCE study-2 conducted in 30 individuals with T2DM by Steven et al.19 suggests that T2DM is potentially a reversible condition, and that remission can be achieved by a robust and sustainable weight loss program. This includes following a VLCD of 624–700 kcal/day for 8 weeks followed by return to isocaloric intake of normal food over 2 weeks in a stepwise manner followed by a structured, customized weight maintenance program over a period of 6 months. Weight decreased to 83.8 ± 2.4 kg from a baseline of 98.0 ± 2.6 kg and remained stable for 6 months (84.7 ± 2.5 kg). Similar weight loss was observed between the responders and non-responders (15.8 ± 0.5% vs 13.6 ± 0.7%, respectively). This study demonstrated that remission of T2DM was maintained in 40% of the responders for at least 6 months. Return to blood glucose levels in the non-diabetes range was sustained even while off all anti-diabetes agents and was characterized by improvement in acute insulin secretion. Improvement in hepatic insulin sensitivity was noted in both responders and non-responders. The structured and individualized weight maintenance program was seen to be effective in preventing weight regain. This also helped in continuing remission of T2DM by achieving fasting plasma glucose of <126 mg/dL for the 40% who responded to VLCD.

In the Diabetes Remission Clinical Trial (DIRECT-1), Lean et al. recruited 296 individuals with obesity (BMI of 27–45 kg/m²), aged 20–65 years, diagnosed with T2DM within the past 6 years, not on insulin therapy, and randomized them to intervention and control groups. Intervention consisted of withdrawal of all anti-diabetes and anti-hypertensive medications. They were initiated on complete meal replacement providing 825–853 kcal/day for 3–5 months, followed by stepwise food reintroduction (2–8 weeks), and structured support of long-term maintenance of weight loss. Remission of T2DM was achieved in 46% of the participants in the intervention group and 4% in the control group. At 12 months, 24% participants in the intervention group (and none in the control group) recorded weight loss of >15 kg.

Remission varied with the degree of weight loss in the entire study group. The intervention group showed an average weight loss of 10 kg while the control group showed an average weight loss of 1 kg. Almost half of the obese/overweight individuals with T2DM <6 years duration who had 10 kg weight loss, achieved diabetes remission.

Quality of life as measured by the EuroQol 5 dimensions visual analog scale, increased by 7.2 points in the intervention group and decreased by 2.9 points in the control group.20

Weight loss led to a decrease in liver fat, very low-density lipoprotein (VLDL)-triglyceride production, and intrapancreatic fat and it remained normalized even after 1 year of remission. Thus, obesity-related disordered fat metabolism seems to be responsible for development and remission of T2DM. Those achieving more than 15 kg weight loss sustained remission even after 2 years.21

Further analysis of the sustainability of the intervention done in the DIRECT trial showed that 17 (11%) participants in the intervention group achieved a sustained weight loss of a minimum of 15 kg and 53 (36%) participants in the intervention group sustained remission of T2DM after 2 years.

Thus, at the 2 years follow-up of the DIRECT trial, more than a third of people with T2DM were seen to sustain remission at 2 years. Continued remission was linked to the extent of sustained weight loss.22 Conversely, it may be stated that in two-thirds of participants with T2DM, despite VLCDs, remission could not be maintained beyond 2 years even in a structured clinical trial mode. Hence, in a real-life situation, sustained remission is likely to be extremely rare.

A VLCD was found to be safe and effective in achieving short-term remission in 20 Thai subjects with obesity and T2DM (<10 years duration). Intervention included 10 weeks of VLCD—600 kcal/day, followed by a stepped-up increase in calories at week 10—800 kcal/day, week 11—1000 kcal/day, week 12—1200 kcal/day, and week 13—1500 kcal/day. The average weight loss achieved during the dietary intervention of 14 weeks was 9.5 ± 1.8 kg, which was found to be equivalent to 13.3 ± 2.2% loss of initial body weight. Remission of T2DM was achieved in 79% of subjects in 8th and 12th week.23

In a single-arm study conducted on 20 individuals with T2DM, a personalized, very-low-calorie ketogenic diet (VLCKD) was administered for 8 weeks with protein supplementation as per lean body mass was given. The key findings were lean body mass preservation, abdominal fat reduction, improvement of metabolic profile, maintenance of resting energy expenditure, and T2DM remission. Weight loss achieved after 4 weeks was 11.07 kg and at 8 weeks was 15.77 kg. There was reduction in waist, abdominal, and hip circumference with 10% decrease in waist and abdominal circumference measurements. It was further seen that the weight loss resulted in reduction of truncal fat by ~20.72%, and reduction of abdominal fat by ~24.8%. There was reduction of 39.7% observed in fasting blood glucose and achievement of HbA1c <6.5% resulting in short-term remission.24

DIADEM-I trial was conducted to compare the impact of an intensive lifestyle intervention (ILI) vs routine medical care on weight loss and glycemic outcomes in 147 adults with obesity and T2DM, ≤3 years duration. The ILI group was put on a total diet replacement (VLCD diet) of 600 kcal/day which was then stepped up to 800 kcal/day at week 10, 1000 kcal/day at week 11, and 1200 kcal/day at week 12, and 1500 kcal/day at week 13 for a year using low-calorie meal replacement formulae followed by stepped-wise reintroduction of food combined with physical activity. This was followed by a maintenance phase for weight loss and it included structured lifestyle support.

Intensive lifestyle intervention led to significant weight loss at 12 months (11.98 kg in the VLCD arm compared to 3.98 kg in the control arm). This was associated with remission of T2DM in 61% of individuals in the VLCD group and 12% in the control group. The investigators concluded that lifestyle intervention allows for a large proportion of young individuals with early onset T2DM to achieve improvements in key cardio-metabolic outcomes, with potential long-term benefits for health and wellbeing.25

Bhatt et al. studied the effect of LCD in individuals with obesity and T2DM. Participants consumed LCD providing 1000 kcal/day (meal replacer formula (30 gm taken with 150 mL skimmed milk) along with one regular meal and two to three small prespecified homemade snacks) for 12 weeks, which resulted in an average weight loss of 7 kg. About 50% of the study population (median baseline HbA1c 9%) attained HbA1c level in non-diabetes range with LCD despite discontinuing all anti-diabetes drugs. Improvement in liver fat, lipid profile, beta cell secretory capacity, indices of insulin resistance, and insulin sensitivity was also observed. There was a greater reduction (30%) in the median HbA1c of the responders as compared to the non-responders (21%)
with similar weight reduction. Improvement in liver fat was measured by ultrasound and a significant reduction was observed in levels of liver transaminases in responders. Non-responders had higher levels of insulin resistance, lower beta cell secretory capacity as well as lower insulin sensitivity at baseline. Those who achieved remission were younger with shorter duration of diabetes and originally required lesser medication for diabetes control compared to those who did not.26

In the Look AHEAD study (2012), adults with obesity and T2DM were divided into two groups—ILI on 1200–1800 kcal/day, reduced total and saturated fat intake, and increased physical activity levels to a goal of ≥175 min/week or diabetes support and education (DSE) where there were three group sessions each year focusing on diet, physical activity, and social support. The ILI group lost more weight as compared to the DSE group in year 1 and year 4. The ILI group was more likely to experience any remission, with prevalence of 11.5% during year 1 and 7.3% in year 4, compared to 2.0% in the DSE group at both time points.27

In the Look AHEAD trial, although carbohydrate intake was not specified, however, the goal for fat and protein intake was specified (<30% of total calories from fat, <10% from saturated fat, and with at least 15% of calories coming from protein). A marked improvement in HbA1c was seen to be 5.1 ± 8.7 kg for LCBD after 1 year compared to 3.1 ± 8.4 kg for conventional diet. Participants on LCBD had more favorable outcomes at 1 year. In spite of similar weight loss, effects on atherogenic dyslipidemia and glycemic control were more favorable with LCBD.31

Westman et al. studied the effect of low-carbohydrate ketogenic diet (LCKD) (<20 gm of carbohydrate daily; n = 38) or low-glycemic index, calorie-restricted diet (LGID) (deficit of 500 kcal/day; n = 46) in 84 obese individuals aged 18–65 years with BMI 27–50 kg/m2 and HbA1c >6% for 24 weeks. Mean weight loss was 11.1 kg (LCKD) vs 6.9 kg (LGID) of initial body weight. Both LGID and LCKD led to improvement in glycemic control, reduction/elimination of anti-diabetes medication, and loss of weight in individuals with overweight/obesity and T2DM over a period of 24 weeks. Greater improvements in glycemic control and reduction/elimination of anti-diabetes medication were seen in the LCKD group compared to the LGID group.32

Based on a meta-analysis of 14 randomized controlled trials (RCTs) that included 1,416 obese individuals, there was a greater reduction in fat mass of 0.77 kg observed in the LCKD group compared to those individuals on a low-fat diet. The subgroup with LCBD showed an additional reduction in fat mass of 0.57 kg over a period of 12 months.33

In a meta-analysis and systematic review of nine RCTs to study the efficacy of the LCBD compared to a high-carbohydrate diet (HCD) in individuals with T2DM, a significant reduction in HbA1c was observed in the LCBD group compared to the HCD group (weighted mean difference (WMD) −0.44). A positive effect on plasma triglyceride levels and HDL cholesterol in the LCBD group was also reported; however, no significant effects on total or LDL cholesterol were reported. Although LCBD reduced body weight initially, there was no significant effect seen in the long term.34

Adoption of LCBD in obese individuals with T2DM showed that there was a spontaneous reduction in calorie intake resulting in weight loss associated with short-term improvement in optimization of glycemic control, insulin sensitivity, and lipid profile.35

A recent meta-analysis of LCBD in >1,350 participants with T2DM, demonstrated that compared to other commonly recommended dietary strategies for management of T2DM (e.g., low-fat diets), the LCBD achieved greater rates of remission of T2DM, weight loss, and improvement in fasting insulin sensitivity and triglycerides was observed at 6 months, however, the effect was seen to be diminished at 12 months. In a recent systematic review of cohort studies, long-term LCBDs were found to be associated with increased mortality, therefore, clinicians may consider short-term LCBD for the management of T2DM, while actively monitoring and adjusting diabetes medication as and when needed.36

Esposito et al. randomized 215 overweight recently diagnosed adults with T2DM to either low-carbohydrate Mediterranean diet (LCMD) (n = 108) or a low-fat diet (n = 107) for 4 years. Participants on LCMD were more likely to experience any remission (partial or complete), with a mean prevalence of 14.7% during year 1 and 5.0% during year 6 as compared to 4.1% in year 1 and 0% in year 6 in the low-fat diet group. In individuals with newly diagnosed T2DM, LCMD resulted in a greater reduction of HbA1c levels, a higher rate of T2DM remission, and a delayed need for diabetes medication compared to the low-fat diet.37

In a study conducted by Unwin et al., 128 (27%) individuals with T2DM and 71 individuals with pre-diabetes opted to follow LCBD for a mean period of 23 months. Mean weight loss was 8.3 kg in individuals with T2DM and 8.4 kg in individuals with pre-diabetes. Remission of T2DM with the withdrawal of drugs occurred in 46% of participants. About 93% individuals with pre-diabetes attained a normal HbA1c. More research is warranted to study the effects of LCBD in achieving long-term glycemic control while ensuring positive metabolic health outcomes.38

A pilot program at Norwood was initiated based on the principle that T2DM control depends on reducing the dietary glucose load. Eighty-five out of the 175 participants who were following LCBD for an average of 30 months achieved drug-free T2DM remission showing significant improvements in cardio-metabolic markers. Withdrawal of drugs led to significant savings.39 This can be the biggest motivational force to improve patient compliance.

Webster et al. assessed the status of diabetes, dietary intake, and personal experiences of 28 individuals with T2DM who followed a low-carbohydrate high-fat (LCHF) diet for a minimum of 6 months. The carbohydrate intake was found
Table 2: Evidence of LCD diets during remission

<table>
<thead>
<tr>
<th>Author/year/country</th>
<th>Subjects</th>
<th>Dietary intervention</th>
<th>Weight loss/remission</th>
</tr>
</thead>
</table>
| Lim et al. (2011), Newcastle, UK Counterpoint Study | 11 T2DM and controls matched for weight, age, and sex | Very low-energy liquid diet (46.4% carbohydrate, 32.5% protein, and 20.1% fat; vitamins, minerals, and trace elements (510 kcal/day) and three daily portions of non-starchy vegetables (90 kcal/day) for 8 weeks) | • 15 ± 1% weight loss of initial body weight
• HbA1c decreased from 7.4 ± 0.3 to 6.0 ± 0.2%
• Decreased hepatic and pancreatic triacylglycerol content
• Increase in the first phase of insulin secretion |
| Steven et al. (2015), Newcastle, UK Counterbalance Study–1 | 29 participants with a T2DM short-duration group of <4 years n = 15, long-duration group of >8 years n = 14 | VLCD (43% carbohydrate, 34% protein, and 19.5% fat; up to 240 gm of non-starchy vegetables (624–700 kcal/day) for 8 weeks) | • 14.8 ± 0.8% and 14.4 ± 0.7% weight loss in short- and long-duration group, respectively
• HbA1c decreased from 7.2 ± 0.2% to 6.1 ± 0.2% in the short-duration group and from 8.6 ± 0.4% to 8.0 ± 0.5% in the long-duration group
• 87% short-duration group and 50% long-duration group achieved nondiabetic fasting plasma glucose levels |
| Steven et al. (2016), Newcastle, UK Counterbalance Study–2 | 30 participants with a T2DM duration of 0.5–23 years | VLCD (43% carbohydrate, 34% protein, and 19.5% fat; up to 240 gm of non-starchy vegetables (624–700 kcal/day) for 8 weeks) | • Weight loss achieved was similar between the responders and non-responders 15.8 ± 0.5% vs 13.6 ± 0.7%
• HbA1c fell from 7.1 ± 0.3 to 5.8 ± 0.2% in responders and from 8.4 ± 0.3 to 8.0 ± 0.5% in non-responders |
| Lean et al. (2018), Scotland and England DIRECT Study–1 | 298 participants with T2DM (149 intervention and 149 control), 0–6 years duration—1 year follow-up | LCD replacement (825–853 kcal/day; 59% carbohydrate, 13% fat, 26% protein, and 2% fiber) for 3 months followed by structured food reintroduction of 2–8 weeks (about 50% carbohydrate, 35% total fat, and 15% protein) for 12–20 weeks | • At 12 months, weight loss of ≥15 kg in 24% participants (n = 36) in the intervention group and no participants in the control group
• Mean HbA1c fell by 0.9% in the intervention group and increased by 0.1% in the control group
• 46% remission in the intervention group and 4% in the control group |
| Lean et al. (2019), Scotland and England DIRECT Study–2 | 298 participants with T2DM (149 intervention and 149 control), 0–6 years duration—1 year follow-up | LCD replacement (825–853 kcal/day; 59% carbohydrate, 13% fat, 26% protein, and 2% fiber) for 3 months followed by structured food reintroduction of 2–8 weeks (about 50% carbohydrate, 35% total fat, and 15% protein) for 12–20 weeks | • At 24 months, weight loss of ≥15 kg in 11% (n = 36) in the intervention group and by 2% (n = 3) in the control group
• 36% remission in intervention and control groups |
| Umphonsathien et al. (2019), Bangkok, Thailand | 20 participants with T2DM (BMI of 23–30 kg/m²), of <10 years duration | 10 weeks of 600 kcal/day followed by a stepwise increase in kcal/day at week 10 (800 kcal/day), week 11, (1000 kcal/day), week 12 (1200 kcal/day), and week 13 (1500 kcal/day) | • 9.5 ± 1.8 kg mean weight loss, equivalent to 13.3 ± 2.2% loss of initial body weight
• 79% remission at 8th and 12th week |
| Romano et al. (2019), Rome, Italy | 20 participants with T2DM for 8 weeks | VLCKD with protein intake depending on lean mass and synthetic amino acidic protein supplementation | • At 8 weeks, 15.77 kg weight loss of initial body weight in VLCKD diet
• Reduction in waist, abdominal and hip circumference with 10% decrease in waist and abdominal circumference measurements
• Short-term remission |
| Taheri et al. (2020), Doha, Qatar DIADEM-I | 147 adults with T2DM, ≤3 years duration (70 in the intervention arm; 77 in the control arm) | 12-week total diet replacement phase, 800–820 kcal/day diet meal replacement products (57% carbohydrate, 14% fat, 26% protein, and 3% fiber; followed by a 12-week structured food reintroduction phase) | • At 12 months, 11.98 kg weight loss in intervention and 3.9 kg in control group
• 61% and 12% remission in VLCD and control arms, respectively |

(Contd…)
to be 20–50 gm/day in 10 participants and 50–115 gm/day in 17 participants. Median weight loss was found to be 16 kg (7–31 kg) from baseline.

At follow-up, it was observed that the majority of the 24 participants who had been following the LCHF diet for 35 (26–53) months were in full or partial T2DM remission. Median time period of following the LCHF diet was 14 (9–38) months and ranged from 6 months to 6 years. This study described the characteristics of a low-calorie high-fat lifestyle and meal options which were seen to be effective and sustainable in a real-world setting.40

Evidence for T2DM remission using LCBD dietary interventions is summarized in Table 3.

Mechanisms of Remission of T2DM with LCD

The most commonly recognized mechanism of T2DM remission with LCD is based on the “Twin cycle” hypothesis by Roy Taylor. This hypothesis is based on the rationale that excess caloric intake, which happens in conjunction with insulin resistance, leads to ectopic fat accumulation in the hepatocytes and islets of Langerhans of the pancreas. This results in increased hepatic insulin resistance, shunting out of VLDL, reduced first-phase insulin secretion, and increased inflammation.41 Excess fat in the liver affects hepatic insulin response, resulting in increased production of glucose. While in the pancreas, because of the fat-induced metabolic stress, beta cells seem to enter a mode of survival and fail to function optimally. Substantial weight loss leading to reduction of excess fat from the pancreas and liver is seen to normalize hepatic insulin response. This is associated with recovery of beta cells, thereby improving insulin secretion in individuals in the early years post diagnosis of T2DM, possibly by redifferentiation. These changes help in normalizing blood glucose levels.42

Thus, reversing the cycle with calorie restriction results in the reduction of liver and pancreatic fat, thereby reducing insulin resistance and enhancing insulin secretion.41

Mechanisms of Remission of T2DM with LCBD

The carbohydrate insulin model of obesity is the rationale behind using LCBD as a weight loss strategy. Diets high in carbohydrate (refined sugar and starches) stimulate post-prandial hyperinsulinemia which lead to fat deposition. Dietary carbohydrates have the most potent effect on insulin secretion, which differ based on the amount and type of carbohydrate.

The LCBD leads to a diminished supply of carbohydrates to the liver, reduced synthesis of fatty acids from excess carbohydrates, and increased lipolysis. There is also a reduction in plasma insulin levels that decrease fat storage in adipose tissue, which ultimately manifests in progressive loss of body fat. Post adoption of the LCBD, gluconeogenesis, and ketogenesis are the two key metabolic processes that occur. A reduced supply of glucose to the liver, muscle, and brain leads to reduced glycolysis synthesis and storage, thereby reducing the capacity for glycolysis. Diminishment of glycolysis results in augmentation of gluconeogenesis as they have a reciprocal and inverse relationship. Gluconeogenesis utilizes lactic acid, glycerol, and certain amino acids (alanine and glutamine) as substrates. Continuous gluconeogenesis over several hours may not be sufficient to provide the required glucose to the body due to limited supply of these substrates. In this scenario, ketone bodies are produced as an alternate fuel source to glucose via ketogenesis. LCBD is associated with low levels of serum insulin which leads to lipolysis. There is an elevated supply of fatty acids followed by conversion to acetoacetate acid and ketones—β-hydroxybutyric acid and aceton. With these physiological insights, LCBD reduces plasma insulin levels and promotes calorie utilization, thereby resulting in reduced storage of fat which in turn facilitates remission.10

Which Dietary Strategy is Best for Inducing Diabetes Remission?

The controversy about LCBD or LCD approaches to remission of T2DM continues. Evidence has shown that both dietary strategies improve metabolic risk factors like BMI, glycomic control, and cardiovascular health. Both LCD and LCBD are effective in bringing about remission of T2DM, and if done under strict medical supervision, both dietary strategies may be considered safe.43

Within 7 days of initiating a LCD of 800 calories/day, fasting plasma glucose is seen to normalize by either dietary intervention or bariatric surgery. There is a substantial reduction observed in hepatic fat content and improvement in hepatic insulin sensitivity. First phase and maximal rate of insulin secretion gradually return to normal over a period of 8 weeks and this change is associated with decreased pancreatic fat content.20

As per the available evidence, VLCD is seen to help achieve 15 kg or greater weight loss. However, maintenance of weight loss is seen to be the main driver and predictor of remission.

If LCBD is sustained, remission of T2DM is seen to be maintained in the absence of weight loss. However, evidence is limited and relapse is likely to occur if carbohydrate restriction ceases. LCBD has shown reduction in fat mass and remission of T2DM for up to 6 months. Long-term studies with LCBD in the sustenance of remission of T2DM are warranted as efficacy of LCBD on weight loss and metabolic benefits beyond 6 months is found to be unsatisfactory.

Limitations of LCBD in the real world include sustainability in the long run due to restriction on food choices. Such diets can be nutritionally deficient, especially when done without medical supervision. Fat intake, especially saturated fat intake, is very high.
Table 3: Evidence of LCBD diets during remission

<table>
<thead>
<tr>
<th>Author/year/country</th>
<th>Subjects</th>
<th>Dietary intervention</th>
<th>Weight loss/remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stern et al. (2004), Philadelphia, USA</td>
<td>132 obese adults with T2DM or metabolic syndrome</td>
<td>LCBD carbohydrate intake &lt;30 gm/day (LCBD) or to restrict caloric intake by 500 calories/day with &lt;30% of calories from fat (conventional diet) for 1 year</td>
<td>Mean weight loss 5.1 ± 8.7 kg for LCBD, 3.1 ± 8.4 kg for conventional diet</td>
</tr>
<tr>
<td>Westman et al. (2008), Durham, USA</td>
<td>84 participants with T2DM and obesity</td>
<td>LCKD group intervention (&lt;20 gm of carbohydrate) or LGID group intervention (&lt;500 kcal/day) for 24 weeks</td>
<td>Meal weight loss 11.1 kg (LCKD) vs 6.9 kg (LGID) of initial body weight</td>
</tr>
<tr>
<td>Bogen et al. (2005), New Jersey, USA</td>
<td>10 obese participants with T2DM</td>
<td>Usual diet for 7 days followed by LCBD (20 gm carbs/day) for 14 days</td>
<td>Mean weight loss 1.65 kg, improved glycemic control with reduction in HbA1c from 7.3 to 6.8%</td>
</tr>
<tr>
<td>Esposito et al. (2014), Naples, Italy</td>
<td>215 overweight, middle-aged men and women with newly diagnosed T2DM</td>
<td>LCMD (n = 108, carbs &lt;50% of calories) or a low-fat diet (n = 107) for 4 years</td>
<td>Decrease in mean plasma triglyceride by 35% and cholesterol levels by 10%</td>
</tr>
<tr>
<td>Webster et al. (2019), Cape town, South Africa</td>
<td>28 participants with T2DM</td>
<td>LCHF for 6 months and followed up for 15 months</td>
<td>At 1 year, LCMD group had significantly greater reduction in weight than the low-fat diet group, absolute between-group difference in weight loss of 2.0 kg</td>
</tr>
<tr>
<td>Unwin et al. (2020), South Port, UK</td>
<td>128 participants with T2DM and 71 with pre-diabetes</td>
<td>LCBD for 23 months</td>
<td>At 6th year, mean difference in weight between the two groups—0.4 kg</td>
</tr>
<tr>
<td>Meng et al. (2017), China</td>
<td>Nine studies with 734 patients with diabetes</td>
<td>A systematic review and meta-analysis of nine RCTs on the efficacy of the LCBD</td>
<td>Remission LCMD 14.7% (13.0–16.5%) during the 1st year and 5.0% (4.4–5.6%) during year 6</td>
</tr>
<tr>
<td>Hashimoto et al. (2016), Kyoto, Japan</td>
<td>Meta-analysis of randomized controlled studies</td>
<td>1,416 obese individuals, 15 RCTs (8–very LCBD – 50 gm/day or 10% of calories; 7–40% of calories from carbohydrates)</td>
<td>Low-fat group 4.1% (3.1–5.0%) in year 1 and 0% in year 6</td>
</tr>
<tr>
<td>Goldenberg et al. (2021), USA</td>
<td>Systematic review and meta-analysis of published and unpublished randomized trial data in T2DM</td>
<td>23 trials, 1357 participants, studied LCBD (130 gm/day or &lt;26% of a 2000 kcal/day diet) and very LCBD (&lt;10% calories from carbohydrates) for at least 12 weeks in eligible adults with T2DM</td>
<td>Remission LCMD 14.7% (13.0–16.5%) during year 1 and 0% in year 6</td>
</tr>
</tbody>
</table>

with low dietary fiber intake predisposing an individual to dyslipidemia, hyperuricemia, poor bone health, renal calculi, insulin resistance, and gut dysbiosis. Such restrictive, extreme diets, if continued for a long time can also take a toll on mental, financial, and emotional status of the individual.  

In studies conducted on mice, if LCBDs are continued for a long time, the fat is seen to reappear. Therefore, more research is required to see the long-term effects of such diets in humans. It must be emphasized that both dietary strategies work only for a targeted population and careful selection of the candidate needs to be done by health care professionals. Both LCD and LCBD need continuous support and follow-up by a multi-disciplinary health care team to prevent weight regain and re-reversal of diabetes.  

Who is the Right Candidate for Such Dietary Interventions?  
The implementation of these dietary interventions in a targeted population is seen to be more effective in a clinical setting and appears to be most appropriate for candidates with less than 6 years and ideally within 2 years of diagnosis of T2DM, preferably males, those with better glycemic control, who are on fewer anti-diabetes drugs, those with good beta cell function and insulin secretion, those with less visceral fat, and lastly with good mental health.  

The ABCDEF formula can help us identify individuals with T2DM most likely to achieve remission.  

- A: A1c or HbA1c—those who do not have markedly elevated A1c are more likely to achieve remission.  
- B: Body weight—greater the body weight, greater the chances of achieving remission
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(15 kg or more weight loss is required to achieve T2DM remission).

- C: C-peptide—higher chances for remission are seen with better levels of C-peptide.
- D: Diabetes duration—greater the chance of remission with shorter duration of diabetes (<6 years).
- E: Enthusiasm—high motivation levels are needed for remission.
- F: Frequent follow-ups—individuals should be willing to follow-up frequently with the health care team.

However, evidence of effectiveness beyond 2 years is limited and more data are required in an ethnically diverse population like Asian Indians with T2DM who have less obesity.

Adjustments of Dosage of Medications before initiating LCBD in Patients with T2DM

- Patients on hypoglycemic agents such as insulin or sulfonylureas may be at an increased risk of hypoglycemia. Hence, regular blood glucose monitoring/GCGM along with reduction in dose/cessation of oral drugs/insulin is crucial to patient safety.
- Patients following LCBD who are on sodium–glucose co-transporter-2 (SGLT-2) inhibitors are at a higher risk of diabetic ketoacidosis. Hence, patients on SGLT-2 inhibitors must avoid following LCBD or discontinue SGLT-2 before following LCBD. This should be done under strict medical supervision.
- The LCBD is associated with reduction in blood pressure levels; therefore, patients on anti-hypertensive drugs may require reduction in dosage or cessation of these drugs to avoid symptomatic hypotension.

Early intervention and review of diabetes medications, especially insulin, sulphonylureas, and SGLT-2 inhibitors are essential in individuals following LCBD. Frequent follow-up and careful monitoring of cardiovascular risk factors are important.

Irrespective of the initial effectiveness of the dietary intervention, “re-reversal” or “relapse” of diabetes can occur in a large percentage of people who discontinue the dietary intervention. Patients should remember that diabetes has only gone into remission and has not been cured, and therefore it can reappear anytime. Hence, regular follow-up and sustenance of the lifestyle modification program are crucial.

Conclusion
While treating individuals with T2DM, we should try to identify the candidates likely to achieve remission. Accordingly, the possibility of and the need for achieving remission should be discussed with them. Both LCDs and LCBDs have demonstrated to be effective in remission of T2DM.

Hence, if appropriately supported and done under strict medical supervision, both dietary interventions may be considered reasonably safe. Normoglycemia can be achieved and maintained in the absence of weight loss in individuals following LCBDs, however, evidence is limited and relapse can occur if carbohydrate restriction is discontinued. In India, long-term carbohydrate restriction is a major challenge.

In VLCDs, weight loss (typically 15 kg or greater) and maintenance is the key driver and predictor of remission.

Use of dietary interventions in carefully selected individuals is seen to be more effective within a clinical setting. Dietary modification needs to be individualized and tailor-made for the individual after careful screening and assessment to ensure long-term adherence and remission.

“Re-reversal” or “relapse” of T2DM can occur in a large percentage of people who discontinue the dietary and lifestyle intervention. Hence, structured programs supporting patients towards achieving remission need to be offered with regular support and follow-ups from the multi-disciplinary health care team especially a qualified dietitian and psychologist for long-term success.

It must also be emphasized that diabetes remission can happen only in individuals with T2DM and pre-diabetes. Type 1 diabetes is an autoimmune condition requiring insulin therapy for survival and at present, there is no evidence for remission or reversal of type 1 diabetes. Attempts to withdraw insulin in such patients can be potentially hazardous and life-threatening.

Finally, it should be understood that while T2DM can go into remission, re-occurrence may happen if the lifestyle and diet control are not maintained. Hence claims such as “cure” or “reversal” of T2DM may be inappropriate, particularly those made by different groups purporting to study the “metabolism” of the individual and instituting personalized “diabetes reversal” programs using unproven and unscientific “apps”.

References
23. Umphonsathien M, Prulanopaj P, Alam-O-Ran J, et al. Immediate and long-term effects of a very-low-calorie diet on diabetes remission and
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