

# Long-Term Durability, Relapse Rates, and Pathophysiological Mechanisms of Type 2 Diabetes Remission: A Comparative Literature Review of Low-Carbohydrate Diets and Severe Caloric Restriction

The clinical management of type 2 diabetes mellitus (T2D) has transitioned from a paradigm of progressive, lifelong pharmacotherapy to one focused on achieving drug-free clinical remission.<sup>1</sup> This transition is supported by evidence demonstrating that the core pathophysiological abnormalities of T2D can be reversed through structured nutritional and lifestyle interventions.<sup>4</sup> The consensus definition of T2D remission is the maintenance of a glycated hemoglobin (HbA1c) level below 6.5% (48 mmol/mol) or fasting plasma glucose below 7.0 mmol/L for at least 3 months in the absence of glucose-lowering medications.<sup>1</sup>

Among non-surgical therapies, two primary dietary strategies have emerged: low-energy diets (LEDs), which rely on severe caloric restriction, and low-carbohydrate diets (LCDs) or ketogenic diets (KDs), which rely on carbohydrate restriction.<sup>7</sup> While both approaches can put T2D into remission, they operate through distinct metabolic levers and exhibit different rates of long-term durability, adherence, and relapse over a multi-year horizon.<sup>7</sup>

Parameter	Low-Energy Diets (LEDs)	Low-Carbohydrate Diets (LCDs) / Ketogenic Diets (KDs)
Primary Metabolic Lever	Severe overall energy restriction to deplete ectopic organ lipids <sup>7</sup>	Strict carbohydrate restriction to prevent glycemic spikes and induce ketosis <sup>7</sup>
Meal Format	Liquid formulas, shakes, and soups (Total Diet Replacement) <sup>7</sup>	Whole-food based (meats, fish, eggs, healthy fats, and low-carbohydrate)

		vegetables) <sup>7</sup>
<b>Daily Energy Target</b>	$\leq$ (typically 800 – ) <sup>7</sup>	Variable; often consumed <i>ad libitum</i> to satiety <sup>7</sup>
<b>Daily Carbohydrate Target</b>	Variable; typically $\geq$ as a consequence of liquid formula composition <sup>7</sup>	LCD: $< 130$ g/day ( $<$ energy) <sup>7</sup> ; KD: 20 – ( $<$ energy) <sup>7</sup>
<b>Medication Management</b>	Pre-emptive withdrawal of all antidiabetic and antihypertensive drugs on day one <sup>8</sup>	Supervised step-wise deprescribing, particularly of insulin and sulfonylureas <sup>12</sup>
<b>Typical Phase Duration</b>	12 – (intensive phase), followed by gradual food reintroduction <sup>7</sup>	Indefinite; designed as a long-term, sustainable lifestyle modification <sup>7</sup>

## Pathophysiological Mechanisms of Nutritional Remission

### The Twin Cycle Hypothesis and Ectopic Lipid Dynamics

The clinical reversal of T2D is explained by the Twin Cycle Hypothesis, which identifies chronic positive energy balance as the primary driver of organ-specific metabolic dysfunction.<sup>5</sup> Excess energy intake forces the liver to undergo *de novo* lipogenesis.<sup>17</sup> Under the influence of high portal insulin levels, the liver accumulates excess fat (steatosis), which impairs the hepatic response to insulin.<sup>4</sup> Consequently, the liver fails to suppress hepatic glucose output, leading to a rise in fasting plasma glucose.<sup>4</sup> This mild hyperglycemia stimulates basal insulin secretion rates, which further drives hepatic *de novo* lipogenesis in a self-reinforcing "liver vicious cycle".<sup>5</sup> As liver fat levels rise, the liver increases the export of triglycerides via very-low-density lipoproteins (VLDL-TG) to the rest of the body.<sup>17</sup> Once subcutaneous adipose tissue storage capacity is exceeded—a threshold dictated by an individual's genetic makeup—lipids accumulate in ectopic depots, including the pancreas.<sup>4</sup>

The chronic exposure of pancreatic  $\beta$ -cells to excess VLDL-TG and local intracellular fatty acid metabolites, such as ceramides and diacylglycerols, induces severe metabolic stress.<sup>4</sup> This

lipotoxic environment causes the  $\beta$ -cells to enter a survival-oriented, inactive state characterized by *dedifferentiation*, resulting in the loss of postprandial insulin secretion and initiating the "pancreatic vicious cycle".<sup>1</sup>

Severe caloric restriction via LEDs interrupts these vicious cycles by forcing a sudden call on endogenous energy stores.<sup>17</sup> This rapid transition drains the intracellular "swamp" of toxic lipid intermediates.<sup>17</sup> Within **7 days** of starting an LED, intra-hepatic triglyceride content falls by approximately **30%**, restoring normal hepatic insulin sensitivity and normalizing fasting

plasma glucose.<sup>5</sup> Over a longer period of **8 weeks**, pancreatic fat content decreases more slowly, reducing local metabolic stress and allowing the dedifferentiated  $\beta$ -cells to redifferentiate, return to a mature phenotype, and recover their functional mass.<sup>4</sup>

## **Beta-Cell Redifferentiation and First-Phase Insulin Response Recovery**

The definitive physiological marker of durable remission is the recovery of the first-phase insulin response—the rapid, acute spike in insulin secretion immediately following a carbohydrate load.<sup>20</sup> This response is essential for:

- Promptly suppressing hepatic glucose output.<sup>20</sup>
- Inhibiting lipolysis in peripheral adipose tissue.<sup>20</sup>
- Enhancing glucose and fatty acid uptake into skeletal muscle.<sup>20</sup>

Without this early postprandial insulin spike, patients experience prolonged hyperglycemia and postprandial lipemia.<sup>20</sup> Clinical trials show that while liver fat normalization occurs in almost all

patients who lose sufficient weight, the capacity of  $\beta$ -cells to redifferentiate and restore the first-phase insulin response declines as T2D duration increases, marking a critical window for intervention.<sup>17</sup>

## **The Personal Fat Threshold and Demographic Variations**

An individual's susceptibility to T2D is governed by their Personal Fat Threshold (PFT), which explains why individuals can develop T2D at a "normal" BMI, and conversely, why some individuals with severe obesity remain metabolically healthy.<sup>17</sup> T2D develops when an individual accumulates more fat than their subcutaneous adipose tissue can safely store, forcing lipids to overflow into ectopic sites.<sup>17</sup>

Consequently, individuals of South Asian ancestry and others with a lower threshold for ectopic fat accumulation develop T2D at younger ages and lower BMIs.<sup>22</sup> These individuals can achieve and maintain remission with modest absolute weight loss, as demonstrated in the STANDby and CMNT trials.<sup>22</sup>

Furthermore, maintaining remission is often more durable for individuals who return to a normal BMI ( $< 24 \text{ kg/m}^2$ ) post-intervention.<sup>24</sup> In these normal-weight cohorts, mild weight

fluctuations do not trigger relapse, as the overall systemic lipid burden remains below their personal metabolic threshold.<sup>24</sup>

## Metabolic Mechanisms Unique to Carbohydrate Restriction

While LEDs rely on significant weight loss to deplete ectopic fat, LCDs and KDs can improve glycemic control through pathways that are partly independent of substantial weight loss.<sup>19</sup> By directly restricting carbohydrate intake, these diets minimize postprandial blood glucose excursions, bypassing the primary driver of glycemic spikes.<sup>7</sup> This rapid reduction in blood glucose alleviates *glucose toxicity*, which is a major contributor to  $\beta$ -cell dysfunction and peripheral insulin resistance.<sup>1</sup> Alleviating glucose toxicity allows  $\beta$ -cells to recover function even before significant weight loss is achieved.<sup>1</sup>

Additionally, several metabolic adaptations occur during carbohydrate restriction:

- **Preserved Amino Acid Signaling:** Although glucose-stimulated insulin secretion is compromised in T2D, amino acid-stimulated insulin pathways remain intact.<sup>20</sup> The higher protein content in LCDs stimulates  $\beta$ -cells directly and enhances the incretin effect, which can double postprandial insulin secretion and safely lower glucose levels.<sup>20</sup>
- **Ketone Body Signaling:** The production of the ketone body  $\beta$ -hydroxybutyrate ( $\beta$ HB) serves as both an alternative energy source and a signaling molecule.<sup>9</sup>  $\beta$ HB regulates gene expression, mitigates oxidative stress, and reduces low-grade systemic inflammation.<sup>29</sup> It significantly reduces inflammatory markers, such as C-reactive protein, which protects pancreatic islets from inflammatory damage.<sup>30</sup>

## Comparative Short-to-Intermediate Term Remission Efficacy

Clinical trials over a 1-to-2-year timeframe demonstrate that both severe energy restriction and carbohydrate restriction are highly effective in inducing remission, though their clinical profiles differ.<sup>8</sup>

### Severe Caloric Restriction Interventions

The benchmark trial for LEDs is the Diabetes Remission Clinical Trial (DiRECT), which randomized 298 primary care patients in the United Kingdom to either standard care or an intensive weight management program.<sup>8</sup> The program utilized an initial 12-to-20-week total diet replacement phase (825 – 853 kcal/day liquid formula), followed by a 2-to-8-week stepped food reintroduction and structured weight-loss maintenance support.<sup>8</sup>

At **1 year** , the intervention group achieved an average weight loss of **10.0 kg** and a **46%** remission rate, compared to a **1.0 kg** weight loss and a **4%** remission rate in the control group.<sup>16</sup> By **2 years** , the intervention group sustained an average weight loss of **7.6 kg** , with **36%** remaining in remission.<sup>8</sup> Remission rates were closely linked to the amount of weight lost:

- **Gained weight:** **0%** achieved remission.<sup>16</sup>
- **Lost 0 – 5 kg :** **7%** achieved remission.<sup>16</sup>
- **Lost 5 – 10 kg :** **34%** achieved remission.<sup>16</sup>
- **Lost 10 – 15 kg :** **57%** achieved remission.<sup>16</sup>
- **Lost  $\geq 15$  kg :** **86%** achieved remission.<sup>16</sup>

The DIADEM-I trial, conducted in a similar cohort with a shorter average disease duration ( **< 3 years** ), reported an even higher remission rate of **61%** at **12 months** associated with an average weight loss of **11.98 kg** .<sup>2</sup> This highlights that early intervention, when the pancreatic  $\beta$  -cell reserve is largely intact, maximizes the probability of successful remission.<sup>5</sup> By contrast, the Look AHEAD trial, which implemented a less restrictive energy deficit ( **1200 – 1800 kcal/day** ) combined with physical activity, yielded lower remission rates of **9.2%** at **2 years** , **6.4%** at **3 years** , and **3.5%** at **4 years** , demonstrating that moderate lifestyle interventions are less effective for inducing complete T2D remission than severe calorie restriction.<sup>2</sup>

## **Low-Carbohydrate and Ketogenic Interventions**

Carbohydrate-restricted interventions rely on a different clinical model.<sup>7</sup> The Indiana University trial, which evaluated the Virta Health continuous care model, enrolled 349 patients with T2D.<sup>13</sup>

The intervention group followed a very low-carbohydrate ketogenic diet ( **< 30 g/day** of non-fiber carbohydrates), supported by remote digital coaching, personalized biomarker monitoring, and physician-supervised medication adjustments.<sup>13</sup>

At **1 year** , the ketogenic group achieved a **47%** diabetes reversal or remission rate and sustained a **13%** average weight loss, accompanied by a **60%** complete discontinuation of insulin therapy.<sup>10</sup> By **2 years** , **38%** of the cohort maintained diabetes reversal, with an

average sustained weight loss of 12% .<sup>10</sup>

Meta-analytic evidence supports these findings but reveals a key temporal pattern.<sup>7</sup> A

systematic review by Goldenberg et al. found that LCDs (< 130 g/day ) achieved

significantly higher rates of T2D remission at 6 months compared to standard low-fat diets,

but this comparative advantage largely disappeared by 12 months .<sup>7</sup>

Another meta-analysis of 22 randomized controlled trials (1,391 participants) comparing low-carbohydrate diets to low-fat diets found that LC diets led to a significantly greater

reduction in HbA1c (mean difference of -0.41% ), body weight, BMI, fasting insulin, and

triglycerides at 3 months .<sup>11</sup> However, by 24 months , there were no significant

differences in glycemic control or cardiometabolic markers between the groups, pointing to a progressive loss of dietary adherence over time.<sup>11</sup>

## Long-Term Remission Durability and Relapse Rates (≥3 Years)

To date, few clinical trials have evaluated the durability of T2D remission beyond 3 years .<sup>8</sup> A comparative analysis of these trials reveals distinct relapse and sustainability profiles between the two dietary paradigms.<sup>8</sup>

### Severe Caloric Restriction: DiRECT 5-Year Extension Study

The 5-year results of the DiRECT trial, which included a 3-year extension study with low-intensity clinical support, showed a significant rate of weight regain and clinical relapse

over time.<sup>8</sup> At 5 years , data were available for 85 participants in the extension group and 118 in the total original intervention group.<sup>8</sup>

The overall remission rate at 5 years declined to 13% of active extension participants, and to 10% when calculated across the entire original intervention cohort.<sup>8</sup> In comparison, only 5% of the control group was in remission at 5 years .<sup>8</sup>

Despite the high rate of clinical relapse, several key health benefits persisted:

- **Sustained Weight Loss:** The extension group maintained an average weight loss of 6.1 kg at 5 years , compared to 4.6 kg in the control group.<sup>8</sup>
- **Long-Term Remission Maintenance:** Of those who were in remission at year 2 , over a quarter ( 26% ) remained in remission at year 5 , maintaining an average weight loss of

8.9 kg<sup>8</sup>

- **Reduced Cardiovascular Risks:** The original intervention group spent 27% of the 5-year study period in remission, compared to just 4% in the control group.<sup>35</sup>
- **Halved Hospitalization Rates:** Serious adverse events in the intervention group were less than half of those in the control group (4.8 vs. 10.2 events per 100 patient-years).<sup>8</sup>
- **Lower Cancer Rates:** There were eight reported cancers in the control group compared to only one in the intervention group.<sup>36</sup>

The durability of intermittent caloric restriction was also evaluated in the Chinese Medical Nutrition Therapy (CMNT) trial.<sup>24</sup> Participants followed six 15-day cycles consisting of 5 days of severe energy restriction (840 kcal/day) followed by 10 days of *ad libitum* eating, achieving a 47.2% remission rate at the end of the 3-month phase.<sup>24</sup>

Crucially, at the 3-year follow-up, 75% of those who achieved remission maintained it without any ongoing structured maintenance.<sup>24</sup> This high durability was attributed to their normal baseline BMI (average  $< 24 \text{ kg/m}^2$ ).<sup>24</sup> Unlike individuals with obesity, normal-weight participants did not face strong biological setpoint pressures to regain weight, allowing them to remain stable after the intervention.<sup>24</sup>

## Carbohydrate Restriction: Virta Health 5-Year Extension Study

The 5-year results of the Virta Health continuous care trial showed high patient retention and durable metabolic improvements.<sup>12</sup> Out of 262 participants in the intervention group, 122 remained active at 5 years.<sup>31</sup>

Among these 5-year completers:

- **Clinical Remission:** Sustained by 20% ( $\text{HbA1c} < 6.5\%$  off all antidiabetic medications for  $\geq 3$  months).<sup>31</sup>
- **Multi-Year Durability:** 15.8% maintained remission for at least 3 consecutive years, and 12.5% maintained it for 4 consecutive years.<sup>31</sup>
- **Reversal and Medication Reduction:** 32.5% maintained an  $\text{HbA1c} < 6.5\%$  off all medications or requiring only Metformin.<sup>31</sup>
- **Significant Weight Loss:** Completers sustained an average weight loss of  $-7.6\%$  over

5 years<sup>12</sup>

- **Insulin Elimination:** Insulin-independent patients reduced their dependency by 50%<sup>12</sup>

To put these rates into perspective, a large U.S. cohort study of 122,781 individuals with T2D receiving standard care showed a spontaneous remission rate of just 1.6% over 7 years (4.6% for those diagnosed for less than 2 years)<sup>10</sup>

An Indian study of 243,400 adults attending a tertiary care center reported a spontaneous remission rate of only 0.11%, with a recurrence rate of 69% to 87% after a median of 2.1 years.<sup>37</sup> These data demonstrate that structured dietary interventions are exponentially superior to standard medical management for achieving and maintaining remission.<sup>8</sup>

Clinical Endpoint	DiRECT (LED Total Diet Replacement)	Virta Health (VLCKD Continuous Care)	CMNT (Intermittent Energy Restriction)
Cohort Size ( $N$ )	$N =$ (Intervention group) 8	$N =$ (Intervention group) 13	$N =$ (Intervention group) 24
Baseline BMI	Mean BMI $\approx$ (range 27 – ) <sup>2</sup>	Severely Obese (Mean BMI = ) <sup>13</sup>	Normal-to-Overweight (BMI < ) <sup>24</sup>
5-Year Retention Rate	57% (85 of 149 active in extension) 8	46.6% (122 of 262 completers) <sup>12</sup>	100% at 3-year follow-up <sup>24</sup>
1-Year Remission Rate	46% <sup>8</sup>	47% (60% off meds except Metformin) <sup>10</sup>	47.2% (at 3 months) <sup>24</sup>
2-Year Remission Rate	36% <sup>8</sup>	38% (54% off meds except	44.4% (at 12 months) <sup>24</sup>



		Metformin) <sup>10</sup>	
<b>Long-Term Remission</b>	13% of active extension (10% of original cohort) at 5 years <sup>8</sup>	20% of 5-year completers (32.5% off meds except Metformin) <sup>31</sup>	75% sustained remission at 3 years <sup>24</sup>
<b>5-Year Weight Change</b>	Average -6.1 kg (all); -8.9 kg (remitters) <sup>8</sup>	Average -7.6% (all completers) <sup>12</sup>	Average -5.93 kg at 3 months; stable at 3 years <sup>24</sup>
<b>Clinical Safety Events</b>	4.8 events/100 pt (vs. 10.2 in Control) <sup>8</sup>	No assisted hypoglycemia; neutral/positive renal and hepatic profiles <sup>30</sup>	No serious adverse events; 77.2% reduction in monthly medication costs <sup>24</sup>

## Behavioral Dynamics and Structured Relapse Intervention Models

The high relapse rates observed in clinical trials indicate that type 2 diabetes remission is rarely permanent.<sup>9</sup> Relapse is driven by a complex interplay of biological, physiological, and behavioral factors.<sup>20</sup>

### The Role of Relapse Management Protocols

The DiRECT trial implemented a structured "Rescue Plan" to address weight regain and clinical relapse.<sup>16</sup> If a participant regained more than 2 kg, they were offered a partial reintroduction of the total diet replacement (TDR) formula to replace one or two meals daily for 4 weeks, combined with optional Orlistat therapy (120 mg three times daily).<sup>16</sup>

If weight regain exceeded 4 kg or if diabetes recurred, a full 4-week TDR phase was reinitiated, followed by a 2-to-4-week food reintroduction phase.<sup>16</sup>

The clinical significance of this rescue protocol is illustrated by a comparative analysis showing that participants who did not adhere to the Rescue Plan had a 5-year remission rate of only 3%, compared to 13% among those who did.<sup>25</sup> This demonstrates that diabetes remission is

a dynamic state requiring ongoing, structured clinical oversight, rather than a single, static weight-loss event.<sup>35</sup>

## **Behavioral Adherence and the Role of Continuous Remote Care**

Maintaining dietary adherence over several years is a major challenge.<sup>34</sup> A Cochrane review of long-term trials found no significant difference in adherence or glycemic benefits between

low-carbohydrate and balanced diets at **2 years**.<sup>34</sup>

Initially, low-carbohydrate diets achieved high compliance, but this reversed by year two, showing a higher incidence of dietary lapses and attrition.<sup>34</sup>

This decline in adherence highlights the limitations of standard, self-directed diets in modern food environments.<sup>35</sup>

To counter this, virtual continuous care models have been shown to improve long-term retention.<sup>12</sup> The Virta Health model, which uses remote digital tracking and health coaching via

text messaging, achieved a **46.6%** retention rate at **5 years**.<sup>12</sup>

In patients following carbohydrate-restricted programs, improvements in behavioral metrics

were observed. Specifically, **45.9%** of participants demonstrated an improvement in Yale

Food Addiction Scale (YFAS) scores, with a **40.7%** average decrease, and **81.1%**

demonstrated improvements in Binge Eating Scale (BES) scores, reflecting a **34.7%** drop from baseline.<sup>40</sup>

This suggests that achieving nutritional ketosis may help reduce cravings and binge eating, helping to stabilize weight and prevent relapse over time.<sup>9</sup>

## **Safety, Contraindications, and Long-Term Tolerability**

While both dietary strategies offer significant metabolic benefits, they present distinct clinical safety considerations and contraindications.<sup>15</sup>

### **Cardiovascular and Lipid Safety**

A primary concern regarding very low-carbohydrate and ketogenic diets is their high saturated fat content, which can increase low-density lipoprotein cholesterol (LDL-C) and potentially elevate long-term cardiovascular risk.<sup>28</sup> Some meta-analyses have characterized this elevation in LDL-C as a significant clinical concern, noting that LCDs may impair long-term quality of life and increase cardiovascular risks in certain individuals.<sup>41</sup>

However, the **5-year** Virta Health trial data showed a more complex, favorable lipid profile.<sup>31</sup>

While triglycerides decreased by **-18.4%** and HDL-C increased by **+17.4%**

(representing a substantial improvement in atherogenic dyslipidemia), there were no significant changes in total cholesterol or LDL-C in the completers.<sup>31</sup>

Additionally, the Virta program was associated with:

- **Reduced Inflammation:** Significant, long-term reductions in systemic inflammatory markers, such as C-reactive protein.<sup>30</sup>
- **Improved Renal Function:** Stable or improved kidney function (eGFR slopes), showing the safety of this approach in patients with early-stage chronic kidney disease (  $\text{eGFR} < 90 \text{ mL/min/1.73 m}^2$  ).<sup>30</sup>
- **Lower Liver Fat:** A 60% reduction in liver fat score, along with a 45% to 75% lower risk of metabolic dysfunction-associated steatohepatitis (MASH) and advanced liver complications.<sup>30</sup>

For LEDs, the safety profile is generally favorable, but the rapid weight loss phase carries temporary risks of micronutrient deficiencies, temporary hair loss, and gallstone formation, requiring close medical supervision and nutrient supplementation during total diet replacement.<sup>8</sup>

## Absolute and Relative Contraindications

The ketogenic diet is not suitable for all patients and has several strict contraindications<sup>15</sup>:

- **Absolute Contraindications:** Rare inborn errors of metabolism affecting pyruvate carboxylase, carnitine transport or utilization, fatty acid oxidation pathways, and porphyria.<sup>15</sup> For example, patients with medium-chain 3-hydroxyacyl-CoA dehydrogenase (MHADD) deficiency cannot convert fats into energy, making a ketogenic diet potentially life-threatening.<sup>15</sup>
- **Relative Contraindications:** Acute pancreatitis, advanced hepatic or renal disease, familial hypercholesterolemia, and concomitant use of SGLT2 inhibitors.<sup>15</sup>

A critical drug-diet interaction involves sodium-glucose cotransporter-2 (SGLT2) inhibitors.<sup>14</sup> Combining SGLT2 inhibitors with a very low-carbohydrate or ketogenic diet significantly increases the risk of euglycemic diabetic ketoacidosis (DKA)—a potentially fatal medical emergency.<sup>14</sup>

Furthermore, patients on insulin or sulfonylureas require immediate, proactive medication reductions on day one of starting either an LED or an LCD to avoid severe, symptomatic hypoglycemia.<sup>8</sup>

Clinical Parameter	Low-Energy Diets (LEDs)	Low-Carbohydrate / Ketogenic Diets (KDs)
<b>Lipid Profile Impact</b>	Decreases LDL-C, triglycerides, and total cholesterol <sup>16</sup>	Significantly decreases triglycerides, increases HDL-C; total and LDL-C may remain neutral or rise <sup>11</sup>
<b>Cardiovascular Risk</b>	Reduces 5-year ASCVD risk	Declines TG/HDL ratio;

	and halves serious clinical events <sup>8</sup>	improves 10-year ASCVD risk score and reduces inflammation <sup>30</sup>
<b>Renal &amp; Hepatic Impact</b>	Normalizes liver fat and pancreas fat content <sup>4</sup>	Stabilizes eGFR slopes; reduces MASH and liver complications by 45 — 30
<b>Primary Adverse Risks</b>	Temporary nutrient deficits, hair loss, gallstone risk, muscle mass loss <sup>28</sup>	Transient "keto flu", gastrointestinal upset, risk of euglycemic DKA with SGLT2i <sup>14</sup>
<b>Absolute Contraindications</b>	Severe active eating disorders, type 1 diabetes <sup>6</sup>	Pyruvate carboxylase deficiency, porphyria, fatty acid oxidation defects (e.g., MHADD) <sup>15</sup>
<b>Medication Hazard</b>	Hypoglycemia from insulin/sulfonylureas; pre-emptive deprescribing required <sup>8</sup>	SGLT2 inhibitors (DKA risk); insulin/sulfonylureas (severe hypoglycemia risk) <sup>14</sup>

# Conclusions and Clinical Synthesis

The current medical evidence demonstrates that type 2 diabetes remission is achievable through intensive dietary interventions, challenging the historical view of the disease as an inevitably progressive condition.<sup>1</sup>

However, long-term follow-up studies spanning  $\geq 3$  years reveal that maintaining remission is difficult, and clinical relapse is common.<sup>8</sup>

A comparison of the two dietary approaches reveals distinct clinical profiles:

- Severe Caloric Restriction (LEDs)** achieved through liquid total diet replacements provides a structured, highly effective pathway to rapid remission (46% at 1 year).<sup>8</sup> This rapid improvement is driven by the depletion of ectopic fat in the liver and pancreas, which restores normal insulin sensitivity and  $\beta$ -cell function.<sup>5</sup> However, long-term durability is limited due to a high rate of weight regain, with the remission rate declining to 13% of active extension participants by year 5.<sup>8</sup> Even when weight is partially regained, this approach provides lasting clinical benefits, including a halving of serious medical events and hospitalizations.<sup>8</sup>

- **Low-Carbohydrate and Ketogenic Diets (LCDs/KDs)** provide a sustainable, food-based lifestyle alternative that can maintain long-term glycemic control and diabetes reversal (20% complete remission and 32.5% partial reversal at 5 years among completers).<sup>12</sup> KDs directly lower postprandial blood glucose, bypassing glucose toxicity and allowing  $\beta$ -cells to recover function.<sup>1</sup> While KDs significantly improve atherogenic dyslipidemia and reduce chronic inflammation, they require long-term behavioral changes that are difficult to maintain without ongoing remote coaching, digital tracking, and clinical support.<sup>13</sup>

Successful clinical remission depends on several key predictors, including a shorter duration of diabetes, an adequate baseline  $\beta$ -cell reserve, and the patient's ability to maintain a healthy body weight below their personal fat threshold.<sup>5</sup>

Ultimately, both low-energy and low-carbohydrate diets are highly effective clinical tools.<sup>7</sup> The choice of intervention should be tailored to the patient's health profile, baseline BMI, and personal preferences, supported by structured relapse management protocols to ensure metabolic improvements are sustained over the long term.<sup>16</sup>

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