REVIEW ARTICLE

Achieving Diabetes Remission: Current Guidelines and Emerging Pharmacotherapies in India

Arpan[1], Navrajbir Singh[2*], Kusum Bali[3], Tarundeep Singh[4]

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Abstract

Type 2 diabetes mellitus (T2DM) remission has emerged as a critical area of research and clinical interest, especially in India, where diabetes prevalence is rising at an alarming rate. Achieving remission through pharmacologic, dietary, and surgical interventions is now an attainable goal for a subset of patients. This systematic review synthesizes evidence from clinical trials, emerging pharmacologic interventions, and current guidelines for diabetes remission. We explore the mechanisms of diabetes reversal, highlighting novel agents such as glucagon-like peptide-1 (GLP-1) receptor agonists, dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 agonists, and sodium–glucose cotransporter 2 (SGLT2) inhibitors. This review also addresses the long-term sustainability of remission, epidemiological trends in India, and current treatment recommendations, integrating data from major studies. The findings underscore the need for a patient-centered, evidence-based approach to diabetes management. Additionally, we discuss the role of continuous glucose monitoring (CGM), dietary interventions, and the benefits of millet consumption in diabetes remission.

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, progressive β-cell dysfunction, and chronic hyperglycemia. The burden of diabetes in India has been increasing at an unprecedented rate, with an estimated 77 million adults diagnosed and an additional 25 million exhibiting impaired glucose tolerance (IGT).[1] If this trajectory continues, the prevalence is expected to reach 134 million by 2045 [International Diabetes Federation (IDF), 2021].[1] Given this growing public health concern, the concept of diabetes remission is being increasingly recognized as an alternative therapeutic goal beyond standard glycemic control. Achieving remission through structured lifestyle interventions, intensive pharmacotherapy, or metabolic surgery could significantly reduce the long-term complications associated with diabetes.

The definition of diabetes remission is based on achieving a glycated hemoglobin (HbA1c) level below 6.5% (48 mmol/mol) for at least 3 months in the absence of glucose-lowering medications..[2] Current research efforts are focused on identifying effective interventions that can help patients attain sustained remission, particularly in populations with a high genetic predisposition, such as in India (Fig. 1).

Here is the bar graph showing the increasing prevalence of diabetes in India based on IDF projections. The data is sourced from the IDF.[1]

Methodology

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. While this review was not registered with PROSPERO, all efforts were made to ensure transparency, reproducibility, and adherence to systematic standards. The decision not to register was due to early-stage resource constraints; however, the methodology followed remains robust and reproducible.

Although no formal meta-analysis was performed, methodological quality was reviewed based on study design and clinical relevance. Risk of bias was noted during screening, prioritizing peer-reviewed randomized controlled trials (RCTs) and well-structured trials.

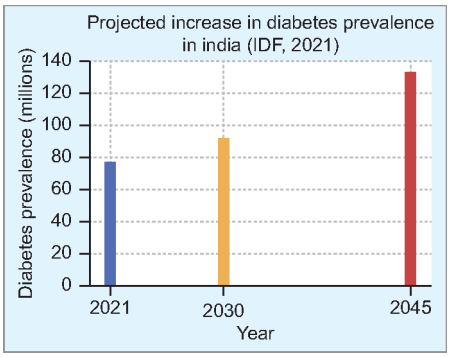

Fig. 1: Diabetes prevalence in India (2021–2045 projections)[1]

A comprehensive literature search was performed using PubMed, Embase, Cochrane Library, and Scopus databases to identify relevant studies published in the last 10 years. The search terms included "diabetes remission," "pharmacotherapy for diabetes reversal," "India diabetes guidelines," "glucagon-like peptide-1 (GLP-1) receptor agonists," "sodium–glucose cotransporter 2 (SGLT2) inhibitors," "combination therapy for diabetes remission," and "bariatric surgery for diabetes" (Table 1).

Inclusion Criteria

- RCTs, meta-analyses, cohort studies, and systematic reviews on T2DM remission.
- Studies evaluating pharmacologic interventions, lifestyle modifications, or metabolic surgery.
- Studies conducted in both global and Indian populations.

Exclusion Criteria

- Case reports and opinion articles.
- Studies lacking objective remission criteria.
- Studies with small sample sizes (<50 participants).

Data extraction was performed independently by two reviewers, and discrepancies were resolved by consensus. The extracted data included study design, intervention type, sample size, remission criteria, follow-up duration, and key findings.

Clinical Trials

Very Low-calorie Diets

The Diabetes Remission Clinical Trial (DiRECT) (2018, UK): The DiRECT trial was a landmark study that demonstrated the

[1,2]Intern; [3]Professor and Head of Department; [4]Associate Professor, Department of Internal Medicine, Punjab Institute of Medical Sciences, Jalandhar, Punjab, India; *Corresponding Author

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effectiveness of very low-calorie diets (VLCDs) in achieving diabetes remission. Participants who adhered to an 825–853 kcal/day diet for 3–5 months experienced a 46% remission rate at 1 year. Sustained weight loss of 10 kg or more was a key predictor of success.[3]

GLP-1 Receptor Agonists and Dual GIP/GLP-1 Agonists

The SURPASS-1 trial (2023): The SURPASS-1 trial investigated the efficacy of tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist. Approximately 52% of participants reached an HbA1c level below 5.7%, which is within the normal range for individuals without diabetes.[4]

The STEP 2 trial (2021): This trial showed participants receiving semaglutide 2.4 mg weekly experienced significant weight loss and improved glycemic control. Specifically, 67.5% of participants achieved HbA1c levels of ≤6.5%, and 45.6% achieved a ≥10% reduction in baseline body weight at week 68.[5]

Table 1: Prisma flow table

Stage	*Count*
Records identified through database searching (PubMed, Embase, Cochrane, and Scopus)	1,240
Records after duplicates removed	980
Records screened (title + abstract)	980
Records excluded (irrelevant, not focused on T2DM remission)	865
Full-text articles assessed for eligibility	115
Full-text articles excluded (e.g., poor methodology, <50 participants, not meeting remission criteria)	87
Studies included in final review	28

SGLT2 Inhibitors

A multicenter, RCT is currently underway to evaluate the remission effect of canagliflozin in patients with newly diagnosed T2DM. Participants will maintain their medication for 3 months after achieving target blood glucose levels and then discontinue it, with a follow-up period of 1 year to assess remission rates. The results of this trial are pending.[6]

Metabolic Surgery

The STAMPEDE trial (2017): This trial demonstrated that Roux-en-Y gastric bypass led to diabetes remission in 70–80% of cases (Table 2).[7]

Current Guidelines for Diabetes Remission in India

Diabetes management guidelines in India are predominantly influenced by global frameworks, with adaptations to meet local healthcare needs. The Research Society for the Study of Diabetes in India (RSSDI)[8] and the Indian Council of Medical Research (ICMR)[9] provide clinical guidelines that align with those issued by the American Diabetes Association (ADA)[10] and the European Association for the Study of Diabetes (EASD).[11] The 2024 ICMR guidelines emphasize a multifaceted approach, including lifestyle modifications, pharmacotherapy, and surgical options where applicable. These guidelines underscore the importance of individualized care plans, integrating patient preferences, and comorbid conditions into therapeutic decisions.

Pharmacotherapy Guidelines

- First-line therapy: Lifestyle modification and metformin remain the cornerstone of initial management.
- GLP-1 receptor agonists and dual GIP/GLP-1 agonists: Recommended for patients with obesity [body mass index (BMI) ≥ 30 kg/m^2] or insulin resistance, and those failing to achieve glycemic control with metformin alone.
- SGLT2 inhibitors: Preferred in patients with chronic kidney disease (CKD), heart failure, or established atherosclerotic cardiovascular disease (ASCVD). These agents can be initiated in patients with HbA1c > 7% despite metformin therapy.
- Combination therapy: The use of metformin, pioglitazone, and repaglinide as a combination. These combinations are recommended for individuals with HbA1c > 8% at diagnosis.
- Insulin therapy and early intensification: In newly diagnosed individuals with severe hyperglycemia (HbA1c > 10% or fasting plasma glucose > 300 mg/dL), short-term insulin therapy may be required before transitioning to oral or injectable agents.

Lifestyle and Surgical Guidelines

- Very low-calorie diets: Recommended for individuals with recent-onset diabetes (<6 years), with potential remission benefits if sustained for at least 12 weeks.
- Bariatric surgery: Recommended for individuals with BMI > 35 kg/m^2 with uncontrolled diabetes, or BMI > 30 kg/m^2

Table 2: Summary of clinical trials

Trial name	*Objective*	*Methodology*	*Findings*	*Reference*
DiRECT trial (2018, UK)	Assess whether structured weight management can induce diabetes remission	Low-calorie total diet replacement (825–853 kcal/day), structured food reintroduction, and long-term support	46% remission at 12 months; 36% sustained remission at 24 months	Lean et al.[3]
ARMMS-T2D trial	Compare metabolic surgery vs medical/lifestyle intervention for diabetes remission	Participants randomized to metabolic surgery (gastric bypass, sleeve gastrectomy) or medical/lifestyle management	37.5% remission in the surgical group vs 2.6% in the medical/lifestyle group at 3 years	Kirwan et al.[12]
SURPASS-1 trial (2023)	Evaluate tirzepatide's role in glycemic control and remission	Participants randomized to receive 5, 10, or 15 mg of tirzepatide vs placebo for 40 weeks	52% of participants on 15 mg achieved normoglycemia (HbA1c < 5.7%) without additional medication	Rosenstock et al.[4]
STEP 2 trial (2021)	Assess semaglutide's impact on T2DM remission in overweight/obese individuals	Participants received semaglutide 2.4 mg weekly for 68 weeks	Significant weight loss and glycemic control; remission rates not explicitly stated	Davies et al.[5]
STAMPEDE trial (2017)	Compare bariatric surgery vs intensive medical therapy for T2DM remission	Participants randomized to Roux-en-Y gastric bypass, sleeve gastrectomy, or medical therapy	29% of surgical group achieved HbA1c ≤ 6.0% without diabetes medications at 5 years	Schauer et al.[7]

with significant obesity-related complications.[8,12]
- Microbiome-based therapies: Although not yet part of standard guidelines, emerging evidence suggests that gut microbiota modulation through probiotic therapy, fecal microbiota transplantation (FMT), and prebiotic dietary interventions may enhance insulin sensitivity and glycemic control.

Dietary Interventions for Diabetes Remission

Diet remains the cornerstone of diabetes remission strategies. The DiRECT trial demonstrated that VLCDs could induce remission in nearly 50% of patients. However, for Indian populations, dietary modifications must be tailored to cultural preferences and traditional food habits.

- Caloric restriction: VLCDs (800–900 kcal/day) have been effective in achieving remission. Intermittent fasting and time-restricted eating are emerging approaches.[3]
- Macronutrient modifications: High-fiber, low-glycemic index (GI) diets are recommended.[13] Increased intake of plant-based proteins and healthy fats (RSSDI, 2023).
- Role of millets in diabetes remission: The World Health Organization (WHO) declared 2023 as the International Year of Millets, recognizing their nutritional value. Millets, such as *jowar* (sorghum), *bajra* (pearl millet), and *ragi* (finger millet), are gaining prominence in diabetes management due to their high-fiber content and low GI properties—Jowar (Sorghum): Rich in polyphenols and resistant starch, improves insulin sensitivity.[13] Bajra (pearl millet): Lowers postprandial glucose spikes.[9] Ragi (finger millet): High calcium content and slow digestion rate aid in glucose control.[13]

Dietary guidelines for Indian populations: Replace refined grains with whole grains and millets.[8] Increase intake of legumes and vegetables.[9] Limit processed foods and sugar intake.[14] Include probiotic-rich foods to improve gut microbiome health.[13] Studies by Saboo et al. emphasize that dietary modifications incorporating millets can significantly improve glycemic control and aid in long-term remission.[13]

The Diabetes Surgery Summit II (DSS-II) 2016 guidelines, endorsed by international organizations, support surgical intervention as a therapeutic alternative for diabetes remission in specific cases.[15]

Dosage Guidelines for Approved Agents

- Semaglutide (GLP-1 agonist): Recommended dose escalation from 0.25 to 1.0 mg weekly, with some studies exploring 2.4 mg weekly for weight loss benefits.
- Tirzepatide (dual GIP/GLP-1 agonist): Initiation at 2.5 mg weekly, with gradual titration to 15 mg weekly.
- Canagliflozin (SGLT2 inhibitor): Standard dose 100 mg daily, increasing to 300 mg daily based on renal function.

Lantidra

Lantidra (donislecel): Approved by the Food and Drug Administration (FDA) in June 2023, Lantidra is the first allogeneic cellular therapy for adults with type 1 diabetes who experience severe hypoglycemia despite intensive management. It involves infusing donor pancreatic islet cells into the patient's liver, enabling insulin production. Clinical trials demonstrated that some patients achieved insulin independence posttreatment.[16]

Continuous Glucose Monitoring in Diabetes Remission

Continuous glucose monitoring (CGM) is an essential tool for monitoring glucose levels and optimizing diabetes remission strategies. It provides real-time data, allowing for early detection of glycemic variability and aiding in personalized dietary and pharmacologic interventions. The ADA and the RSSDI recommend CGM for individuals aiming for remission, particularly those undergoing intensive lifestyle interventions or using insulin-sensitizing agents. CGM enables: Continuous tracking of glucose fluctuations, identification of early signs of relapse, tailoring dietary and exercise interventions, and adjusting pharmacologic regimens dynamically. Studies have shown that CGM use in remission strategies leads to better long-term glycemic control and increased adherence to lifestyle modifications (Table 3).[13]

Relevance in the Indian Population

The relevance of diabetes remission strategies in India is profound due to the high prevalence of central obesity and insulin resistance. Genetic predisposition plays a significant role in the progression of T2DM, making lifestyle interventions challenging for many individuals. The dietary patterns in India, which are often carbohydrate-rich, further complicate adherence to low-calorie and

Table 3: Clinical guidelines comparison table: India vs Global

Aspect	*RSSDI/ICMR (India)*	*ADA/EASD (Global)*
Definition of remission	HbA1c < 6.5% for ≥3 months without glucose-lowering medication	Same definition (per ADA Consensus Report 2021)
First-line therapy	Lifestyle + Metformin	Lifestyle + Metformin
GLP-1 receptor agonists	Recommended for BMI ≥ 30 kg/m^2 or insulin resistance	Recommended for ASCVD, obesity, or when weight loss is a priority
SGLT2 inhibitors	Preferred in patients with CKD, heart failure, or HbA1c > 7%	Same; strong evidence for cardiovascular and renal benefits
Combination therapy	Metformin + pioglitazone + repaglinide in patients with HbA1c > 8%	Metformin + GLP-1 RA or SGLT2i or sulfonylureas, depending on comorbidities
Insulin	Short-term insulin for HbA1c > 10% or FPG > 300 mg/dL	Same recommendation
VLCDs	Recommended for recent-onset diabetes (<6 years)	Recommended but with close medical supervision
Metabolic surgery	Recommended for BMI > 35 or BMI > 30 with comorbidities	BMI > 30 with inadequate control, especially in Asian populations
Continuous glucose monitoring (CGM)	Recommended in intensive interventions or insulin use	Widely recommended for type 1 and insulin-requiring type 2 diabetes

Note: ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; FPG, fasting plasma glucose; ICMR, Indian Council of Medical Research; RSSDI, Research Society for the Study of Diabetes in India

low-carbohydrate interventions. Therefore, pharmacologic interventions, such as GLP-1 receptor agonists and SGLT2 inhibitors, have gained importance in remission strategies. Moreover, the high cost of metabolic surgery limits accessibility for a significant portion of the population, necessitating cost-effective and sustainable alternatives. Thus, socioeconomic factors also play a crucial role, as cost-effective pharmacologic alternatives, such as SGLT2 inhibitors and combination therapies, may be more viable than bariatric surgery for many patients.[8]

Future Directions

Research into β-cell regeneration, microbiome modulation, and artificial pancreas systems offers promising avenues for diabetes remission. PDX-1 targeting drugs aimed at improving β-cell function are under investigation, while FMT is being explored as a potential intervention for metabolic diseases. The development of smart insulin delivery systems integrating CGM with insulin pumps may revolutionize diabetes management in the near future.

Ongoing Clinical Trials

Several ongoing trials are investigating novel pharmacologic interventions for diabetes remission: Phase 3 trials of high-dose GLP-1/GIP receptor agonists (e.g., Tirzepatide) evaluating long-term remission potential, trials exploring combination therapies, including SGLT2 inhibitors with GLP-1 receptor agonists, aiming for superior glycemic control and weight loss, and β-cell regeneration studies utilizing novel peptide therapies to enhance insulin secretion.

Conclusion

Diabetes remission is a tangible goal, with a growing body of evidence supporting structured lifestyle interventions, pharmacotherapy, and metabolic surgery as viable pathways. The adoption of new pharmacological agents, including GLP-1 receptor agonists, SGLT2 inhibitors, and combination therapies, provides an expanded toolkit for clinicians. CGM plays a critical role in monitoring and sustaining remission. Dietary interventions, particularly incorporating millets, provide a culturally appropriate and effective strategy for the Indian population. In India, addressing sociocultural and economic barriers remains crucial for achieving widespread remission outcomes. Future research should focus on personalized treatment strategies that cater to the unique metabolic profile of the Indian population.

Orcid

Arpan https://orcid.org/0009-0006-1246-4007
Navrajbir Singh https://orcid.org/0009-0003-7071-659X
Kusum Bali https://orcid.org/0009-0000-1134-734X
Tarundeep Singh https://orcid.org/0009-0008-1723-5128

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