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Type 2 Diabetes Remission Through Weight Loss: A Structured Systematic Review (SWiM) of Mechanisms, Durability, and the New Pharmacological Frontier

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ADMINISTRATIVE INFORMATION

Support - Self-funded. Supported by University of Hail College of Pharmacy academic resources. No pharmaceutical industry or commercial funding was received for this review.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 June 2026 and was last updated on 22 June 2026.

INTRODUCTION

Review question / Objective In adults with type 2 diabetes, what is the effectiveness, durability, and mechanistic basis of weight-loss interventions (lifestyle/dietary, pharmacological, and metabolic/bariatric surgery) for achieving and sustaining diabetes remission, and how does the probability of remission relate to the magnitude of weight loss achieved?.

Rationale Substantial, sustained weight loss can induce and maintain type 2 diabetes remission across lifestyle (DiRECT, DIADEM-I, Look AHEAD), metabolic/bariatric surgery (STAMPEDE, Mingrone, Swedish Obese Subjects, ARMMS-T2D), and — increasingly — pharmacological routes (GLP-1 and dual GIP/GLP-1 receptor agonists), with a consistent dose-response between weight lost and remission probability and a coherent mechanistic basis (loss of ectopic liver and pancreas fat with recovery of first-phase insulin secretion; the twin-cycle and personal-fat-threshold models). However, no single review integrates all three modalities together with the mechanistic and durability evidence under the harmonised 2021 consensus remission definition, and the new pharmacological agents have not been evaluated against that off-therapy remission standard. This structured systematic review (SWiM) addresses that gap, standardising on the consensus definition, stratifying remission by magnitude of weight loss, and explicitly distinguishing drug-induced glycaemic normalisation from formal remission, to provide an up-to-date and clinically actionable synthesis for diabetes and clinical-pharmacy practice. The review is registered at protocol stage; full-text retrieval of identified studies is in progress and database searches have not yet been executed.

Condition being studied Type 2 diabetes mellitus and its remission through weight loss.

METHODS

Search strategy MEDLINE/PubMed, Embase, Cochrane CENTRAL, Scopus, Web of Science,

CINAHL, and PsycINFO, plus LILACS, with trial-registry and grey-literature checks (ClinicalTrials.gov, WHO ICTRP) and backward and forward citation searching of included studies and prior systematic reviews. Planned search execution 01 June 2026 to 31 August 2026; publication date coverage 01 January 2000 to 31 May 2026; no language restriction at the search stage. Search terms combine controlled vocabulary (MeSH/Emtree) and free text for: type 2 diabetes; diabetes remission; diabetes reversal; weight loss; caloric restriction; very low energy diet; total diet replacement; GLP-1 receptor agonist; tirzepatide; bariatric surgery; metabolic surgery; gastric bypass; sleeve gastrectomy; beta-cell function; liver fat; pancreatic fat.

Participant or population Adults (≥18 years) with a diagnosis of type 2 diabetes mellitus by recognised criteria (ADA/WHO). Studies in people with type 1 or monogenic diabetes only, or paediatric-only samples, are excluded.

Intervention Weight-loss interventions delivered to achieve diabetes remission, grouped into three modalities: (1) lifestyle/dietary — very-low-energy/total-diet-replacement, caloric restriction, and structured lifestyle programmes; (2) pharmacological — GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists used for weight reduction; and (3) metabolic/bariatric surgery (Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic diversion).

Comparator Usual care, standard glycaemic management, an alternative weight-loss strategy or modality, lower-intensity intervention, or no comparator (single-arm cohorts). Comparator type will be recorded and examined as a potential effect modifier.

Study designs to be included All study designs are eligible: randomised controlled trials (including cluster-RCTs), non-randomised interventional studies, prospective and retrospective cohort studies, controlled before-after studies, and mechanistic physiology studies. Narrative reviews, editorials, and conference abstracts lacking extractable primary data are excluded but may inform the discussion.

Eligibility criteria Inclusion: adults (≥18 years) with type 2 diabetes; a weight-loss intervention (lifestyle/dietary, pharmacological, or metabolic/bariatric surgery); a remission, durability, weight-change, or mechanistic outcome reported or calculable; any study design carrying primary data.Exclusion: type 1 or monogenic diabetes only; paediatric-only samples (<18 years); no extractable remission/weight/mechanistic outcome; narrative reviews, editorials, commentaries, and conference abstracts without primary data; duplicate or overlapping reports (most complete version retained); and any retracted publication.

Information sources MEDLINE/PubMed, Embase, Cochrane CENTRAL, Scopus, Web of Science, CINAHL, PsycINFO, LILACS (plus ClinicalTrials.gov and WHO ICTRP for grey literature).

Main outcome(s) Type 2 diabetes remission defined per the 2021 ADA/EASD/Diabetes UK consensus (Riddle et al.): HbA1c <6.5% (<48 mmol/mol) measured at least 3 months after cessation of glucose-lowering pharmacotherapy (or ≥3 months after metabolic surgery). Remission rates will be reported by modality and by magnitude of weight loss achieved.

Additional outcome(s) Durability of remission and relapse over time; magnitude of weight loss (kg and %); change in HbA1c and fasting glucose; mechanistic correlates of remission (hepatic and pancreatic fat, first-phase/beta-cell insulin secretion); predictors of durable remission versus relapse (diabetes duration, baseline HbA1c, insulin use, degree and maintenance of weight loss); and downstream clinical outcomes of remission (micro-/macrovascular complications, cardiovascular events) where reported.

Data management Two reviewers (A.S.A., B.A.A.) will independently screen titles/abstracts and full texts using Rayyan, with disagreements resolved by consensus or third-party adjudication. Data will be extracted into a pre-piloted standardized form capturing study identifiers, design, setting and country, population characteristics (age, baseline BMI, baseline HbA1c, diabetes duration, ethnicity), intervention modality and comparator, weight loss achieved (kg and %), remission definition used, remission rate (with confidence intervals), follow-up duration, mechanistic and durability outcomes, funding source, and declared conflicts of interest. Retraction status of every included record will be checked against the Retraction Watch database and Crossref before extraction.

Quality assessment / Risk of bias analysis Risk of bias will be assessed independently by two reviewers using design-appropriate tools: Cochrane RoB 2 for randomised trials, ROBINS-I for non-randomised interventional studies, and the Newcastle-Ottawa Scale for cohort and case-control studies. The certainty of evidence for each outcome (remission by modality, durability,

mechanism) will be rated using GRADE. Disagreements will be resolved by discussion or a third reviewer. Industry funding and investigator conflicts will be tabulated and considered in interpretation.

Strategy of data synthesis This is a structured systematic review using the Synthesis Without Meta-analysis (SWiM) reporting guideline as the primary synthesis method; a formal meta-analysis is NOT planned because the evidence base is heterogeneous in remission definition, design, population, and follow-up. Studies will be grouped into pre-specified comparisons by modality (lifestyle, pharmacological, surgical) and stratified by magnitude of weight loss achieved; a standardised metric (remission proportion with 95% CI) will be defined per outcome; and results will be synthesised using structured tabulation, effect-direction plots, and vote-counting by direction of effect, with the rationale for grouping and the standardised metric reported per SWiM items. The single planned quantitative element is a pre-specified meta-regression of remission probability against percentage weight loss (the one homogeneous dimension across the literature), conducted only if ≥6 studies report compatible weight-loss and remission data; this complements rather than pools across modalities. Certainty of evidence is rated per outcome using GRADE. Should a sufficiently homogeneous set of remission-endpoint RCTs (harmonised Riddle definition, comparable populations, ≥2-year follow-up) emerge within a modality, upgrading that stratum to a random-effects meta-analysis would be considered as a documented protocol amendment.

Subgroup analysis Intervention modality (lifestyle vs pharmacological vs surgical); magnitude of weight loss (e.g., <10%, 10–19%, 20–29%, ≥30%); baseline diabetes duration; baseline HbA1c; insulin use at baseline; baseline BMI (including normal-weight/personal-fat-threshold T2D); follow-up window; and study design.

Sensitivity analysis Restriction to studies using the consensus (Riddle 2021) remission definition; restriction to randomised designs; restriction to studies with ≥2 years follow-up; exclusion of studies at high/critical risk of bias; and leave-one-out examination within any meta-regression.

Language restriction No language restriction at the screening stage; non-English full texts will be translated where feasible.

Country(ies) involved Saudi Arabia.

Other relevant information Endocrinology; Clinical Pharmacy; Bariatric Medicine; Nutrition

Keywords type 2 diabetes; diabetes remission; weight loss; low energy diet; bariatric surgery; GLP-1 receptor agonist; tirzepatide; beta-cell function; durability;.

Dissemination plans Peer-reviewed publication in an endocrinology, diabetology, clinical-pharmacy, or metabolic-medicine journal; open-access preferred. Findings may also be presented at relevant scientific meetings.

Contributions of each author

Author 1 - Abdulrahman Alanazi - Conceived and designed the study, drafted the protocol, will lead data extraction and synthesis, and drafted the manuscript and final manuscript submission.
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Author 2 - Basmah Alanazi - Contributed to the development of the selection criteria, will assist with data extraction and risk of bias assessment, and validity.
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