Weight maintenance interventions for people with type 2 diabetes mellitus: A systematic review protocol

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Protocol

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Abstract

Background: Weight loss maintenance is a challenge for people with Type 2 Diabetes Mellitus (T2DM), which attenuates the long-term benefits of weight loss for diabetes management. Medication, specific dietary requirements, and the psychosocial burden of T2DM signify that weight loss maintenance designed for obesity may not suit people with T2DM. The primary objective of this review is to comprehensively evaluate existing weight maintenance interventions for people with or at high risk of T2DM.

Methods: We registered a protocol for the systematic review and meta-analysis of randomised and non-randomised weight maintenance interventions for T2DM. Studies included will have been carried out in adults with clinical diagnosis of T2DM or pre-diabetes. All intervention types will be accepted (*e.g.* behavioural/lifestyle change and pharmacological). The primary outcomes will be weight control, glycaemic control, and adverse effects. Secondary outcomes will include cardiovascular risk factors (*e.g.* total cholesterol, LDL-cholesterol, blood pressure control), psychological wellbeing (including health-related quality of life), change in glucose medication and waist circumference. Multiple electronic databases will be searched such as MEDLINE, EMBASE, Web of Science, PsychINFO and international registers (e.g. Cochrane Central Register of Controlled Trials, WHO ICTRP). OpenGrey will be searched for grey literature. Two researchers will screen all citations and abstracts. This process will also be conducted by an additional researcher using a semi-automated tool to reduce human error. Full-text articles will be further examined by the researchers to select a final set for further analysis, and a narrative synthesis of the evidence will be presented. Potential sources of heterogeneity will be assessed, and a meta-analysis will be conducted if feasible. Risk of bias will be evaluated using the Cochrane risk of bias tool and the certainty of evidence using the GRADE (grading of recommendations, assessment, development, and evaluation) approach.

Discussion: This review will critically appraise existing weight maintenance interventions targeting T2DM. Findings will inform future intervention development to support people with T2DM delay weight regain and prolong successful diabetes management.

Systematic Review Registration: PROSPERO 168032

Background

The international diabetes federation reports that in 2019 approximately 463 million adults between ages 20 and 79 were living with diabetes mellitus, with projections estimating a rise to 700 million by 2045 (1). The existence of multiple comorbidities and an augmented risk of mortality have placed diabetes mellitus as a global health and development challenge (1). More than 90% of people with diabetes mellitus have type 2 diabetes mellitus (T2DM). Although a genetic predisposition results in an increased susceptibility among some individuals, excess weight, due to poor diet and insufficient physical activity, is the key

modifiable risk factor (2). Hence, lifestyle change to maintain a healthy weight is a fundamental component of existing prevention and management strategies (3).

Weight loss interventions have proven to ameliorate cardiometabolic health and HbA1c control (4,5). Multifaceted lifestyle change can lower body mass index (BMI) and reduce the risk of T2DM in at-risk individuals (Schellenberg et al., 2013). More recently, it has been shown that a very low-calorie diet encouraging weight loss enabled participants to reach a T2DM remission-like state (7). However, patients with T2DM struggle to maintain the weight lost once weight loss interventions have terminated (8). At 12-month follow-up, the intervention benefits for weight, HbA1c levels, lipids and blood pressure are less clear (9). Furthermore, there is some evidence that weight loss maintenance is short-lived in people with T2DM compared to nondiabetic people with obesity (10) or people at high risk (6).

The primary target for diabetes management is glucose control (3), and commonly used pharmacological treatments for glucose regulation facilitate weight gain (3,11). Medication used to treat psychiatric comorbidities and diabetes-related medical complications can have a similar side effect (12,13). The specific dietary requirements and the psychosocial burden of diabetes self-management can also influence adherence to physical activity and dietary guidelines among this clinical group (14). Behavioural interventions shown to be beneficial for weight loss maintenance in obesity (15,16) may therefore not be equally applicable to people who additionally have T2DM.

The prescription of weight maintenance programmes is among the American Diabetes Association's recommendations for medical care in diabetes (17). Further, 4-year weight maintenance (<5% change from baseline measure), particularly when combined with glycaemic control, has been found to result in a reduction in medical costs, compared to a 14% increase when weight gain occurs alongside an incremental increase in mean A1C levels (18). Given the importance of weight maintenance for diabetes-related health outcomes and the economic savings for the healthcare system, development and implementation of weight maintenance interventions that are effective for people with or at high risk of T2DM is crucial.

Aims

The systematic review described in this protocol aims to comprehensively evaluate the effectiveness of existing weight maintenance interventions that have targeted people with or at high risk of T2DM. It will consider glucose regulation and weight as primary outcomes, in order to discern features of current interventions that may aid patients adhere to treatment targets and to identify challenges to be addressed by novel interventions.

A second objective of this review is to further evaluate the applicability of text-mining tools and machine learning to support clinical systematic reviews. As the rate of publication rises across disciplines, evidence synthesis is becoming increasingly more time consuming (19). Automated tools/processes may reduce workload for researchers. However, the use of varied terminology to define medical phenomena and clinical interventions often requires complex decision-making that may be difficult to predict prior to

screening. Therefore, the traditional systematic review screening process will be carried out in parallel to a protocol using automated approaches in order to identify where human judgement may be needed when conducting systematic reviews of studies evaluating clinical interventions.

Methods

The systematic review will be conducted and reported in accordance to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 checklist' (20). View Additional file 1 for the completed checklist relevant to this review protocol. The protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (ID number: 168032).

Eligibility criteria

Both published and unpublished studies including a weight maintenance intervention will be analysed. Studies will be included irrespective of the country where they have been carried out and the language of the report. Studies may be both randomised and non-randomised, and blinding is not required given that it is not always possible in behavioural interventions. The use of the findings from this review to develop a novel intervention and design a randomised controlled trial justify the inclusion of non-randomised studies (21). Studies meeting the following criteria will be deemed eligible for analysis (PICO structure):

Types of Participants

Participants will be adults (age ≥ 18 years), with a clinical diagnosis of T2DM or pre-diabetes according to the criteria of the World Health Organisation (22) or equivalent international standards (e.g. 23). When it is unclear whether a diagnosis was conducted, the study authors will be contacted to obtain the information. Further, studies where participants display impaired fasting glucose or non-diabetic hyperglycaemia will also be included. Participants will additionally have had to achieve weight loss within 24 months prior to the start of the weight maintenance intervention or have been instructed to maintain their weight as a preventative measure. No restriction will be placed on the amount of weight loss achieved during a weight loss programme given differential targets and success rates across studies (24). Participants may have been recruited from the general community, hospital, clinical care centre or other health services. Exclusion criteria include individuals with overweight or obesity who do not have a diagnosis of pre-diabetes or T2DM, individuals with type 1 diabetes mellitus, and individuals with conditions requiring antipsychotic drugs.

Types of Intervention

Interventions applied can focus on behavioural/lifestyle change, pharmacological (drugs must be approved as a weight loss drug by the European Medicines Agency), can be delivered online or in-person, and can entail food replacement(s)/supplement(s). Both stand-alone and combined interventions will be included. Papers will be excluded if the intervention focuses solely on weight loss or the weight loss component is not clearly distinguished from the weight maintenance phase. Single-cohort studies will be

accepted, as well as studies where the comparator is no intervention, standard or minimal care, waitlist, or the use of a placebo. When the details of the information are unclear, authors will be contacted to provide further information.

Types of outcomes

The primary outcomes will be weight, glycaemic control (including HbA1c, fasting plasma glucose, insulin sensitivity/resistance), and adverse effects (recovery of weight lost, physical and/or psychological side effects such as disordered eating behaviour). Secondary outcomes will include cardiovascular risk factors (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triacylglycerol, diastolic blood pressure, systolic blood pressure), psychological wellbeing (including health related quality of life), change to glucose medication and waist circumference. Quantitative (both continuous and categorical) outcomes will be considered.

Should amendments be necessary, these shall be documented, reported, and fully justified.

Search Strategy

A systematic search of the literature available from 1940 to present will be carried out in Web of Science, Medline, PsychINFO (via OVID), Embase, international trial registers (Cochrane Central Register of Controlled Trials, WHO International Clinical Trials Registry portal (ICTRP) and ClinicalStudyResults.org). We will additionally conduct hand searches of reference lists, and we will review the grey literature (e.g. conference papers/conference proceedings, theses, dissertations, studies published in non-indexed journals) via OpenGrey. Personal letters and e-mails will be sent to the corresponding authors of papers in the field of weight management in T2DM. The authors will be asked for information regarding unpublished or ongoing studies.

Search terms identified for each of the following relevant categories: population (“type 2 diabetes” or “diabetes mellitus” or “diabetes mellitus type 2” or “pre-diabetes” or “prediabetes” or “hyperglycaemia”), intervention (“weight maintenance” or “maintained weight” or “weight maintenence” AND “behav*” or “lifestyle*” or “online” or “computer” or “web” or “pharma*” or “food repla*” or “*supple*”), and outcome (“weight” or “body mass index” or “BMI” or “glycaemic* control” or “cardiovascular*” or “psych*”). Boolean searches will be carried out with terms combining categories and variations of the terms (via truncation). Medical Subject Headings (MeSH) keywords and Emtree keywords will be used. See Additional file 2 for the draft search strategy for MEDLINE.

Data management

The search will be managed using the Rayyan (http://rayyan.qcri.org) software app. Results will be imported into Rayyan, which automatically detects duplicates. Duplicates will also be detected through the manual data screening process.

Selection process

Two authors of the team will screen all titles and abstracts identified by the search strategy based on the inclusion criteria. Articles that appear to meet the inclusion criteria will be extracted and reviewed in full by two authors. Inconsistencies will be discussed, and if unresolved another member of the team will be brought in to make the final decision. Studies deemed irrelevant will be excluded, and reason will be provided. Authors of unpublished studies will be contacted.

Semi-automated screening

Search results will additionally be uploaded to AbstrackR, a citation screening programme functioning on an algorithmic framework that predicts the likelihood citations are relevant for further inspection (25). Screening will be initiated by two authors until the programme indicates it is ready to make predictions. Citations extracted through this approach will be compared and cross-checked against the output of the manual screening and selection process. Precision, false negative rate, number of relevant citations missed, and researcher time saved will be examined to determine the usefulness of AbstrackR.

Data extraction and quality assessment

Two authors will independently extract the data of the included studies using a standardised data extraction form (Additional file 3) and the GRADE pro software (https://gradepro.org/). The authors will extract information needed to assess the methodological quality of the studies, as well as sample characteristics (size, inclusion/exclusion criteria, sex, age), intervention details, and outcome measures. Inconsistencies in data extraction will be discussed and recorded. If needed, a third author will be included in the discussion to reach a final decision. When data is missing or inadequately described, three attempts will be made to request the information from the corresponding author.

The Cochrane Risk of Bias Version 3 tool (26) will be used for randomised controlled trials, while the ROBINS-I tool (27) for observational studies. The strength of the overall body of evidence for each outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (28). Any discrepancies will be solved by a third author.

Data analysis

A narrative synthesis of eligible studies will be conducted. A qualitative summary of all extracted data will be provided, and quantitative data will be reported in a table. One author from the team will synthesise all the data, and another will review the process. Inconsistencies will be resolved by a third author. Overall effect size on weight will be reported as weighed mean differences with 95% confidence intervals. If there is homogeneity in the outcome variables, a meta-analysis of the studies will be carried out with the Comprehensive Meta-Analysis software (29). Clinical heterogeneity between studies will be evaluated by identifying variability in participants, baseline data, interventions, and outcomes. The I^2 statistic will be calculated to quantify and interpret statistical heterogeneity (30). Funnel plots will be carried out to assess publication bias (if over 10 studies are identified). Pooled risk ratios (RRs) and 95% confidence intervals (CIs) will be calculated for dichotomous outcomes. Pooled mean differences and 95% Cis or

standardised mean differences and 95% CI will be calculated for continuous outcomes when results are reported on the same scale (or can be converted to the same scale), or if results are reported on different scales, respectively.

A random effect model will be generated, where study weighing is based on in-study and between-study variances. When available data does not enable statistical pooling, results will be reported in a narrative format.

Missing data

If data is not available in the format required, we will first contact study authors or we will back-calculate the data if possible (e.g., standard deviation from standard errors or 95% CIs, mean and standard deviation from median and range, etc.). Reasons for missing data will be recorded (e.g. drop-outs, losses to follow-up and withdrawals).

Sensitivity analyses

A sensitivity analysis will be conducted including only trials classified as low risk of bias.

Discussion

Multiple weight loss interventions have been trialled for people with T2DM, showing substantial benefits for diabetes management (31). Yet, weight regain shortly after the completion of a weight loss programme is common in T2DM. Cost-effective interventions to prolong weight loss maintenance in T2DM are urgently needed. This review will examine the effectiveness of existing weight maintenance interventions for T2DM with the scope to inform the development of future interventions that are tailored to the needs of this clinical population. By comparing the step-by-step outputs of the systematic process when conducted solely by researchers versus when the review is supported by automated tools, we will further ascertain the amount of time saved when these tools are applied and when human input is required for accurate outcomes. We aim to use the information to generate a standardised protocol that researchers can adhere to when employing automated tools to conduct systematic reviews on complex clinical interventions. A speedier critical appraisal of the existing literature without compromising quality will accelerate the development process of evidence-based interventions. A limitation of using semi-automated tools to assist screening is that these tools are highly reliant on there being enough eligible studies for ‘training’ the system. Hence, though semi-automated tools are highly promising to facilitate reviews with large datasets, they may be less applicable with more systematic reviews targeting a less explored field of research. Any amendments made to this protocol will be recorded on PROSPERO and reported in the final review manuscript.

Abbreviations

T2DM: Type 2 Diabetes Mellitus

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests

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Author contributions

The protocol was developed by all authors. SS is the guarantor of the review and drafted the manuscript. JB, JC, CE, RP provided edits for manuscript improvement.

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