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INTRODUCTION

Type 2 diabetes (T2D) is a highly prevalent disease, especially among individuals who are overweight or obese and at a higher age [1]. The interaction between T2D, obesity, and ageing places individuals at high risk for adverse health outcomes, including physical disability and sarcopenia [2]. This may lead to a vicious cycle that further worsens metabolic and physiologic abnormalities [3]. Obesity management is beneficial in the treatment of T2D [4] and may break that vicious cycle. While hypocaloric diet has been recognized as a main strategy to achieve weight loss since many years [4], lifestyle interventions (including hypocaloric diet and exercise) are gaining more attention as an appropriate weight loss strategy [5]. The additional effect of exercise in this weight loss strategy for overweight or obese individuals with T2D is however not clear.

A hypocaloric diet can lead to the recommended weight loss of ≥5% of total body weight, and has been shown to reduce glycated haemoglobin (HbA1c) and the need for glucose lowering medications [6, 7]. However, caloric restriction not only reduces regional and total fat mass, it may also lead to a significant decrease in lean body mass [8]. This can result in functional decline and reduced metabolic rates [2, 9], which complicates further weight loss or weight maintenance. Exercise seems a logic addition to the hypocaloric diet, to counteract decrease in lean mass and functional decline. Besides that, there is substantial evidence that exercise improves glycemic control in individuals with T2D [10, 11]. Exact working mechanisms are not fully known, but exercise induces beneficial adaptations in many tissues, like muscle, liver, pancreas, fat cells, and vascular tissue, leading to improvements in glycemic control [12]. Such improvements depend on exercise type and intensity [13].

In obese individuals, adding exercise to a hypocaloric diet leads to improved cardiovascular fitness, muscle strength, and body composition outcomes, as shown by two systematic reviews including one meta-analysis [14, 15]. Previous systematic reviews and meta-analyses on the effectiveness of lifestyle interventions in T2D patients found no to modest reductions in body weight, without reports on body composition, and modest to clinically meaningful reductions in glycemic control [7, 16, 17]. These studies did not compare the effects of lifestyle interventions (including hypocaloric diet and exercise) with hypocaloric diet alone, therefore the additional effect of exercise is not clear. This systematic review and meta-analysis aims to evaluate the added value of exercise in addition to hypocaloric diet on body weight, body composition, and metabolic health in overweight or obese individuals with T2D. Secondarily, we explore the associations between exercise type and intensity and the change in body weight, body composition and metabolic health in this population.

METHODS

This systematic review complies with the PRISMA guideline [18]. The study protocol was registered in FigShare, an online open access repository in March 2021.

Eligibility criteria

Studies to be included meet the following criteria:

- Examining an adult human population with type 2 diabetes and a mean BMI of ≥25 kg/m^2.
- Implementation of any type of dietary weight loss intervention in combination with physical activity.
- A comparison with a control group that received the dietary weight loss intervention without physical activity.
- Reporting at least one of the following physical outcome measures: fasting blood glucose level, glycated hemoglobin (HbA1c), 2h glucose level, measures of insulin sensitivity/resistance (e.g. Matsuda-index, HOMA-IR), body weight, BMI, waist circumference, measures of body composition (muscle mass, lean body mass, fat mass), measures of physical performance (leg strength, chair stand, walking speed, VO_2peak).
- A randomized controlled design.
- Published in English.

There is no restriction with regard to year of publication.

Search strategy

We will search the following electronic databases for eligible studies: Embase, Medline (Ovid), Web of Science and Cochrane Central. The specific search strategies were created by a health science librarian with expertise in systematic review searching. The Embase search strategy is presented in Appendix 1. The final Embase strategy was adapted to the syntax of other databases. In addition to the database search, reference lists of included studies as well as relevant reviews will be checked manually to identify additional studies for inclusion.

Study selection

The records will be exported into Endnote X9 where duplicates will be removed. All titles and abstracts will be screened independently by two reviewers (MH, AH), followed by full text evaluation for final study inclusion. Any disagreement about inclusion/exclusion will be resolved by a discussion and in consultation with a third reviewer (RM).

Data extraction

Two reviewers will extract the data from the included papers using a table with pre-specified items. Items to be extracted are:

- Study details (author(s), year of publication)
- Study characteristics (duration, number of groups)
- Population characteristics (number of participants, population, mean age or age range, % male)
- Dietary intervention characteristics (type of diet, calories)

- Exercise intervention characteristics (type of exercise, duration, dose, intensity)
- Baseline and post-intervention scores of the following outcome measures:
  - Body weight
  - BMI
  - Waist circumference
  - Parameters of body composition: muscle mass, lean body mass, fat-free mass, fat mass
  - Parameters of blood glucose: fasting blood glucose, HbA1c, 2h glucose from OGTT
  - Insulin sensitivity/resistance (e.g. Matsuda index, HOMA-IR)
  - Parameters of physical performance: leg strength, chair stand, walking speed, VO2peak

Risk of bias assessment

Two reviewers (MH, AH) will independently assess the risk of bias of all included studies using the revised Cochrane risk of bias tool (RoB 2) [19]. Our aim is to assess the effect of adhering to the intervention, with failures in implementation and non-adherence as selected deviations.

Data synthesis and analysis

Study characteristics and results will be summarized narratively. In addition, a meta-analysis will be conducted for outcomes that are reported by at least three studies. Resulting post-intervention mean differences (PMD) compared to baseline will be used for a random effects meta-analysis. Standard errors (SE) will be converted into standard deviations (SD) using the following equation:

$$SD = \sqrt{(N)} * SE$$

Reported confidence intervals (CI) for PMD will be converted into SD, using the following equation:

$$SD = \frac{(\text{upper limit} - \text{lower limit}) / 3{,}92}{\sqrt{((1/N_1)+(1/N_2))}}$$

When PMD and/or SD are unavailable, the following equation will be used:

$$SD_{change} = \sqrt{(SD_{baseline}^2 + SD_{Post}^2 - (2 * Corr * SD_{baseline} * SD_{Post}))},$$

in which 'corr' refers to the correlation coefficient. To sustain similarity, a correlation coefficient will be sought within the study, resulting in an average within-study-correlation coefficient from which SD_{change} can be calculated. When the within-study-correlation coefficient cannot be calculated, an average correlation coefficient will be used, based on the

other studies. This correlation coefficient will be calculated for the applicable parameters, for each group seperately.

For meta-analysis, R (The R Foundation) will be used in combination with the 'meta' and 'metafor' libraries. Raw effect size data will be imported in R and random effects meta-analysis will be performed using the Hartung-Knapp-Sidik-Jonkman estimator. Standardized mean differences and 95% confidence intervals will be reported and visualized in a forest plot.

Heterogeneity across studies will be explored by visually examining forest plots and by computing I^2, where I^2 greater than 75% indicates significant effect heterogeneity. In that case, meta-regression analyses will be considered to explore whether participant (e.g. age, BMI) or intervention level characteristics (e.g. type of exercise) explain heterogeneity in treatment effects. Publication bias will be assessed using Eggers' test and by visually exploring the funnel plots generated in R.

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APPENDICES

Appendix 1

Table 1. Search strategy in Embase

Concept	Search terms
Population	('diabetes mellitus'/de OR 'non insulin dependent diabetes mellitus'/de OR 'diabetic patient'/de OR (diabet* OR t2D OR t2dm):ab,ti) AND ('diet therapy'/de OR 'diet restriction'/de OR 'low calorie diet'/exp OR 'low fat diet'/de OR 'low carbohydrate diet'/de OR 'caloric restriction'/exp OR (((diet* OR calor* OR fat OR carbohydrate*) NEAR/3 (restrict* OR avoid* OR low)) OR (diet* NEAR/3 (interven* OR therap*))):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT (('insulin dependent diabetes mellitus'/exp OR (type-1 OR type-I OR dm-1 OR dm-I OR t1dm OR t1d OR prediabet* OR pre-diabet* OR gestation* OR Pregnan* OR maternal*):ab,ti) NOT ('non insulin dependent diabetes mellitus'/exp OR (type-2 OR type-ii OR dm-2 OR dm-ii OR t2dm OR t2d):ab,ti)) NOT ([animals]/lim NOT [humans]/lim)
Intervention	AND ('exercise'/exp OR 'kinesiotherapy'/exp OR 'physical activity'/exp OR 'sport'/de OR 'training'/de OR (exercise* OR (physical* NEAR/3 activit*) OR training OR ((Resistance* OR Strength OR Aerobic*) NEAR/3 program*) OR (Weight NEAR/3 (lift* OR bear*)) OR walking OR cycling OR running OR kinesiotherap* OR kinesitherap*):ab,ti) NOT ('bariatric surgery'/exp/mj OR 'bariatrics'/mj OR (bariatr*):ti)
RCT	AND ('Controlled clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/de OR 'Single-blind procedure'/de OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups):ab,ti,kw)
	NOT [conference abstract]/lim AND [English]/lim