Association between physical activity interventions and functional capacity in middle-aged adults and older individuals with type 2 diabetes: a protocol for a systematic review and meta-analysis of randomized or non-randomized clinical trials

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a growing health problem, with increasing proportions in the world population, with a higher prevalence in older people. This age group is also quite affected by reductions in functional performance, which seems to be more pronounced in patients with T2DM. Therefore, we aimed to summarize the potential changes (if any) in the functional capacity of middle-aged adults and older individuals with T2DM who participate in structured physical activity interventions.

Methods: This article protocol is reported based on the PRISMA-P recommendations. Comprehensive searches of the PubMed (via website), PEDro Physiotherapy Evidence Database (via website), Cochrane Library (via website), SportDiscus (via Periódicos CAPES), and Lilacs (via BVS). Open Grey and Google Scholar for grey literature will be completed using the following keywords: aging, diabetes, exercise therapy, and related entry terms. Studies to be included should consist of randomized controlled trials or non-randomized controlled studies in English, Spanish or Portuguese, with T2DM participants, of any gender, with an average age of 45 years or older; interventions with structured physical activity; with measurements of predefined outcomes of functional capacity. Relevant data will be extracted in duplicate using a customized data extraction sheet. The risk of bias of the included studies will be assessed in duplicate using the Checklist DOWNS & BLACK. If possible, with the permitted numeric data, we will carry out a meta-analysis using a random effects model (with a 95% confidence interval). Subgroup and sensitivity and meta-regression analyses will be carried out if possible. The review will be mostly based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions, Version 6.

Discussion: This systematic review aims to provide a high-quality synthesis regarding the effects of structured exercise programs on the functional capacity of middle-aged adults and older individuals with T2DM. This review may refine clinical recommendations that are still generic for the older population with T2DM.

Systematic review registration: PROSPERO CRD42020162467

Keywords: Aging, Type 2 diabetes mellitus, Physical activity, Functional capacity.

BACKGROUND

Diabetes mellitus is an increasingly prevalent chronic-degenerative disease, generating a burden on public health. The number of cases and the prevalence of the disease have steadily increased [1]. In 2019, the International Diabetes Federation estimated that 1 in 11 adults in the world population aged 20 to 79 lived with diabetes, equivalent to 463 million people [2]. Type 2 diabetes mellitus (T2DM) is the most common form of the disease, present in 90% - 95% of cases [3] and more prevalent in adults over 65 years [4].

Especially for the development of T2DM, age, increased life expectancy, overweight, dyslipidemia, hypertension, and physical inactivity are known risk factors [5]. Additionally, the disease costs are high both for patients and for health services [1]. Estimates show that 75% of the global health expenses with the disease in 2015 were with people aged 50 to 79 years [6]. Aging is a multifactorial process causing changes in the neuromuscular system, body composition, and metabolism. This process decreases functionality related mainly to lower limb muscle parameters such as reducing muscle strength, power, and the speed of muscle contraction and movement [7]. In addition to the common morbidities associated with the aging process, elderly people with diabetes have greater loss of muscle strength, power, and muscle mass than their peers without the disease [8–10]. The risk of physical disability for people with diabetes increases by about 50 to 80% compared to those without diabetes [11]. Compared to healthy elderly people, those who have T2DM have greater reductions in neuromuscular function [8, 12] functional status [13], as well as worse performance in functional tests [8, 12], with a tendency for disability to worsen with age [14, 15]. Thus, with the performance affected in their daily activities [8, 9], their physical activity level decreases, consequently reducing the quality of life [16]. Less is known about the link between diabetes and physical disability in middle-age, where the impact of complications associated with the disease are also less

known. However, exploratory evidence indicates that diabetes explained, to a small extent, physical disability in midlife [17]. Likewise, diabetes contributes to explaining the variance in the age trajectory of physical disability [18].

The functional capacity of the cardiovascular system, assessed by maximum oxygen consumption (VO_{2max}), also decreases with advancing age [19], being an independent risk factor for cardiovascular mortality and all-cause mortality [20, 21]. T2DM results in loss of cardiorespiratory fitness and exercise tolerance [22, 23], with evidence that maximum aerobic capacity of T2DM patients is reduced compared to individuals non-diabetics [24–26]. Additionally, the peak of oxygen consumption (VO_{2peak}) of these individuals has also been shown to be lower in T2DM individuals than in non-diabetic individuals [26]. These alterations in the functional capacity of the cardiovascular system mean an impaired exercise capacity, which may have relevant clinical consequences in addition to cardiovascular risks, such as an early reduction in the independence of daily activities.

Noted trials such as Look AHEAD Study [27] and Italian Diabetes and Exercise Study (IDES) [28] have shown that exercise/physical activity within lifestyle programs can improve physical performance in patients with T2DM [27–30]. In contrast, there are also studies that demonstrate that some physical function variables may not change after exercise or physical activity interventions [31, 32]. The importance of assessing, maintaining, and improving functional capacity in T2DM is known. But there are still no specific guidelines in this scope. To note, the strength of the relationship between physical activity and functional performance possibly varies depending on the specific measures taken and the training method selected in each study. The training specificity suggests that the performance adaptations will be greater in activities or testing that mimic the kinematics, resistance, and movement speed used in the training program [33, 34].

Our systematic review addresses functional outcomes relevant to patients with T2DM, aiming to synthesize different exercise regimens and their effects. Therefore, we will summarize the changes (if any) of different modes of exercise training in outcomes related to the functional capacity of middle-aged and elderly people with T2DM undertaking structured physical activity compared to those who do not, observing interventions and factors associated with varied effect sizes on these outcomes.

METHODS/DESIGN

The protocol for this systematic review was registered on PROSPERO (CRD42020162467) and will be reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [35]. Our methodological approach will follow the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions, Version 6.1, 2020 [36].

Aims

The primary purpose is to summarize either randomized controlled trials or non-randomized controlled studies the changes (if any) in functional capacity (functional, muscle strength, physical fitness parameters) in middle-aged adults and older individuals T2DM through a systematic review and meta-analyses of studies using structured physical activity interventions, when compared with non-training groups. The secondary specific aim is to evaluate which intervention is the most effective for these functional outcomes.

Criteria for considering studies for this review

Type of studies

We will include all randomized controlled trials (RCTs) or non-randomized controlled studies (NRS) that have been published in the journal, in English, Spanish, or Portuguese. We will include articles without year/date restriction.

Type of participants

For both groups (intervention group and the comparator group), we will consider the following criteria: middle-aged adults and older individuals (average age of 45 years or older, both gender) with a diagnosis of T2DM.

We will exclude studies in which patients are diagnosed with neurodegenerative diseases (ataxias, Alzheimer's, Parkinson's); neuromuscular diseases (congenital/progressive, for example: dystrophies, myopathies); severe cognitive impairment; severe cardiovascular

disease (congestive heart failure) or recent cardiovascular events (within the last 6 months, such as acute myocardial infarction or stroke); cancer in the treatment period.

Type of interventions

We will include all trials which reported the interventions with structured physical activity component (e.g., physical activity, strength training, power training, aerobic training or combined training; pilates, functional training, etc.,) lasting at least eight weeks, compared with a control group without physical activity/exercise component.

We will consider purely structured exercise and physical activity interventions. Lifestyle interventions will not be considered, like other interventions associated with exercise/physical activity such as diet.

Types of outcome measures

Primary Outcomes:

- i) Functional parameters evaluated by Timed Up and Go test (TUG); chair stands (5-chair stand test; 30-second chair stand test); walking performance (6-minute-walk, 400-meter walk);
- ii) Muscle strength parameters evaluated by strength isometric (handgrip); strength measures of lower limb muscle function (one repetition maximum (1RM) of knee extension and leg-press);
- iii) Physical fitness parameter evaluated by maximal oxygen consumption (VO₂max, VO₂peak).

Search methods for identification of studies

The systematic electronic search will be conducted in the following databases: PubMed (via website), PEDro Physiotherapy Evidence Database (via website), Cochrane Library (via website), SportDiscus (via Periódicos CAPES), and Lilacs (via BVS). Open Grey and Google

Scholar for grey literature. All searches will be conducted from inception until 13 December 2019.

The search strategies will be developed using medical subject headings (MeSH) and text words. MESH DESCRIPTOR and EXPLODE TREES were used for terms: Aged, Exercise Therapy, Exercise Movement Techniques, Exercise. For the other terms the title (TI) or title and abstract (TIAB) field was used that will be combined with words to exclude studies other than clinical trials.

PubMed search strategy is described in table 1.

Table 1 PubMed Search Strategy	
Aged	1.(Aged[Mesh] OR Aged[tiab] OR Elderly[tiab] OR Older[tiab] OR "Older Adults"[tiab] OR "Frail Older"[tiab] OR Aging[tiab] OR "Frail Elderly"[tiab] OR "Seniors"[tiab])
Diabetes	2.("Diabetes"[tiab] OR "Mellitus"[tiab] OR "Non Insulin Dependent"[tiab] OR "T2DM"[tiab] OR "Diabetic*"[tiab] OR "Diabetes Mellitus Noninsulin Dependent"[tiab])
Exercise Therapy	3.("Exercise Therapy"[Mesh] OR "Exercise Therapy"[tiab] OR "Exercise Movement Techniques"[Mesh] OR Pilates[tiab] OR "Combined Training"[tiab] OR "Concurrent Training"[tiab] OR "Power Training"[tiab] OR "High-intensity Power Training"[tiab] OR "High-Velocity Resistance Exercise"[tiab] OR "Resistance Training"[Mesh] OR "Resistance Training"[tiab] OR "Exercise"[Mesh] OR "Exercise"[tiab] OR Exercises[tiab] OR "Isometric Exercise"[tiab] OR "Aerobic Exercise"[tiab] OR "Aerobic Exercises"[tiab] OR "Aerobic Exercise"[tiab] OR "Training Resistance" [tiab] OR "Strength Training"[tiab] OR "Weight Lifting"[tiab] OR "Strengthening Program" [tiab] OR "Strengthening Programs"[tiab] OR "Physical Exercise"[tiab] OR "Physical Exercises"[tiab] OR "Physical Activity"[tiab] OR "Physical Activities"[tiab])
Studies not included	4.(Review[ti] OR Cohort[ti] OR Cross-sectional[ti] OR "Observational"[ti] OR Case-control[ti] OR "Case report"[ti] OR Meta-analysis[ti] OR Synthesis[ti] OR Consensus[ti])
Final Search	#1 AND #2 AND #3 NOT #4

Data collection and analysis

Selection of studies

The entire review process will be conducted by pairs of independent reviewers.

Pairs of reviewers will independently assess each title and abstract for suitability for inclusion according to predetermined selection criteria. A pilot screen of 400 articles, at the level of titles and abstracts, will be carried out to standardize the eligibility criteria.

After finalizing the eligibility of titles and abstracts, the full-text reading of articles potentially eligible for extraction will be carried out.

Any disagreement arising in the selection processes will be solved consensus or, if needed, by a third reviewer.

Data extraction and management

Peers reviewers will data extract from studies independently. This process will be carried out in standardized coded data extraction sheet, which includes general characteristics of included trials (e.g., author, year of publication, journal, total sample size, etc.); details of participants (e.g., gender, age, health-related data, etc.); details of interventions (e.g., type, duration, frequency, etc.) and outcomes (functional parameters: TUG, chair stands [5-chair stand test, 30-second chair stand test], walking performance [6-minute-walk, 400-meter walk]; muscle parameters: muscle strength [strength isometric: hand grip, strength measures of lower limb muscle function: 1RM of knee extension and leg-press]; physical fitness parameters: VO₂max, VO₂peak).

This data extraction sheet will be designed and tested before use. Differences in data extraction will be resolved by referring back to the original articles and establishing consensus. A third reviewer will be consulted to help resolve differences, if necessary.

For continuous outcomes, we will extract the results with raw data of means and standard deviations (SDs).

Quality assessment and of the risk of bias in individual studies

Paired reviewers will independently evaluate the methodological quality and risk of bias from each selected study using the Checklist DOWNS & BLACK [37], which can be used to evaluate both randomized and non-randomized controlled trials. With regard to the following items: reporting, external validity, internal validity (bias), internal validity (confounding - selection bias), and power. The last item on the checklist that examines the power of the results will be used in a simplified way for a score of 0 (no sample size calculation) or 1 (reported sample size calculation) [38]. The checklist is composed of 27 questions, with a total possible score of 28 for randomized and 25 for non-randomized studies. With the following scoring ranges: excellent (26–28); good (20–25); fair (15–19); and poor (≤ 14).

To determine the methodological quality and risk of bias of a study, for each criterion, we will evaluate the presence of sufficient information and the likelihood of potential bias. Disparities will be resolved by involving a third author.

Measures of treatment effect

For results from continuous outcomes, we will use the mean difference (if the same scale is available) or standardized mean difference (if different scales were used) with 95% confidence intervals (95% CI) [36].

Dealing with missing data

For missing data in primary studies, we will follow the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions. If data are unreported, we will contact the original authors to request the missing data, when possible, or we will carry out the imputation of the missing data with replacement values. In either case, the option adopted will be reported [36].

Data synthesis

If possible, we will perform a meta-analysis (i.e., when a group of studies is sufficiently homogeneous in terms of participants, interventions, and outcomes to provide a meaningful summary and analysis power). Statistical analysis and forest plots will be conducted using R software (version 4.0.1), using the metafor package for R.

If a combination of the studies does not make clinical sense, the meta-analysis will not be performed, and a narrative synthesis of the available data will be conducted.

A random effects model will be used. The evaluation of heterogeneity across trials will be assessed using I² statistics, which represents the proportion of heterogeneity that is not due to chance (but rather due to real differences across studies populations and interventions). The values of 0% to 40% (might not be important); 30% to 60% (may represent moderate heterogeneity); 50% to 90% (may represent substantial heterogeneity); 75% to 100% (considerable heterogeneity) [36].

Subgroup analyses and meta-regression

When sufficient data is available (at least 10 studies), we plan to perform sex-stratified subgroup analysis and meta-regression with glycated hemoglobin values.

If any subgroup analysis or meta-regression has not been specified in this protocol, but it is clearly of great importance and justified by external evidence, we will explore them and this will be reported in the final article [36].

Sensitivity analysis

If there are at least 10 studies that present data from patients with peripheral neuropathy, we plan to perform a sensitivity analysis [36] to assess whether this comorbidity may have influenced the heterogeneity of results. We also plan to conduct a sensitivity analysis for randomized and non-randomized studies. Regarding the duration of T2DM diagnosis, we plan to split study samples by short and long time durations of the disease (>8 years).

If any sensitivity analysis is not specified in this protocol, but it is clearly important to perform it, we will explore it and this will be reported in the final article [36].

We will also use the “leave-one-out” approach to check whether removing a single study at each time has a major influence (e.g., change in the direction of results) on meta-analytic estimates.

Assessment of reporting biases

If we can include at least 10 studies, we will produce a funnel plot and will analyze the funnel plot for signs of publication bias [36].

DISCUSSION

The importance of maintaining functionality in individuals with T2DM is well accepted, and the regular practice of different modes of structured exercise can contribute to improve or preserve indicators of physical function. Well-defined scientific evidence is needed to facilitate the implementation of exercise programs for distinct age groups and health service settings.

The literature shows that the results on functional outcomes in the population with T2DM are presented in a very conflicting way. This occurs both in relation to the functional capacity outcomes that are evaluated, as well as in the structured activity methods that are used in the interventions. We know that all this has to do with the training method chosen and the test that was chosen to assess the outcome of interest [39, 40].

Thus, in this systematic review, we will demonstrate different modes of structured physical activity and their influence on functional capacity (if there are gains and which they are), and which mode demonstrates the best results in functionality. Such data synthesis can provide more explicit information on the effects of different methods of structured physical activity in the functional outcomes in middle-aged adults and older individuals with T2DM.

Modifications in the following items in relation to registration in PROSPERO

Due to the COVID-19 pandemic, it was not possible to report these changes to the study protocol registered with PROSPERO. Therefore, we are recording these changes in this document. As soon as possible, changes will be made on the PROSPERO website.

Items	Modifications

1. Title	“Association between physical activity interventions and functional capacity in elderly individuals with type 2 diabetes: a systematic review and meta-analysis of randomized or non-randomized clinical trials” changed for: “Association between physical activity interventions and functional capacity in middle-aged adults and older individuals with type 2 diabetes: a protocol for a systematic review and meta-analysis of randomized or non-randomized clinical trials”
2. Age inclusion	“60 years or more” changed for: “Average age of 45 years or older”
3. Inclusion of a co-author	Beatriz D'Agord Schaan

LIST OF ABBREVIATIONS

T2DM: Type 2 diabetes mellitus

VO2max: Maximum oxygen consumption

VO2peak: Peak of oxygen consumption

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

RCTs: Randomized controlled trials

NRS: Non-randomized controlled studies

TUG: Timed Up and Go test

1RM: One repetition maximum

SDs: Standard deviations

DECLARATIONS

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and/or analyzed during the current study are available in the **Open Science Framework (OSF)** repository, available in: <https://osf.io/h47r8/>

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions:

LOP conceived the study and drafted the protocol. ATN, LXNS, DMN, CEB, JLT and BDS participated in the drafted and reviewed the protocol. DU participated in its design and coordination and helped to draft the protocol. All authors read and approved the final manuscript.

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