INPLASY PROTOCOL

To cite: Han et al. The relationship between sodium-glucose co-transporter 2 inhibitors and muscle loss in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Inplasy protocol 2022120061. doi: 10.37766/inplasy2022.12.0061

Received: 15 December 2022

Published: 15 December 2022

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Support: **No.**

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

Conflicts of interest:
None declared.

The relationship between sodium-glucose co-transporter 2 inhibitors and muscle loss in patients with type 2 diabetes mellitus: a systematic review and meta-analysis

Han, YF[1]; Yin, CH[2]; Geng, RY[3]; Liu, ZF[4]; Yu, MK[5]; Xia, CD[6].

Review question / Objective: **To assess the association between SGLT-2i treatment and muscle loss in patients with T2DM.**
Condition being studied: **Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) are a new type of oral hypoglycemic agents, which lower blood glucose primarily by promoting urinary glucose excretion and are widely used in patients with type 2 diabetes mellitus (T2DM) because of cardiovascular and renal benefits. SGLT-2i may lower blood glucose while also causing mild weight loss by altering body composition and reducing body fat mass. However, whether SGLT-2i causes muscle loss in patients with T2DM and whether there are harmful effects on muscle remain controversial.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 December 2022 and was last updated on 15 December 2022 (registration number INPLASY2022120061).

INTRODUCTION

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composition and reducing body fat mass. However, whether SGLT-2i causes muscle loss in patients with T2DM and whether there are harmful effects on muscle remain controversial.

METHODS

Participant or population: Adults with T2DM.

Intervention: SGLT-2 inhibitors including canagliflozin, dapagliflozin, empagliflozin, tofogliflozin, ipragliflozin, luseogliflozin and so on, which have been prescribed to patients with T2DM. SGLT-2 inhibitors could be used as monotherapy or add-on treatments to other interventions in any dose and frequency.

Comparator: Placebo or non-SGLT-2i diabetes drugs.

Study designs to be included: Randomized controlled trials (RCTs).

Eligibility criteria: Studies will be included in the systematic screening if they meet the following criteria: 1. the study was conducted in adults with T2DM; 2. use of SGLT-2i, including canagliflozin, dapagliflozin, empagliflozin, tofogliflozin, ipragliflozin, luseogliflozin and so on, which have been prescribed to patients with T2DM; 3. single or add-on therapy with SGLT-2i as an intervention, with no restrictions on dosage or frequency of use; 4. data on at least one of the outcome indicators of muscle mass, skeletal muscle mass, fat free mass or lean body mass was provided information on the mean and standard deviation of the change in the above outcome indicators during the study period (skeletal muscle mass was defined as lean body mass minus connective tissue, skin and other organ mass; fat free mass was defined as total body weight minus total fat mass; lean body mass was defined as body weight without fat minus total bone mass);5. the design was a randomized controlled trial. Studies will be excluded if: 1. conducted in pregnant women; 2. studied in adults with non-diabetes; 3. treated with SGLT-2i prior to the intervention; 4. combination formulations of SGLT-2i in fixed-dosage combinations with other commonly used drugs; 5. intervention period of less than 4 weeks; 6. lack of required outcome data; 7. non-randomized controlled trials; 8. duplicate reports.

Information sources: We will search six databases of PubMed, Web of science, Embase, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI) and Wan Fang Database for randomized controlled trials of SGLT-2i for T2DM, supplemented by manual searches of relevant journals from January 1, 2012, to September 1, 2022, with no language restrictions.

Main outcome(s): Change in muscle mass, skeletal muscle mass, fat free mass, or lean body mass.

Quality assessment / Risk of bias analysis: We will assess each included study's risk of bias based on a modification of the Cochrane Risk of Bias tool which consists of the following aspects: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias) and other bias. For each of these aspects, the assessment tool has three options: "low risk of bias," "unclear risk of bias," and "high risk of bias". In addition, we will use the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system to grade the quality of evidence for primary outcomes.

Strategy of data synthesis: We will use Review Manager 5.4 to synthesize the extracted data. Muscle mass, skeletal muscle mass, fat free mass and lean body mass will be considered as continuous variables, analyzed using standardized mean differences (SMD), assessed using the inverse variance. P-values and 95% confidence intervals (95% CI) will be obtained.

For studies that failed to report any critical information, we will attempt to contact the first author or the corresponding author to obtain information via emails or telephone calls.

Subgroup analysis: The heterogeneity between studies will be assessed according to I2 statistic. When heterogeneity is not significant (I2 <50%), we will use a fixed-effect model to synthesize the data. When heterogeneity is significant (I2 ≥50%), the random-effect model will be used. Subgroup analyses will be performed according to SGLT-2i alone or in combination with the intervention, measurement method, and treatment duration.

Sensitivity analysis: We will perform sensitivity analyses to assess the robustness of the meta-analysis by excluding trials with poor methodological quality (those with insufficient randomization methods and trials with selective reporting bias).

Country(ies) involved: China.

Keywords: SGLT-2i; muscle loss; type 2 diabetes mellitus; systematic review; meta-analysis.

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