

Project Title	The effect of glucose-lowering therapies on exercise capacity: A systematic review
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Lead discipline (please select one)

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| <input type="checkbox"/> Nursing and Midwifery | <input type="checkbox"/> Health Economics |
| <input type="checkbox"/> Allied Health | <input type="checkbox"/> Biostatistics |
| <input checked="" type="checkbox"/> Medicine | <input type="checkbox"/> Value-based Healthcare |
| <input type="checkbox"/> Pre-clinical | <input type="checkbox"/> Epidemiology |
| <input type="checkbox"/> Health Policy | <input type="checkbox"/> Other |

Outline of the project 250 words max

Exercise capacity (also known as cardiovascular fitness or aerobic fitness), is a well-known mortality predictor, in diabetic and non-diabetic people (1). While exercise interventions are usually planned for patients with T2DM to enhance their exercise capacity, their mental health and to promote the quality of life (2-4), little is known about the impact of other diabetes therapies on this important therapeutic strategy.

Although the strong evidence supporting the importance of exercise in T2DM management, its adoption and maintenance is often lacking. Multiple challenges to initiate and maintain regular exercise as part of a treatment plan have been identified and hence targeted behaviour-change strategies has been proposed to address lot of these challenges.(5) Could the concurrently prescribed hypoglycaemic drugs be an overlooked factor that might hinder the adoption and maintenance of exercise in patients with T2DM and hence necessitate the healthcare giver's attention?

Although the paucity of evidence examining the effect of glucose lowering therapies on exercise metabolism, metformin, the first line drug in T2DM treatment, has been shown to inhibit the mitochondrial respiratory-chain complex 1 (6) and could potentially alter exercise tolerance. Moreover, sulfonylurea has been shown to induce a rapid decrease in blood glucose levels (7) which could potentially have an indirect impact on exercise capacity. These drugs are among the commonly prescribed glucose lowering pharmacologically agents that include also dipeptidyl peptidase-IV inhibitors, glucagon-like peptide-1 receptor agonists, sodium-glucose-cotransporter-2 inhibitors and insulin.

Therefore, this project aims to investigate the current literature to gauge evidence to

synthesize a sensible idea about the effect of commonly used hypoglycaemic drugs on the ability to exercise.

Proposed research methods

Literature Search Strategy – Databases:

1. Medline (1950 to date; the US National Library of Medicine database encompassing biomedicine and health);
2. EMBASE (1980 to date; the Excerpta Medica biomedical and pharmaceutical database, including biomedical engineering and instrumentation)
3. British Nursing Index (1985 to date; database of English language nursing journals and related disciplines);
4. CINAHL (1981 to date; database of nursing and allied health-care professions)
5. The Cochrane Library (consisting of the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database and the NHS Economic Evaluation Database).

Literature Search Strategy – Keywords

These databases will be searched using the following keywords and Boolean combinations

- ‘VO₂ peak’ OR ‘VO₂ Max’ OR ‘anaerobic threshold’ OR ‘time to exhaustion’ OR ‘rating of perceived exertion’,

AND

- ‘biguanides’ OR ‘metformin’ OR ‘sulfonylurea’ OR ‘sulphonylurea’ OR ‘glinides’ OR ‘GLP-1 receptor agonist’ OR ‘Glucagon-Like Peptide 1 Receptor Agonists’ OR ‘DPP-4’ OR ‘dipeptidyl peptidase-IV inhibitors’ OR ‘SGLT-2’ OR ‘sodium-glucose-cotransporter-2 inhibitors’ OR ‘insulin treatment’.

The search will be conducted looking for English language articles. First, the titles of the articles will be screened for their relevance. The abstracts of those initially identified by title will then be screened further, and following this screening, the full text of all the articles judged to be relevant will be retrieved. Articles will be independently screened by two authors, who subsequently will retrieve abstracts, and if necessary, the full text of articles to determine suitability. Disagreement resolution will be done by another independent author.

On reading the full text, articles will be included for data analysis where they investigate the effect of a hypoglycaemic drug on the ability to exercise. Articles will be excluded where they investigate the effect of exercise on glycaemic control in synergy with the hypoglycaemic drug(s).

In order to keep the review as broad and extensive as possible (due to the paucity of evidence), studies will be included from any population, ethnicity and age group including healthy, athletes, diabetic, prediabetic patients and/or patients with any other chronic disease.

primary outcome:

VO₂peak

secondary outcomes:

VO₂ at lactate threshold, time to exhaustion, the Anaerobic Threshold (AT), pyruvate,

lactate/pyruvate ratio, insulin, glucose, respiratory exchange ratio (RER), Percent of energy from carbohydrate (CHO) and fat, heart rate, rating of perceived exertion (RPE), SBP

Data Analysis & Interpretation

Once the literature search and “citation tracking” is complete data extraction will be carried out independently by 2 authors using a preformatted data extraction spreadsheet. No assumptions or simplifications will be made during data extraction. The included studies will be assessed for risk of bias. Meta-analysis will be performed wherever adequate data were available for primary and/or secondary outcomes using Review Manager (RevMan) (v5.3)

Preferred study discipline being undertaken by the student

Medicine
Medical Science

Benefits to the student and to the department

The student will be introduced to the basics of evidence-based medicine, systematic review and meta-analysis research skills through tackling a timely, crucial and interesting research question.

The results of this project should gauge the current knowledge and hence inform healthcare professionals’ approach in promoting physical activity in patients with T2DM, should vigilance and readiness to adjust medications and/or exercise plan be needed in some cases to ensure efficient adoption and maintenance of exercise as a part of their management plan.

Alignment with Government Research Priorities 100w max

This project is concerned with optimising medications for use in people with type 2 diabetes and obesity. For this reason, the project aligns with ACT Health’s goals of value-based healthcare.

Department within ACT Health Directorate / Canberra Health Services where the student will be based

Department of Diabetes and Endocrinology.

Please submit form to preclinical.research@act.gov.au

References:

1. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *New England journal of medicine*. 2002;346(11):793-801.
2. Boulé NG, Kenny GP, Haddad E, Wells GA, Sigal RJ. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in Type 2 diabetes mellitus. *Diabetologia*. 2003;46(8):1071-81.

3. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. *Diabetes care*. 2016;39(11):2065-79.
4. Warburton DE, Bredin SS. Health benefits of physical activity: a systematic review of current systematic reviews. *Current opinion in cardiology*. 2017;32(5):541-56.
5. Williams A, Radford J, O'Brien J, Davison K. Type 2 diabetes and the medicine of exercise. *Australian Journal for General Practitioners*. 2020;49:189-93.
6. Vial G, Detaille D, Guigas B. Role of Mitochondria in the Mechanism(s) of Action of Metformin. *Frontiers in endocrinology*. 2019;10:294-.
7. Larsen JJ, Dela F, Madsbad S, Vibe-Petersen J, Galbo H. Interaction of sulfonylureas and exercise on glucose homeostasis in type 2 diabetic patients. *Diabetes care*. 1999;22(10):1647-54.