Metabolism Open 15 (2022) 100207

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.sciencedirect.com/journal/metabolism-open

SGLT2 inhibition reduces myocardial oxygen consumption

Esben Søndergaard [a,b,*], Esben S. Lauritzen [a], Katrine M. Lauritsen [a,b], Axel Åkerblom [c], Pirjo Nuutila [d], Jonas Oldgren [c], Lars C. Gormsen [e]

[a] Steno Diabetes Center, Aarhus, Denmark
[b] Danish Diabetes Academy, Odense University Hospital, Odense, Denmark
[c] Uppsala Clinical Research Center and Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[d] Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland
[e] Department of Nuclear Medicine and PET Centre, Aarhus University Hospital, Aarhus, Denmark

ARTICLE INFO

Keywords:
Myocardial external efficiency
Myocardial oxygen consumption
SGLT2 inhibitors
Type 2 diabetes
Meta-analysis

ABSTRACT

Aims/hypothesis: SGLT2 inhibition is associated with a reduced risk of cardiac disease that is still largely unexplained. According to one hypothesis, improved myocardial energetics may explain the cardioprotective effects of SGLT2i. However, recent mechanistic studies that have addressed this question have lacked the power to detect discrete but still clinically significant effects.
Methods: We pooled data from two recent randomized clinical trials and performed a meta-analysis to determine the effect of SGLT2 inhibition on myocardial oxygen consumption and myocardial external efficiency measured by positron emission tomography.
Results: SGLT2 inhibition reduced myocardial oxygen consumption (−1.06 [95%CI: 0.22–1.89] mL/100 g/min (n = 59, p = 0.01)), but did not affect myocardial external efficiency (2.22 [95%CI: 0.66-5.11] % (n = 59, p = 0.13))
Conclusions: /interpretation: SGLT2 inhibition reduces myocardial oxygen consumption at rest, which may contribute to the drugs' cardioprotective effects.

1. Introduction

Sodium–glucose cotransporter 2 inhibition (SGLT2i) has consistently been demonstrated to reduce the risk of cardiovascular disease, especially reduction in heart failure hospitalizations [1–3], but no mechanistic explanation for this effect has been convincingly established. Several hypotheses have been suggested including improvement in myocardial function and energy production [4]. Recently, our groups have published two randomized clinical SGLT2i trials (empagliflozin and dapagliflozin) addressing this hypothesis with measurements of myocardial oxygen consumption and myocardial external efficiency (MEE) (ratio between cardiac workload and oxygen consumption) by positron emission tomography (PET) [5,6]. However, both studies were relatively small and may have failed to detect discrete, but clinically significant effects of SGLT2i on myocardial energetics and myocardial blood flow. We therefore pooled our data to increase our sample size to assess whether SGLT2i has an effect on myocardial oxygen consumption and myocardial external efficiency.

2. Research design and methods

2.1. Study selection

We included the two clinical randomized placebo-controlled studies from our groups assessing myocardial oxygen consumption and MEE after treatment with a SGLT2i compared with placebo. We performed a literature search to identify other studies measuring myocardial oxygen consumption and MEE but did not find other studies.

2.2. Literature search

MEDLINE, CENTRAL and EMBASE were systematically searched with keywords and controlled vocabulary terms. Medline search strategy: (cardiac oxygen consumption OR cardiac oxygen consumption [MeSH] OR external myocardial efficiency OR external myocardial efficiency [MeSH] AND (Empagliflozin OR Dapagliflozin OR Canagliflozin OR Canagliflozin [MeSH] OR Ertugliflozin OR Sodium-Glucose

* Corresponding author. Steno Diabetes Center Aarhus, Hedeager 3, 8200 Aarhus N, Denmark.
E-mail address: esben.sondergaard@clin.au.dk (E. Søndergaard).

https://doi.org/10.1016/j.metop.2022.100207
Received 3 August 2022; Accepted 18 August 2022
Available online 23 August 2022

Transporter 2 Inhibitors OR SGLT2 inhibitors OR Sodium-Glucose Transporter 2 Inhibitors [MeSH]). EMBASE search strategy: ('sodium glucose cotransporter inhibitor'/exp OR 'sodium glucose cotransporter inhibitor' OR 'empagliflozin'/exp OR 'empagliflozin' OR 'canagliflozin'/exp OR 'canagliflozin' OR 'ertugliflozin'/exp OR 'ertugliflozin' OR 'dapagliflozin'/exp OR 'dapagliflozin') AND ('heart muscle oxygen consumption'/exp OR 'myocardial oxygen consumption' OR 'myocardial external efficiency'). CENTRAL search strategy: (MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] explode all trees OR sodium glucose cotransporter inhibitor OR SGLT2 OR 'empagliflozin' OR MeSH descriptor: [Canagliflozin] explode all trees OR 'canagliflozin' OR 'ertugliflozin' OR 'dapagliflozin') AND ('myocardial oxygen consumption' OR 'myocardial external efficiency'). Final search was conducted 07/08/2021. During the search, no filters or restrictions were applied.

2.3. Data extraction

The end-of-treatment means, mean differences and the standard deviations for the means and mean differences between SGLT2i and placebo were extracted for myocardial oxygen consumption and MEE. Left ventricular external work (LVW) was extracted and included in the analysis as supporting data. We also extracted type, dose and duration of SGLT2i treatment, number of participants, gender, age, BMI, HbA1c. Data were extracted in duplicate by ES and ESL.

2.4. Risk of bias

Risk of bias on the outcome level was evaluated by ES, AÅ and ESL by using the second version of the Cochrane risk-of-bias tool [7]. Two persons evaluated each study and did not evaluate studies they authored.

2.5. Statistics

All statistical analyses were performed in STATA 16 (StataCorp, TX, USA). As all outcomes were on the same scales, the crude mean differences between SGLT2i and placebo were used. Heterogeneity was assessed by Chi-squared tests and inconsistency by I-squared tests [8]. To account for potential clinical and methodological heterogeneity, the random effects model was applied in the meta-analyses. Data in study characteristics are means ± SD or medians (interquartile ranges).

3. Results

3.1. Study characteristics and risk of bias

Lauritsen et al. [6] conducted a placebo-controlled crossover study in which 13 individuals with T2DM were treated for 4 weeks with once-daily empagliflozin 25 mg or placebo in randomized order (10 male and 3 female; 62 ± 6 years; BMI: 31.5 ± 5.0 kg/m$^{2;}$, diabetes duration: 4.6 ± 3.0 years; HbA1c: 57 ± 6 mmol/mol). The study received low risk of bias within all domains, but only data from 10

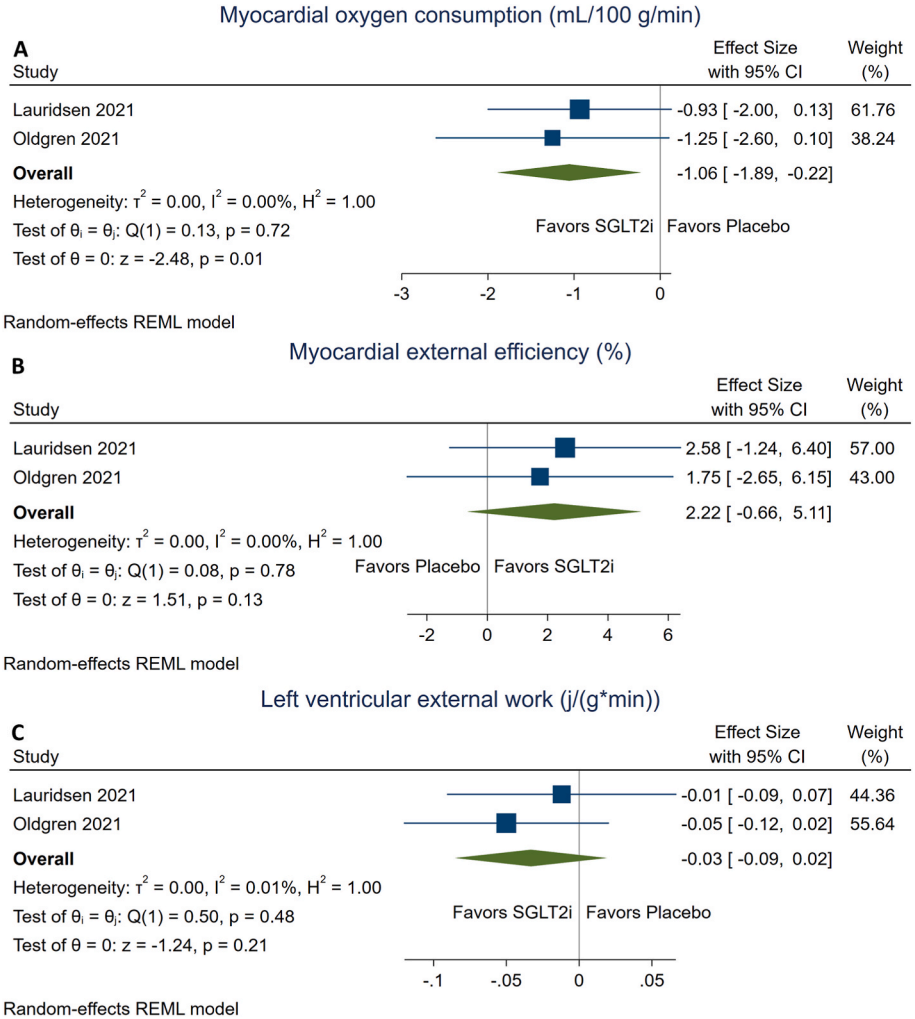

Fig. 1. Meta-analysis of A: Myocardial oxygen consumption (ml/100 g/min), B: Myocardial external efficiency (%) and C: Left ventricular external work (j/g*min). Blue squares represent the mean differences of the individual studies and the horizontal blue lines extending form the blue squares represent the 95% confidence intervals of the difference. The middle of the green diamond represents the pooled mean difference and the width of the green diamond represent the 95% confidence interval of the difference. All meta-analyses were performed with the random-effects model. Heterogeneity is evaluated with τ2, I2 and H2 analyses. "θi = θj" is the chi-squared test for homogeneity. "θ = 0" is the test of the null hypothesis. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

participants were available for the outcomes of this meta-analysis.

Oldgren et al. [5] conducted a placebo-controlled parallel-arm study in which 49 individuals with T2DM were randomized to 6 weeks with once-daily dapagliflozin 10 mg (17 male and 8 female; 64 ± 8 years; BMI: 30.2 ± 3.6 kg/m^2; diabetes duration: 5.3 (0.6–16.3) years; HbA1c: 50 ± 7 mmol/mol) or placebo (9 male and 15 female; 65 ± 7 years; BMI 30.1 ± 3.8 kg/m^2; diabetes duration 3.8 (0.7–27.8) years; HbA1c: 49 ± 8 mmol/mol). The study received low risk of bias within all domains.

3.2. Meta-analysis

There was no signs of heterogeneity or inconsistency for the analysis of myocardial oxygen consumption or MEE or LVW (Fig. 1A–C).

The crude mean differences for myocardial oxygen consumption, MEE and LVW from the individual studies together with the pooled estimates are available in Fig. 1A–C. Myocardial oxygen consumption was reduced after SGLT2i compared with placebo (n = 59, p = 0.01), but there were no significant effects of SGLT2i on MEE (n = 59, p = 0.13) and LVW (n = 59, p = 0.21).

4. Conclusions

This pooled analysis was performed to determine whether SGLT2i affects myocardial oxygen consumption and MEE. Here, we report the important novel finding that short-term SGLT2i treatment (4–6 weeks) reduces myocardial oxygen consumption in individuals with type 2 diabetes with no history of heart failure, whereas MEE and LVW are not significantly affected.

Such rapid effects of SGLT2i illustrate that the cardioprotective properties of the drug are unlikely to be caused by left ventricular remodeling or other more slowly evolving changes in myocardial function. This is also strongly supported by data from large randomized clinical trials, which show significantly reduced hospitalization for heart failure within 17 days and 28 days of treatment initiation, respectively [9,10]. The observed reduction in myocardial oxygen consumption is likely clinically relevant, since it mirrors the effect of β-blockade in individuals with aortic valve stenosis (−1.1 vs. −1.4 mL/100 g/min) [11].

No significant change in MEE was observed in the meta-analysis. Of note, the two included studies did not include patients with a history of heart failure, and an increase in an already normal MEE may therefore not be expected. It has been hypothesized that SGLT2i may improve MEE by redirecting oxidative metabolism from oxygen demanding fatty acid oxidation towards less oxygen requiring ketone body oxidation [12]. This was not observed in either of the two studies, where no change in myocardial fatty acid uptake or oxidation was observed [5,6]. However, individuals with severe heart failure take up more ketone bodies in the myocardium [13] than patients with no history of heart failure. Therefore, it is possible that MEE increases in patients with HF treated by SGLT2 inhibitors. However, subgroup analyses of the large clinical trials have shown similar cardioprotective effects of SGLT2i in individuals with and without heart failure [2,14]. This argues against a protective mechanism that is specific for individuals with heart failure.

In conclusion, SGLT2i reduces myocardial oxygen consumption at rest, which may convey a cardioprotective effect by alleviating the strain on the myocardium during times of increased oxygen demand.

Author contributions

E.S. wrote the first draft of the manuscript. E.S, K.M.L., E.S.L. A.Å, P. N., J.O., L.C.G. contributed to discussion. E.S. and E.S.L. researched the data. E.S. and L.C.G conceptualized the study. K.M.L., E.S.L. A.Å, P.N., J. O., L.C.G reviewed and edited the manuscript. L.C.G., and E.S. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Sources of funding

The study was funded by grants from The Novo Nordisk Foundation, the Danish Diabetes Academy supported by the Novo Nordisk Foundation, The Danish Council for Independent Research | Medical Sciences, the Health Research Fund of Central Denmark Region and Steno Diabetes Center Aarhus.

Declaration of competing interest

JO reports fees to his institution from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Novartis, Portola, Pfizer, Roche Diagnostics and Sanofi. AÅ has received speaker's fees and participated in Advisory Board meetings with AstraZeneca. PN reports fees to her institution from AstraZeneca and Glaxo Smith Kline PLCES. ES, ESL, KML and LCG have no financial disclosures.

References

[1] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373(22):2117–28.
[2] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2018;380(4):347–57.
[3] McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381(21):1995–2008.
[4] Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose Co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. JACC Basic Transl Sci 2020;5(6):632–44.
[5] Oldgren J, Laurila S, Åkerblom A, Latva-Rasku A, Rebelos E, Isackson H, et al. Effects of 6 weeks of treatment with dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on myocardial function and metabolism in patients with type 2 diabetes: a randomized, placebo-controlled, exploratory study. Diabetes Obes Metabol 2021;23(7):1505–17.
[6] Lauritsen KM, Nielsen BRR, Tolbod LP, Johannsen M, Hansen J, Hansen TK, et al. SGLT2 inhibition does not affect myocardial fatty acid oxidation or uptake, but reduces myocardial glucose uptake and blood flow in individuals with type 2 diabetes– a randomized double-blind, placebo-controlled crossover trial. Diabetes 2020:db200921.
[7] Sterne JACSJ, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366(I4898).
[8] Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Available from www.training.cochrane.org/handbook.
[9] Verma S, Leiter LA, Zinman B, Sharma A, Mattheus M, Fitchett D, et al. Time to cardiovascular benefits of empagliflozin: a post hoc observation from the EMPA-REG OUTCOME trial. ESC Heart Failure 2021;8(4):2603–7.
[10] Berg DD, Jhund PS, Docherty KF, Murphy SA, Verma S, Inzucchi SE, et al. Time to clinical benefit of dapagliflozin and significance of prior heart failure hospitalization in patients with heart failure with reduced ejection fraction. JAMA Cardiol 2021;6(5):499–507.
[11] Hansson NH, Sörensen J, Harms HJ, Kim WY, Nielsen R, Tolbod LP, et al. Metoprolol reduces hemodynamic and metabolic overload in asymptomatic aortic valve stenosis patients. Circulation: Cardiovascular Imaging 2017;10(10):e006557.
[12] Ferrannini E, Mark M, Mayoux E. CV protection in the EMPA-REG outcome trial: a "thrifty substrate" hypothesis. Diabetes Care 2016;39(7):1108–14.
[13] Bedi KC, Snyder NW, Brandimarto J, Aziz M, Mesaros C, Worth AJ, et al. Evidence for intramyocardial disruption of lipid metabolism and increased myocardial ketone utilization in advanced human heart failure. Circulation 2016;133(8):706–16.
[14] Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur Heart J 2016;37(19):1526–34.