Empagliflozin improves cardiorespiratory fitness in type 2 diabetes: Translational implications

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ABSTRACT (200 words)

SGLT2 inhibitors have been shown to prevent heart failure and reduce cardiovascular death in patients with type 2 diabetes (T2DM) and cardiovascular disease (CVD). Whether or not SGLT2 inhibitors improve indices of cardiorespiratory fitness (CRF), an independent predictor of mortality in patients with CVD, remains unknown.

We evaluated the effects of empagliflozin on indices of CRF in patients with T2DM. Twenty patients with T2DM received either empagliflozin 10mg or usual care. Baseline and 3 to 6-month post-treatment measurements of CRF were evaluated using CPET on a cycle ergometer.

Treatment with empagliflozin led to an increased peak oxygen consumption (VO_2), reduction in VE/VCO_2 slope and improvement in heart rate recovery.

Our results suggest that SGLT2 inhibitors may improve markers of cardiorespiratory fitness in patients with type 2 diabetes. This may help provide important clues into the mechanism of benefit of SGLT2 inhibitors in clinical trials and provide a translational framework for the ongoing large studies of SGLT2 inhibitors in the treatment of heart failure.

Keyword:

Diabetes , SGLT2 Inhibitor , Heart function , Heart failure , Cardiorespiratory fitness

INTRODUCTION

SGLT2 inhibitors have been demonstrated to prevent heart failure and reduce cardiovascular death in patients with type 2 diabetes and cardiovascular disease (CVD) (Zinman et al. 2015; Neal et al. 2017; Farkouh et al. 2018; Verma et al. 2018). While several mechanisms have been suggested (Verma et al. 2017; Byrne et al. 2017; Verma and McMurray 2018), whether or not SGLT2 inhibitors improve indices of cardiorespiratory fitness (CRF) remains unknown.

Cardiorespiratory fitness, as assessed by measuring peak oxygen consumption (VO_2) and other measured obtained through cardiopulmonary exercise testing (CPET), is an independent predictor of mortality in patients with CVD (Chaudhry et al. 2018). Moreover, evaluation of cardiorespiratory fitness, now recognized as a clinical vital sign, allows for an objective assessment of functional performance and exercise capacity (Ross et al. 2016). Peak VO_2 is also a well-accepted measure of determining response to therapy in patients with and at risk of heart failure. Pharmacotherapy, including ACE inhibitors and beta-blockers, improve markers of CRF including peak VO_2 and the minute ventilation/carbon dioxide production (VE/ VCO_2) slope (Guazzi and Arena 2009).

In the present analyses, we evaluated the effects of empagliflozin on indices of CRF in patients with type 2 diabetes, to further gain insight into the mechanisms by which empagliflozin exerts its cardioprotective effects.

METHODS

Study Design

Twenty consecutive patients with type 2 diabetes received either empagliflozin 10mg or usual care. Participants receiving usual care received standard medical therapy excluding empagliflozin for the management of diabetes and cardiovascular risk and there were no significant changes to their medication regimen during the study period. Patients were recruited from a community cardiology clinic specializing in cardiopulmonary exercise testing in Whitby, Ontario. Informed patient consent and research ethics approval were obtained.

Study Participants

Eligible patients included male and female subjects with a history of type 2 diabetes, and had either established or were considered high risk for cardiovascular disease. All patients were required to have an estimated glomerular filtration rate > 30 mL per minute per 1.73^2 of body surface area as per the product monograph.

Study Procedures

Study participants received either empagliflozin 10mg orally daily or usual care. All patients underwent CPET at baseline and three to six months post-intervention. Symptom-limited CPET was performed on an electromagnetically-braked cycle

ergometer using a customized linear-ramp protocol designed to elicit fatigue within 8 to 12 min of exercise. Details of the protocol and equipment have been described earlier (Chaudhry et al. 2009). The ventilatory anaerobic threshold (VAT) was determined using the V-slope method (Beaver et al. 1985). Breath-by-breath measured parameters and predicted equations were collected and interpreted as described by Wasserman et al. (2012). Numerical results were reported as a 10 second average and graphical results were displayed using a 20 second average. All systems were owned and operated by MET-TEST with centralized calibration and equipment performance monitoring from the data center. All technicians were trained and monitored by MET-TEST and each technician acted as a biological control for their system.

Study Outcomes

Primary outcome measures included peak oxygen consumption (VO_2) and the minute ventilation/carbon dioxide production slope (VE/ VCO_2). Secondary outcomes included additional markers of cardiorespiratory fitness such as the oxygen uptake efficiency slope (OUES), peak O2-pulse, heart rate recovery (HRR), anaerobic threshold, respiratory exchange ratio (RER), delta VO_2/delta WR.

Statistical Analysis

Independent t-tests were used to assess for differences in subjects pre and post treatment in both the treatment and control groups. A two-sided P value of less than 0.05 was considered to indicate statistical significance for all tests. All data is presented as absolute values (± standard deviation).

RESULTS

The baseline demographics of the two groups were similar (Table 1). Mean (SD) age was 67.3 (±8) and 66.4 (±10) in empagliflozin vs. usual care groups. Baseline cardiovascular risk factors, LDL-C cholesterol, blood pressure, and hemoglobin A1C, were similar between groups (Table 1). None of the patients were on diuretics.

Mean treatment duration was 170.57 (±52.63) days. Treatment with empagliflozin was associated with improved glycemic control with a reduction in HbA1c consistent with previous data although not statistically significant [8.7% [72mmol/mol] (1.5%) [16mmol/mol] to 7.9% [63mmol/mol] (0.7%) [8 mmol/mol] post, p>0.05). There were no significant differences in resting heart rate and blood pressure after treatment with empagliflozin.

For the primary outcome measure, treatment with empagliflozin led to a marked increase in peak VO_2 [16.55 ±3.48 to 20.50 ±3.85 $mLO_2 \bullet kg^{-1} \bullet min^{-1}$, p=0.01). This was coincident with a 15.8% reduction in VE/VCO_2 slope [30.24 ±3.94 to 26.12 ± 2.84, p=0.02]. Heart rate recovery (HRR) was also improved from 43.2 (±13.85) to 61.0 (±15.29) beats per minute (p=0.006) after treatment with empagliflozin, and there was also an improvement in the VO_2 at anaerobic threshold noted [11.36 (±2.19) to 13.54 (±1.73) mL/kg/min, p=0.031]. There were no significant differences found in other markers of CRF including peak end-tidal CO_2, O2 pulse at peak exercise and the oxygen uptake efficiency slope in patients treated with empagliflozin. There were no significant differences found in any markers of CRF assessed in the control group. Respiratory exchange ratio (RER) in both treatment and control groups was greater than 1.0, suggesting adequate effort for prognostic purposes. There were no significant

difference in RER or peak heart rate between baseline and follow-up with treatment with empagliflozin suggesting there was no difference in volitional effort with treatment.

DISCUSSION

To the best of our knowledge, this is the first demonstration that an SGLT2 inhibitor improves markers of cardiorespiratory fitness in humans with type 2 diabetes. The significant improvement in peak VO_2 and the VE/VCO_2 slope are independently associated with improved prognosis in patients with and without heart failure, and the fact that these changes are observed within 6 months of treatment are consistent with clinical trial data wherein the Kaplan-Meier curves for CV mortality and heart failure hospitalizations separate early after treatment initiation (Zinman et al. 2015).

Prior publications have provided mechanistic insights on how SGLT2 inhibitors improve cardiorenal outcomes (Farkouh et al. 2018; Verma et al. 2017; Verma and McMurray 2018). However, there are no data on the effects of therapy on indices of functional capacity in type 2 diabetes. Increased peak VO_2 and anaerobic threshold (AT) are both a function of peak cardiac output and peripheral extraction whereby peak VO_2 is effort dependent and AT is not and both parameters in this study are consistent with increased aerobic capacity. There was concomitant improvement in heart rate recovery (HRR). Heart rate recovery (HRR) is considered a marker of parasympathetic reactivation and there are some data to suggest poor heart rate recovery is indicative of arterial stiffness (Guazzi and Arena 2009). The improvement in HRR seen in patients treated with empagliflozin may further support the hypothesis that SGLT2 inhibition improves cardiac output secondary to an improvement in arterial stiffness. In addition,

left sided heart failure results in increased pulmonary pressure from fluid congestion thereby impairing gas exchange measured by the VE/VCO_2 slope. Improved cardiac function in patients with systolic and/or diastolic dysfunction would result in decreased pulmonary congestion and improve gas exchange efficiency as observed in this small study.

Other well-established therapies in heart failure have also been evaluated using cardiopulmonary exercise testing. Beta-blockers have not been shown to improve peak VO_2 but may decrease the VE/VCO_2 slope by approximately 9% (Chaudhry et al. 2009). ACE inhibitors increase peak VO_2 by approximately 15% and reduce VE/ VCO_2 by 11% (Chaudhry et al. 2009). We report a 23.9% increase in peak VO_2 and a 15.8% reduction in VE/ VCO_2 – effect sizes similar to these previously well validated therapies for heart failure and cardiovascular disease.

We acknowledge there are several limitations to this study. The key limitation to this study is small sample size and thus this study was not powered adequately to assess for the primary outcome. Larger studies evaluating functional capacity particularly in well-defined populations of patients with heart failure with reduced and preserved ejection fraction are currently underway (EMPERIAL – Preserved, EMPERIAL- Reduced, in progress). Moreover, all CPET data was collected by a single analyst who was not blinded to the treatment allocation. In addition, we did not collect data assessing symptom and quality of life improvement. Only 3/20 patients included in this study had evidence of systolic dysfunction and thus it is unknown whether this data can be extrapolated in the heart failure population.

CONCLUSION

In summary, although limited by a small sample size and not randomized, the present study demonstrating a marked association between empagliflozin and improvements in measures of cardiorespiratory fitness, may provide important clues into the mechanism of benefit of SGLT2 inhibitors in clinical trials. These data also provide a translational framework for the ongoing large studies of SGLT2 inhibitors in the treatment of heart failure.

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