Extended Abstract
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Clinical Cardiology Congress 2019:An Audit of Glucose Lowering Therapies In Patients With Type 2 Diabetes And Hospitalisation for Heart Failure

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Abstract

Background:
The CSANZ Heart Failure (HF) guidelines state that sodium-glucose co-transporter-2 inhibitors (SGLT2i) are the preferred second line agent in patients with type 2 diabetes mellitus (T2DM) and cardiovascular (CV) disease to reduce CV events and HF hospitalisation.
Aim: To review glucose lowering therapies in patients with T2DM who had been hospitalised with HF at Austin Health, and the percentage of patients who may be eligible for SGLT2i therapy.

Methods: A retrospective analysis of glucose lowering therapies in patients with a discharge diagnosis of HF and T2DM from 1/1/2016 to 31/12/2018. Eligibility for SGLT2i therapy was based on insufficient glycaemic control (HbA1c ≥7%), eGFR ≥30 mL/min/1.73m2 and age ≤84 years.

Results: We identified 1182 patients with T2DM who had a discharge diagnosis of HF. After exclusion of patients aged >84 years, eGFR <30 mL/min/1.73m2 and/or HbA1c <7%, 318 (27%) patients were potentially eligible for SGLT2i therapy. Of these, 36 were already on SGLT2i therapy leaving 282 (24%) patients eligible for SGLT2i therapy. They had a mean (±SD) age of 70±10 years and HbA1c of 8.6±1.8%. Medication for heart failure included diuretics (94%), ACEi/ARB (58%), beta blockers (72%). Patients were on a median of 2 glucose lowering agernts including metformin (61%), sulfonylureas (35%), gliptins (23%), GLP-1 analogues (4%), insulin (71%).

Fasting blood glucose, postprandial blood glucose and glycated haemoglobin are considered three important indicators for diabetes treatment. There is increasing evidence that glucose variability has more detrimental effects on the coronary arteries than does chronic sustained hyperglycaemia. This overview summarises recent findings in the field of glucose variability and its possible relationship with coronary artery disease. Glucose variability may be a marker of increased progression of coronary disease and plaque vulnerability. It might be a potential new therapeutic target for secondary prevention of coronary artery disease. Future studies will focus on the early detection and control of glucose variability to improve the clinical outcomes in patients with coronary artery disease. This is a retrospective observational study utilising data collected after patients had left the hospital. This study was performed on 137 non-diabetic patients undergoing coronary artery bypass grafting from January 2011 to June 2013. Blood glucose at 72 hours post operation was obtained and glucose variability was measured by mean postoperative blood glucose and mean of daily difference (MODD). Short-term outcomes included duration of intensive care unit (ICU) stay, mechanical ventilation time, length of hospital stay, and occurrence of arrhythmia. Patients with mean postoperative blood glucose ≥7.00 mmol/L were defined as hyperglycaemic, and patients with MODD ≥1.40 mmol/L were considered to be abnormal. Outcome variables were compared between patients in euglycaemic and hyperglycaemic groups, and between patients in normal and abnormal groups.

The diabetic heart is a complex entity with multiple contributing mechanisms. One of these mechanisms is the increased flux through the hexosamine biosynthesis pathway leading to O-GlcNAc post–translational modification, which has emerged as a potential therapeutic target. Two enzymes regulate this post–translational modification: O-GlcNAc transferase (OGT) facilitates the addition of the O-GlcNAc substrate to Ser/Thr residues, and O-GlcNAcase (OGA) facilitates its removal. The aim of the current study was to investigate the role of cardiac O-GlcNAc signalling in the diabetic heart. Streptozotocin-induced diabetic mice were administered a single intravenous injection of recombinant-adeno-associated-virus-6 (rAAV6)-O-GlcNAc transferase (OGT), rAAV6-O-GlcNAc-ase (OGA), or empty null-vector (2 × 10 11 vg each). Mice were then maintained for a further 8 weeks before further in vivo/ex vivo analyses. Administration of rAAV6-OGT to non–diabetic mice impaired left ventricular (LV) diastolic function (↓E/A 20 ± 10%), increased cardiac collagen content (↑177 ± 5%), and gene ANP expression (↑155 ± 73%), resembling the characteristics of diabetic cardiomyopathy (all p<0.05 vs sham-null). In contrast, administration of rAAV6-OGA to diabetic mice limited LV diastolic dysfunction (↑E/A 29 ± 15%; p = 0.05) and cardiac fibrosis (↓collagen content 73 ± 13%; p < 0.001). A more marked improvement was evident with the higher dose of rAAV6-OGA (1 × 10 12 vg) diabetic mice (↑E/A 39 ± 15%, ↓LV collagen 57 ± 10% and ↓ANP 34 ± 16%; p < 0.05, p < 0.001, and p = 0.06, respectively, vs diabetic-null). This marked improvement seen in high-dose rAAV6-OGA treated diabetic mice was accompanied by restoration of cardiac PI3Ka and its downstream target Akt signalling. In conclusion, we demonstrate that cardiac O-GlcNAc modification play a vital role in modulating characteristics of diabetic cardiomyo-

pathy, and may represent a novel therapeutic approach for diabetes-induced heart failure.

Conclusion: As many as 24% of patients with T2D and HF seen in in real world clinical practice are eligible for SGLT2i therapy. We suggest that increasing familiarity and utilisation of SGLT2i may improve cardiovascular outcomes in this high-risk population. In our study, patients with hyperglycaemia spent more time staying in ICU ($p< 0.01$), and patients with large glucose variability (abnormal MODD) had higher incidences of arrhythmia (23% vs 4.2%, $p< 0.05$). Regression analysis showed that MODD can affect occurrence of arrhythmia ($p = 0.004$) and that mean postoperative blood glucose levels can affect duration of ICU stay ($p< 0.001$).

This work is partly presented at 25th World Cardiology Conference on July 01-02, 2019