3 Year PhD Studentship available to start in September 2019

Department: Cardiovascular Sciences

Supervisors: Professor Gerry McCann gpm12@leicester.ac.uk

Eligibility: UK/EU applicants only

Project Title: Effects of a low-calorie diet in patients with type 2 diabetes and heart failure with preserved ejection fraction.

Project Description:

Pilot study of low-calorie diet Meal Replacement Plan in HFpEF patients with T2D

This project addresses a key strategic aim of the NIHR BRC: to integrate lifestyle measures across the different themes and is directly relevant to the LPMI.

Heart failure with preserved ejection fraction (HFpEF) is projected to be the predominant phenotype in the near future.[1, 2] While treatments have improved outcomes in heart failure with reduced ejection fraction, similar therapies have failed in HFpEF and there remain no specific, evidence-based treatments.[3] Despite representing 6% of the population, patients with diabetes account for one third of all patients hospitalised with HF and represent at least 40% of cases with HFpEF.[4]

Pilot data:

Characterisation of patients with Type 2 Diabetes(T2D) and HFpEF. In a CV BRU study we have phenotyped 140 patients with HFpEF, 50% (70) of whom had diabetes. Patients with diabetes were younger, more symptomatic and obese (BMI 36 v 31) with greater concentric left ventricular (LV) remodeling (mass/volume), higher LV filling pressures (E/e') but lower atrial volumes and greater systemic inflammation than non-diabetic patients (table Appendix). Similar findings have been found on echocardiography.[5] These differences highlight that mechanisms leading to HFpEF, and therefore treatments required, are likely to be different in patients with and without diabetes, and may partly explain the lack of effective treatments. One small trial has suggested that a 20-week restricted calorie diet and exercise programme may be beneficial in unselected HFpEF patients, which increased
exercise capacity but not quality of life. Moreover the dietary intervention was not pragmatic with each meal being prepared individually for subjects supervised by hospital dieticians.

**Effects of low calorie diet MRP in younger T2D.** (Figure appendix) We have confirmed previous study results that a low-calorie Meal Replacement Plan (MRP, 810kCal/day) results in dramatic weight loss, puts diabetes in remission in most patients and dramatically lowers blood pressure despite stopping most anti-hypertensives and hypoglycaemic agents.[7, 8] Blinded analysis of the cardiac MRI are underway to confirm that we will see reductions in mass/volume, diastolic dysfunction, and arterial stiffness that have been shown with weight loss in obesity, and myocardial and liver steatosis in T2D.[9-11] Moderate intensity exercise training has resulted in a 10% increase in fitness but with no effect on glycaemic control and minimal effect on blood pressure.[12] Moreover a full MRP low-calorie diet can be successfully implemented in primary care and induces remission of diabetes in 46% of patients at 12 months, and allows withdrawal of anti hypertensives in up to 50% of subjects.[13] Therefore the MRP treats underlying conditions associated with HFpEF and is likely to be a specific treatment to reverse cardiac remodelling in patients with T2D.

**Aims: To assess whether a low-calorie MRP in HFpEF with T2D:**
1. Leads to favourable cardiac remodelling
2. Improves functional capacity and quality of life
3. Shifts in metabolism from lipolytic to glycolytic pathways.
4. Undertake a systematic review of lifestyle interventions in HFpEF

**Design:** open, single arm intervention, single-centre pilot study.

**Inclusion criteria:** 1. T2D 2. Obesity (BMI > 30kg/m² or >27.5kg/m² if Asian/black). 3. Symptoms limiting exercise capacity in normal daily activities (dyspnoea or fatigue) or an established diagnosis of HF; 4. EF> 50% with objective evidence of cardiac dysfunction- left ventricular hypertrophy, > grade 2 diastolic dysfunction or reduced global longitudinal strain (>18%).

**Exclusion criteria:** 1. Unwilling to undertake low-calorie diet. 2. Weight loss > 5kg in preceding 3 months (unless related to hospitalisation for HF) 3. Contraindications to MRI. 4. Severe renal impairment eGFR<30ml/min/m²

**Intervention:** The MRP (Cambridge Weight Plan) contains ~810 kcal/day (40% protein, 50% carbohydrate, 10% fat) and complies with all current guidance and government legislation for macro- and micro nutrient content and quality.[14] The diet will be stopped, and a maintenance diet re-introduced once 50% excess body weight has been lost, or by 12 weeks, whichever comes first. Following completion of the intervention, participants will be offered the option to enter a thrice weekly, supervised 60 minute session of moderate intensity aerobic exercise, in line with prevailing guidelines. Throughout the study patients will receive health coaching and support from a dietician, and the student/clinicians as appropriate. After 12 weeks, if weight increases by more than 2.5Kg patients will be offered “rescue” MRP for 2 days per week. **Endpoints:** Will be assessed at baseline and at 12 weeks and 1 year following the intervention. 1. Clinical anthropometry (Wt, BMI; waist:hip ratio) and 24hour blood pressure 2. Imaging efficacy endpoints will include: LV mass; mass/volume; atrial volumes; myocardial strain/diastolic strain rate and myocardial perfusion reserve; adiposity. 2. Functional- exercise capacity (peak VO₂, 6 minute walk test); quality of life measures and disability free survival using the WHO Disability Assessment Schedule (WHODAS) 2.0.[15] and 3. Glycometabolic
profile (Insulin resistance; glycaemic control) and markers of LV strain/injury: BNP; high sensitivity troponin. 4. Metabolomics.

References:

Funding details:
This studentship is funded by the College of Life Sciences (CLS) and is for three years, starting by September 2019. The funding will provide a Fee waiver at UK/EU rates and a Stipend at UK Research Council rates. (for 2019/0 this will be £15,009 pa)

Entry requirements:
Applicants are required to hold/or expect to obtain a UK Bachelor Degree 2:1 or better in a relevant subject or overseas equivalent.

The University of Leicester English language requirements apply where applicable.

How to apply:
You should submit your application using our online application system.

Apply for Cardiovascular Sciences Research

In the funding section of the application, please indicate you wish to be considered for College of Life Sciences Studentship

In the proposal section please provide the name of the supervisor and project.

Include a CV and a personal statement explaining your interest in the project and why we should consider you together with all other relevant application documents.

Project / Funding Enquiries: Prof Gerry McCann gpm12@leicester.ac.uk

Application enquiries to pgradmissions@le.ac.uk

Closing date for applications 7th May 2019