**University of Leicester**

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| **Project Reference** | BRC Studentships |

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| **Additional Supervisor** | ​Professor Melanie Davies​ |

**Section 2 – *Project Information***

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| **Project Title** | Skeletal muscle pathology in obesity related conditions​ |
| **Project Highlights:** | 1. | Identifying commonalities in skeletal muscle dysfunction between obesity related conditions |
| 2. | Linking whole body insulin sensitivity to changes within skeletal muscle |
| 3. | Developing an understanding of the effect of weight loss drugs on skeletal muscle mass and function |
| **Project Summary**  |
| **Background**: ​Obesity is associated with poor outcomes and the accumulation of obesity driven long-term conditions, such as diabetes. It is also associated with profound changes within skeletal muscle that reduces physical activity, increasing morbidity and mortality and reducing quality of life. In addition, the prevalence of sarcopenia within obesity is rising, further impacting on physical function and outcomes. The mechanisms that drive obesity related changes in muscle mass and function are not completely understood. It is also unknown if there are common mechanisms between individuals with obesity with and without type 2 diabetes. Understanding this is crucial to the development of strategies to protect muscle mass in these individuals.  Weight loss drugs, such as GLP-1 receptor agonists, are commonly prescribed and effectively reduce body mass and improve insulin sensitivity, but their effects upon skeletal muscle at the tissue and cellular level is not well researched.  Weight loss may occur at the expense of skeletal muscle mass, with potential negative consequences for physical function and frailty. ​ **Aim**: ​To understand the skeletal muscle endotype of patients with obesity driven long term conditions, and the impact of weight loss drugs​ **Research Plan**: ​ * Part 1: A systematic review of the effect of obesity related conditions on skeletal muscle pathology.
* Part 2: Cohort study of individuals with BMI >30 +/- type 2 diabetes. Outcome measures: skeletal muscle biopsy, Magnetic Resonance Imaging (MRI), physical function tests, and measures of whole-body insulin sensitivity using the hyperinsulinemic clamp technique. This will allow us to map insulin resistance severity to the extent of changes within skeletal muscle. Biopsies analyzed for fibre type distribution and size with fibre specific RNA sequencing, markers of protein degradation, inflammation, mitochondrial function and intramuscular fat infiltration.
* Part 3: Longitudinal study of individuals with obesity (BMI>30) due to start on a weight loss drug (i.e. incretin based therapy, dual or triple agonists either recently been licensed or in development). Outcome measures: skeletal muscle biopsy, MRI, physical function tests, and measures of whole-body insulin sensitivity using the hyperinsulinemic clamp technique. Tests will be repeated after the individual has been on the drug for 3-months. Skeletal muscle biopsies analysed as above.​

**Expected impact**: ​Identification of different skeletal muscle endotypes in obesity related chronic disease that may help identify treatment strategies to help improve skeletal muscle health. This Understanding the effect of weight loss drugs on skeletal muscle may help develop guidance to preserve muscle mass whilst taking such medication.  |
| **References** |