TRAM (Train and Retain Academic Musculoskeletal clinicians)
MB-PhD Project Summary

PhD project Title
Skeletal Muscle Involvement In Osteogenesis Imperfecta

PhD supervisors (please provide name, affiliation and email) *[At least two supervisors]*	
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Background

Osteogenesis imperfecta (OI) is an inherited condition characterised by low bone mineral density and a predisposition to fragility fractures and bone deformities. The majority of cases of OI are due to abnormalities in connective tissue with mutations identified in the *collagen type 1* gene. Collagen type 1 forms a large proportion of the extracellular matrix of bone, and in OI the abnormal collagen leads to a state of increased bone turnover. In addition to bone deficits in OI, other tissues may also be affected by abnormal type 1 collagen, for instance in skeletal muscle. Type 1 collagen is present in the extracellular matrix of the endo-, peri-, and epimysium of muscle, as well as in the ligaments and tendons which are critical for force transfer.

Recent studies suggest that muscle deficits and weakness are present in patients with OI and may be viewed as a form of mild muscular dystrophy. Recent data from animal studies of OI also point to the evidence of metabolic dysfunction and skeletal muscle mitochondrial dysfunction. A recent study from Glasgow in ambulant children with OI (82% mild OI) showed that median lean mass index Z-score was -2.5 and 61% had Z-scores of < -2.0 (M Gilani et al J Clin Densitom 2021). Muscle weakness is believed to contribute to fatigue which is common in OI and significantly impairs quality of life. As people with OI grow older and into adulthood, there is evidence to suggest that fracture frequency is lower than in childhood. In adulthood, non-skeletal complications like muscle weakness and fatigue are of greater concern to the patient population. Muscle weakness may also perpetuate the underlying bone defect, and a greater understanding of the underlying skeletal muscle involvement in OI is, therefore, clinically relevant and may open avenues to improve therapies for people with OI. These include new pharmacological approaches but also physical therapy like exercise intervention. Preliminary results from a survey of a small group of adolescents with OI who attend the paediatric complex bone clinic in Glasgow suggest that the majority that do take part in exercise perform walking and swimming. Given the skeletal muscle deficits in OI, interventions to improve muscle mass and function are of interest. Information on physical function of these individuals and their attitude towards exercise interventions, such as resistance training, which can improve skeletal muscle and bone outcomes is unknown.

Aims

1- To evaluate differences in lean mass and fat mass in OI using DXA (retrospective analysis) with follow-up.
2- To evaluate muscle and physical function (assessments using lower limb mechanography, muscle function testing and monitored physical activity using accelerometer) in children/adolescents and adults with OI in comparison with aged and sex matched healthy controls and with follow-up.

3- To evaluate structural and metabolic skeletal muscle abnormalities using high resolution 3T MRI 31P magnetic resonance spectroscopy in a case control study of adolescents and adults with OI in comparison with healthy controls.
4- To conduct an online survey and series of qualitative interviews involving carers of children with OI and older adolescents/adults on OI on the feasibility and design of an exercise intervention study.
5- To perform a short term (4 weeks) exercise intervention pilot feasibility resistance training exercise intervention.

Training and experience provided *[Include types of methodologies that will be employed]*

The student will be exposed to a range of research skills including skills like assessment of muscle function and physical activity, paediatric bone densitometry and interpretation, high resolution MRI imaging of skeletal muscle and conduct of qualitative interviews. The student will receive formal training on research aspects of paediatric assessment of bone-muscle health from the primary supervisor(s), a paediatric bone densitometrist attached to the department and members of the MRI physics team. Opportunities to present research findings at joint meetings will be available through three monthly planned meetings. Regular (1-2 weekly) meetings with the primary supervisor will ensure that progress is checked and the student is well supported. Clinical experience is also available through the complex bone clinic at the Royal Hospital for Children Glasgow. Structured post-graduate seminars which cover other aspects of generic and transferable skills including time, project management, team working, leadership and research related skills are delivered by the University of Glasgow

Expected outcomes

The outcome of the work completed in this thesis will allow clarification of the extent of skeletal muscle deficit and the underlying mechanism in OI. Results will also inform further larger scale exercise intervention for people with OI and the intergration into clinical care. It is also anticipated that outcome measures that can be used in the clinic will be developed to allow clinical assessment of skeletal muscle/function.

References

1. M Gilani et al Evaluation of body composition in paediatric osteogenesis imperfecta. J Clin Densitom 2021
2. VL Gremminger et al Impact of intrinsic muscle weakness on muscle bone cross talk in OI. Int J Mol Sci 2021
3. VL Gremminger et al Skeletal muscle specific mitochondrial dysfunction and altered energy metabolism in a murine model of severe OI. Mol Genet Metab 2021
4. CL Phillips et al Osteogenesis imperfecta: Muscle-bone interactions when bi-directionally compromised. Curr Osteoporos Rep 2018