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

PhD project Title
Osteoporotic vertebral fracture in Duchenne Muscular Dystrophy: Frequency, predictors and impact on quality of life

PhD supervisors (please provide name, affiliation and email) *[At least two supervisors]*	
1. Dr. Jarod Wong, University of Glasgow (jarod.wong@glasgow.ac.uk)	2. Dr. Shuko Joseph, NHS Greater Glasgow & Clyde (shuko.joseph@nhs.net)
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Background

Duchenne muscular dystrophy (DMD) is a rare X-linked muscular dystrophy affecting mostly boys, where the current standard of care is with long term oral glucocorticoid as disease modifying therapy (initiated around the age of 5 years and continued indefinitely into adulthood) with proven health benefits. Muscle weakness leads to impairment in bone accrual and long-term use of oral glucocorticoid compounds the insult to the skeleton leading to high risk of skeletal fragility.

A recent study by Dr Joseph and Dr Wong showed that fragility fractures including vertebral fractures are seen in approximately 50% of young boys with DMD managed within the Scottish Muscle Network. Further published work by both supervisors utilizing clinical data from the UK NorthStar database in almost 800 boys with DMD demonstrated that fracture frequency differs in relation to GC regimen used in DMD (commonest in daily Deflazacort, followed by daily Prednisolone and lowest in intermittent Prednisolone). Vertebral fracture (VF) the hall mark and clinical diagnostic criteria of paediatric osteoporosis is very common in GC treated conditions including DMD. Identification of VF requires screening with lateral spine imaging as a proportion will be present without any symptoms of back pain. VF is often associated with chronic low grade back pain which impacts on quality of life. Severe and multiple VF may lead to kyphosis and restrictive lung disease compounding the lung disease due to the skeletal muscle weakness. Our preliminary results in a cohort of boys with DMD from Glasgow show that almost 50% have evidence of VF on spine imaging.

Current care consensus recommends IV bisphosphonate therapy upon the identification of moderate or severe vertebral fracture even without back pain. We have preliminary data to suggest that the majority of boys with DMD with moderate or severe VF experience backpain, therefore a screening spine imaging programme (as recommended by current international care consensus in DMD 2018) should identify mild vertebral fracture for bisphosphonate treatment to be initiated prior to the onset of back pain. Given the extent of osteoporotic VF in DMD, identifying predictors of vertebral fracture (clinical factors and biomarkers) may help identify a group of boys at highest risk for fractures for bisphosphonate therapy to be initiated prior to first fracture. Finally, whilst the extent and spectrum of osteoporosis is beginning to be clarified in this population, the burden of osteoporosis and its impact on quality of life of these young individuals and the family is unknown but important to guide future clinical care recommendations.

Aims

1- To compare the fracture frequency in DMD across the lifespan in comparison with healthy controls utilizing data linkage records.
2- To characterise the extent of osteoporosis in particular VF in GC treated boys with DMD with routine screening spine imaging utilizing data from a completed clinical research study, and developing a retrospective research study utilizing data from other UK North Star clinical sites.

3- To identify clinical characteristics of first VF in GC treated boys with DMD and develop a risk score.
4- To explore the role of biomarkers as predictors of VF utilising data and biological samples from a completed research study.
5- To conduct an online survey and series of qualitative interviews involving carers of boys with DMD and adolescents with DMD who have experienced painful VF; and those who have sustained a low trauma long bone fracture to evaluate burden and impact on day to day living, and also the impact of treatment with bisphosphonate therapy.

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 systematic review of the literature, large data-set analysis, vertebral fracture assessment (Genant semi-quantitative method, morphometric analysis), paediatric bone densitometry and interpretation, novel biomarkers (like microRNA) and conduct of qualitative interviews. The student will receive formal training on research aspects of paediatric assessment of bone health from the primary supervisor(s) and a paediatric bone densitometrist attached to the department. 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 joint neuromuscular-bone/endocrine paediatric and transition young adult clinics; and also the NorthStar DMD clinics. Structured post-graduate seminars which covers 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 osteoporotic VF in boys with DMD and the potential for the development of an at-risk score. The output has the potential to inform and alter international standards of care of osteoporosis in DMD. Dr. Wong is the clinical lead of the bone/endocrine working group of a national UK wide project (DMD Care UK, www.dmdcareuk.org) aiming to implement standards of care for DMD in the UK. The results generated by the student will have direct impact on clinical care. Understanding the burden of musculoskeletal complication in this population and also the treatment will allow better development of care pathways which are acceptable to the patient group. The student will also gain experience in specialised musculoskeletal research techniques but also generic research skills including scientific writing and presentation which will be beneficial for a career as an academic musculoskeletal clinician. Finally, whilst the work involves a group of patients with a rare condition, GC is used widely in growing children and adults for a whole variety of reason-GC induced osteoporosis remain the second commonest cause of osteoporosis world-wide (after post-menopausal osteoporosis).

References

1. H Martin et al. Observer agreement of vertebral fracture grading using DXA vertebral fracture assessment in DMD. J Clin Densitom 2021
2. SC Wong et al. A survey of the feasibility of developing osteoporosis clinical trials in DMD. Clin Trails 2021
3. S Joseph et al. Fracture and linear growth in a nation wide cohort of boys with DMD with and without glucocorticoid treatment. JAMA Neurol 2019
4. SC Wong et al. 236th ENMC Workshop. Bone protective therapy in DMD: Determining the feasibility and standards of clinical trials. Neuromuscul Disord 2019
5. S Joseph et al. Fractures and bone health in boys with DMD managed within the Scottish Muscle Network. Neuromuscul Disord 2019