8711 The Effect of Testosterone Therapy Upon Bone Remodelling in Testosterone Deficient APOE -/- Mice Fed a High Fat Diet [abstract only]

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Steroid Hormones_Nuclear Receptors_ and Coregulators

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The Effect of Testosterone Therapy Upon Bone Remodelling in Testosterone Deficient APOE$^{-/-}$ Mice Fed a High Fat Diet

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Introduction: Low testosterone can lead to bone loss in males, but the mechanisms are not fully characterised. This study investigates the effects of testosterone depletion, and subsequent testosterone treatment on parameters of bone

remodeling in a murine model of cardiometabolic disease. **Methods:** At 8 weeks of age, high-fat diet-fed ApoE-/- mice were randomised into three groups: sham surgery + placebo treatment (control, n=9), orchidectomy + placebo treatment (n =8), and orchidectomy + testosterone treatment (n=10). 25 week old mice were sacrificed and tissues collected for analysis. Left tibiae were decalcified, paraffin embedded and sectioned prior to immunostaining of bone turnover markers including receptor activator of nuclear factor κB ligand (RANKL), Osteoprotegerin (OPG), runx2, Alkaline Phosphatase (ALP), adiponectin and marrow lipid content. Right tibiae underwent mechanical 3-point bend testing at 0.05mm/s using a CellScale Univert. **Results:** μCT demonstrated a significant decrease in trabecular bone volume, number, and bone mineral density (BMD) and increased trabecular thickness in orchidectomised mice compared to controls. These parameters returned to control levels in testosterone treated orchiectomised mice. No significant differences were observed in cortical bone. Lipid deposition within the bone marrow was significantly increased in testosterone deficient mice compared to testosterone replete mice. No significant differences in ALP immunopositivity were detected between groups, and runx2 was significantly decreased in orchiectomised mice treated with testosterone compared to controls. The ratio of RANKL/OPG immunopositivity was significantly increased in testosterone deficient mice compared to testosterone replete mice. 3-point bending demonstrated no significant differences in maximal force between groups despite a downward trend in orchiectomised groups compared to controls. Osteoclast number quantified from TRAP-stained sections was not different between groups. ***Discussion:*** Testosterone depletion accelerates trabecular bone loss, mediated by increased osteoclastogenesis via the RANKL/OPG pathway and increased bone marrow adiposity, an effect reversed by testosterone treatment. While this study highlights the benefits of testosterone upon trabecular bone health in male mice these changes may not alter fracture risk as 3-point-bend maximal force was not affected.

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