Effects of Thyroparathyroidectomy on Clinical Pathology and Bone Density in the Rat

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1 INTRODUCTION

Parathyroid hormone is critical in the maintenance of calcium homeostasis, and in the formation and maintenance of bones. A thyroparathyroidectomy (TPTx) model can potentially be used to evaluate the efficacy of new drugs for hypoparathyroidism and hypocalcaemia. However, the model has not been well characterized and subsequently has limited translation to the clinic. The objective of the present work was to investigate the effect of TPTx on serum and urine biochemistry, bone density and bone turnover markers over a period of 5 weeks following TPTx surgery.

2 MATERIALS AND METHODS

Female Sprague-Dawley rats (N=10) had surgery (Sham or TPTx) performed at Charles River Laboratories in Raleigh, NC. Thyroxine pellets (L-thyroxine T4, 0.25mg; 60 days slow release; Cat. number: ST-131; Supplier: Innovative Research of America) were implanted subcutaneously to compensate for the removal of the thyroid gland and to ensure that any observed effects were related to PTH. Animals were fed PMI Nutrition Diet 5CR4.

Blood samples were collected at various intervals for calcium and phosphorus analysis, and urine samples were collected on Days 1, 14 and 27 for the analysis of calcium, phosphorus and creatinine levels. At termination, a blood sample was collected for a full biochemistry panel. Femurs were collected for pQCT analysis with one section obtained from the right distal femur metaphysis and analysed for total, trabecular and cortical/subcortical area, bone mineral content and bone mineral density. A second section of the diaphysis was obtained and analyzed for bone geometry parameters.

3 RESULTS

Significant decreases (2.2 to 4.8 mg/dL) in calcium levels were observed in the TPTx animals when compared to the sham controls and levels were generally unchanged over the 28 days of the study. Significant differences in serum phosphorus were also observed in the TPTx animals, with levels being higher (2.0 to 6.1 mg/dL) than sham controls (Figure 1). In urine samples, calcium (corrected for creatinine) and phosphorus (total and corrected for creatinine) were generally decreased in TPTx animals (Figure 2). At study termination, changes in biochemistry included decreased triglycerides, marginal decreases in ALP (surrogate bone formation marker) and increased creatinine and urea nitrogen (Figure 3). Changes in the bone parameters evaluated included statistically significant increases in bone mineral content (BMC) in the metaphysis (total, trabecular and cortical/subcortical sites), while bone mineral density (BMD) was statistically increased in the trabecular site only (Figure 4). No statistically significant differences were noted in bone geometry or densitometry parameters at the diaphysis. The increased BMC and/or BMD at the metaphysis is likely due to low bone turnover in the model; however, these changes are not consistent with the loss of bone reported in the clinic. The changes in creatinine and urea nitrogen suggest impaired kidney function and are consistent with clinical findings in patients with hypoprathyroidism.

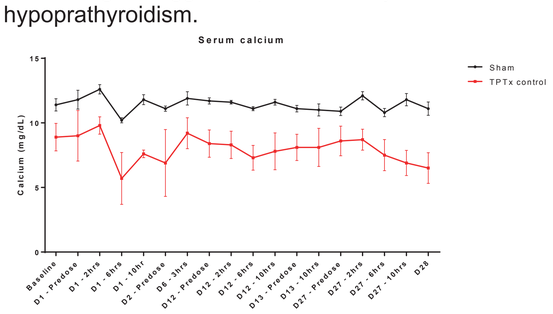

Figure 1a: Group Mean ± SD Serum Calcium Over 28 Days

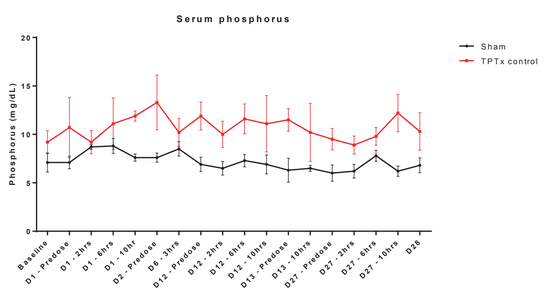

Figure 1b: Group Mean ± SD Serum Phosphorus Over 28 Days

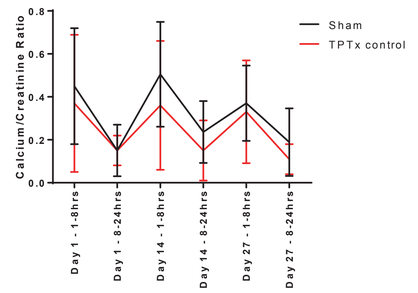

Figure 2a: Group Mean ± SD Urine Calcium/Creatinine

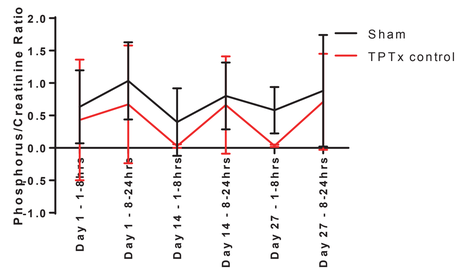

Figure 2b: Group Mean ± SD Urine Phosphorus/Creatinine

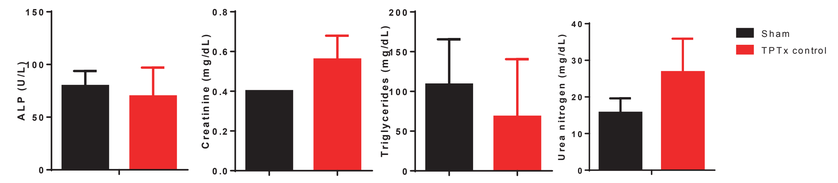

Figure 3: Group Mean ± SD Biochemistry Parameters

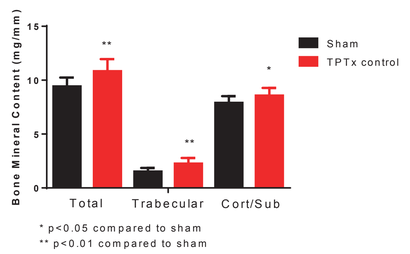

Figure 4a: Group Mean ± SD Bone Mineral Content – Femur Metaphysis

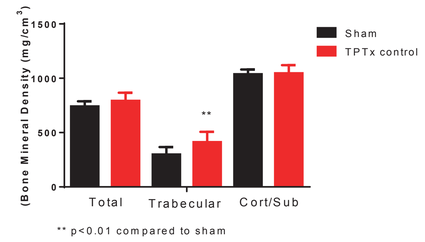

Figure 4b: Group Mean ± SD Bone Mineral Density– Femur Metaphysis

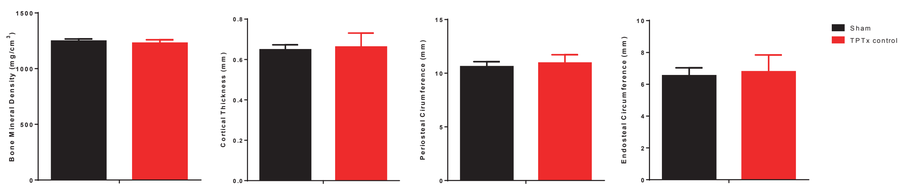

Figure 5: Group Mean ± SD Bone Density and Geometrics - Diaphysis

4 CONCLUSION

As expected, TPTx surgery followed by thyroxin supplementation had an effect on lowering serum calcium levels. The effect on kidney function was also consistent with reported findings in patients with hypoparathyroidism. However, the increases in bone density are in contrast with reported bone loss associated with clinical hypocalcaemia and hypoparathyroidism. Ongoing bone turnover evaluations will further assist in the characterization of this model.

5 ACKNOWLEDGEMENT

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