Dear CPEG Committee,

In 2020 I was very fortunate to receive funding from CPEG to complete a one-year fellowship in calcium metabolism and bone disorders. This funding also allowed me to continue my Master's Degree (MSc) in Nutritional Sciences at the University of Toronto under the supervision of Dr. Daniel Roth. Dr. Jennifer Harrington has also been an amazing mentor and co-supervised me during this year.

In addition to the opportunity to further research in this area, I was able to gain further clinical knowledge and expertise in the world of calcium and bone health. For the last 6 months of my training I was given the opportunity to independently run calcium and orthopedic bone health clinics with the support of Drs. Julia Sorbara and Etienne Sochett, whose mentorship I am thankful for.

I will always be very grateful for the opportunities I was afforded this year, the wonderful academic and clinical mentorship I received and the skills I gained to become an independent researcher and specialized clinician.

My primary project during this research year, and the main axis of my MSc, focused on infantile rickets in Dhaka Bangladesh. This was a sub-study nested in the Maternal Vitamin D for Infant Growth Trial, a randomized placebo-controlled trial carried out by Dr. Roth and his team assessing the effect of maternal vitamin D supplementation on infant linear growth. The methods and findings are outlined in the abstract below. This was presented at CPEG 2021 in addition to the Sick Kids Resident Research Day. The manuscript for publication is in preparation for review.

Understanding the Role of Maternal Vitamin D supplementation in Early Infantile Rickets in Dhaka, Bangladesh

Maria-Elena Lautatzis (1), Ulaina Tariq (2), Abdullah Al Mahmud (3), Tahmeed Ahmed (3), Farhana K. Keya (3), Carol Lam (5), Talia Wolfe (2), Shaun Morris (6), Jennifer Stimec (7), Stanley Zlotkin (2,4) Jennifer Harrington (1), Daniel E. Roth (2,4)

(1) Department of Pediatrics, Division of Endocrinology, University of Toronto, The Hospital for Sick Children, Toronto, ON, Canada(2) The Centre for Global Child Health, The Hospital for Sick Children, Toronto, ON, Canada (3) Centre for Nutrition and Food Security, International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh (4) Department of Pediatrics, University of Toronto, Toronto, ON, Canada (5) Department of Pediatrics, Division of Endocrinology, University of British Columbia, BC Children's Hospital, Vancouver, BC, Canada (6) Department of Pediatrics, Division of Infectious Diseases, University of Toronto, The Hospital for Sick Children, Toronto, ON, Canada(7) Department of Pediatrics, Body Imaging Division, University of Toronto, The Hospital for Sick Children, Toronto, ON, Canada

Background: Vitamin D deficiency remains a global health concern, even in tropical regions where sun exposure is presumed adequate; however, controversy remains around its role in rickets in low-middle income countries. In a secondary post-hoc analysis of a large maternal vitamin D supplementation trial in Bangladesh, we aimed to estimate the effect of a range of maternal vitamin D supplementation doses, compared to placebo, on risk of infantile biochemical rickets at ages 6 – 12 months.

Methods: In the Maternal Vitamin D for Infant Growth (MDIG) trial in Dhaka Bangladesh, 1300 women randomized to one of five groups of vitamin D supplementation: placebo, 4200 IU/week, 16800 IU/week, or 28000 IU/week from 2nd trimester to delivery and 28000 IU/week prenatally and 28,000 IU/week 0-6 months post-partum. The primary outcome of the rickets sub-study was 'biochemical rickets', defined as ALP >450U/L **OR** ALP >350U/L and one of: calcium <2.2mmol/L or phosphate <1.6mmol/L or PTH > 6.9pmol/L. Infants were included if they had alkaline phosphatase (ALP) measured between ages 6 – 12 months (n=790). For each vitamin D group versus placebo, we estimated the relative risk (RR) and 95% confidence interval (95%CI) of rickets using modified Poisson regression analysis.

Results: Overall, 39 of 790 infants had biochemical rickets. The highest risk was in the placebo group (7.8%), but prevalence among infants whose mothers received only pre-natal weekly vitamin D supplementation (4200 IU, 16800 IU and 28000 IU) were not significantly different: 3.8% (RR:0.48, 95%CI: 0.19,1.22), 5.8% (RR: 0.74, 95%CI: 0.33,1.69), 5.7% (RR: 0.73, 95%CI: 0.32, 1.65) respectively. However, infants whose mothers received weekly 28000 IU vitamin D3 prenatally and postnatally had a significantly lower risk of developing rickets compared to placebo (1.3%; RR:0.16, 95% CI: 0.03,0.72). Vitamin D deficiency (defined as 25-hydroxyvitamin D concentration less than 30 nmol/L) was observed at least once in most of the infants with biochemical rickets between birth and 12 months of age.

Conclusions: The risk of biochemical rickets was significantly lower in infants of mothers receiving both high dose maternal prenatal and postnatal vitamin D supplementation, versus placebo. A range of antenatal supplementation doses (4200 IU, 16800 IU, 28000 IU) used without postnatal supplementation in lactating mothers did not appear to decrease the risk of biochemical rickets significantly despite total cases of rickets in these groups being fewer compared to placebo. Further research is needed to define optimal postpartum vitamin D supplementation dosing in lactating mothers in this population.

The second and third aims of my MSc stemming from the same MDIG study are as follows, and the preparation of publications from these results are in progress.

2) To evaluate the biochemical (25(OH)D, FGF23, RANKL, OPG, osteocalcin) and anthropometric characteristics of infants who screened positive for rickets between 6 – 12 months (n=39) compared to infants who did not (n=751) around time of diagnosis using linear regression models.

3) To assess the effect of various maternal, perinatal and early/late infant factors on the relative risk of biochemical rickets. This was achieved using multivariable regression models.

During this time, I was also able to work on unrelated projects including working with Oncology colleagues on a case series looking at the presence of osteoporosis at presentation in children with osteosarcoma. The abstract below has been submitted for publication.

Bone Health in Pediatric Osteosarcoma

Authors:
Malcolmson, Caroline MD[1]; Lautatzis, Maria-Elena MD[2]; Malkiel, Sarah MD[3]; Lenherr-Taube, Nina MD[2]; Traubici, Jeffery MD[4]; Gupta, Abha MD[1]; Hopyan, Sevan MD[5]; Sochett, Etienne MD[2]; Grant, Ronald MD[1]

1) Division of Pediatric Hematology-Oncology, Department of Pediatrics, University of Toronto, The Hospital for Sick Children, Toronto, Ontario, Canada 2) Division of Pediatric Endocrinology, Department of Pediatrics, University of Toronto, The Hospital for Sick Children, Toronto, Ontario, Canada 3) The Chaim Sheba Medical Center, Department of Pediatric Hematology-Oncology, Tel-Aviv University Sackler School of Medicine, Tel-Hashomer, Israel 4) Department of Diagnostic Imaging, University of Toronto, The Hospital for Sick Children, Toronto, Ontario, Canada 5) Division of Orthopedics, Department of Surgery, University of Toronto, The Hospital for Sick Children, Toronto, Ontario, Canada

Abstract:
Osteosarcoma (OS) is the most common pediatric malignant bone tumor. Concomitant osteoporosis has typically been attributed to oncologic therapy. The present case series is aimed to describe three patients who presented with osteoporosis or osteopenia prior to, or early, in their oncology treatment. In our patients, bone health and its complications significantly impacted patients including bony pain, reduced mobility, prolonged admission, and delays in recovery. Our patients, experienced improvement in pain with resection of the tumor and bisphosphonate infusion. Future areas of study should include determination of the prevalence of bone findings and analysis of the RANKL expression in bone samples of patients who have already undergone surgical resection for dysregulation. More data is required on the role of bisphosphonates in the treatment of pediatric patients with osteosarcoma.