

Dear Canadian Pediatric Endocrine Group Fellowship Committee,

Thank you for the generous funding support provided to me through the CPEG fellowship. This grant was awarded to me in 2016 however, the funding was deferred by one year and took place from July 2017 to June 2018.

Funding from this fellowship enabled me to pursue a Master's degree through the Institute of Medical at the University of Toronto under the supervision of Dr. Jill Hamilton. My thesis centered on analysis from a collaborative study with adult researchers, which prospectively followed a longitudinal cohort of mothers with and without gestational diabetes (GDM) and their offspring. The primary goal was to understand the impact of this in-utero exposure and other early postnatal environmental factors on the outcomes of insulin sensitivity, adiposity and adipokines. My project involved participation in this ongoing cohort study with a specific focus on analysis of outcomes in offspring up to five years of age.

My primary research objective was to determine the association between *in utero* exposure to GDM on the outcome of insulin resistance (HOMA-IR) in the offspring from one to three years of age. My secondary objective was to identify the association between anthropometric measures of adiposity and cardio-metabolic health in children from one to five years of age, including (i) waist to height ratio, (ii) BMI z score, (iii) weight for length z score and (iv) sum of skin fold thickness. During this year, I gained hands on experience in data collection, study recruitment and study design. Concurrently, I completed the Clinician Investigator Program through the University of Toronto which involved online module work as well participation in academic seminars. My thesis defence was completed in July 2018.

In addition to my primary thesis work, I was also involved in other academic and clinical projects. This included a project exploring body composition in a genetically diverse cohort of children with osteogenesis imperfecta under the supervision of Dr. Jennifer Harrington as well as preparation of a manuscript evaluating the use telemedicine in pediatric obesity care. I completed a quality improvement initiative to improve illness management knowledge among patients with type 1 diabetes. Finally, this fellowship provided me with the opportunity to hone my clinical skills in the area of pediatric obesity medicine. In this report, I have summarized my thesis as well as abstracts and publications which arose from work completed during this fellowship.

Thank you again for this opportunity,

Nicole Coles

Thesis Abstract

Background: The evolution of increased cardio-metabolic risk in offspring exposed to maternal gestational diabetes (GDM) is not well understood.

Purpose: (i) To evaluate the impact of GDM exposure on insulin resistance in early childhood, and (ii) To evaluate waist-to-height ratio as a surrogate measure of cardio-metabolic risk (CMR) in children under 5 years of age.

Methods: A prospective cohort of infants born to mothers with and without GDM underwent metabolic characterization between birth and 5 years of age.

Results: Among non-GDM children, male gender predicted a 35.1% lower HOMA-IR ($p=0.03$). In GDM offspring, a 1 unit increase in maternal insulin sensitivity predicted a 17.7 % decrease in HOMA-IR ($p=0.002$). Waist-to-height ratio was not superior in predicting CMR.

Conclusions: There are no differences in IR of children with or without GDM exposure however the determinants of IR are different. BMI-z score is the preferred measure of adiposity in this age group.

Publications

Coles N, Patel BP, Li P, Cordeiro K, Steinberg A, Zdrakovic A, Hamilton JK. Breaking barriers: Adjunctive use of the Ontario Telemedicine Network (OTN) to reach adolescents with obesity living in remote locations. *J Telemed Telecare*. 2018 Dec 10.

Introduction: Implementation of telemedicine has been shown to improve health outcomes, such as BMI. However, it is unclear whether telemedicine is useful alongside traditional weight management programs for adolescents with complex obesity. The objective was to evaluate implementation of the Ontario Telemedicine Network (OTN), a video-conferencing program, as an adjunctive tool to face-to-face counselling within the setting of an established interdisciplinary obesity treatment program.

Methods: Our observational cohort included two groups of adolescents enrolled in a clinical obesity management program over a 2-year period. Adolescents (n=50) in group 1 attended both in-person and virtual visits (OTN group) and adolescents (n=50) in group 2 received only in-person visits (comparison group). Within the OTN group, satisfaction survey responses were compared between patients and health care professionals. Change in BMI per month, Pediatric Quality of Life scores, session attendance, and demographic variables were compared between groups.

Results: OTN subjects averaged 4.9 telehealth visits per adolescent over the 2-year program. Both OTN and comparison groups had similar changes in BMI ($p = 0.757$), with increases over time ($p = 0.042$). Pediatric Quality of Life scores in both groups improved over time compared to baseline ($p < 0.001$), with higher scores for children compared to parents-for-child ($p = 0.008$). Both adolescents and health care professionals using OTN were similarly satisfied with their experience.

Discussion: Adjunctive use of OTN within the setting of a weight management program is feasible, well-accepted by families and health care providers, and led to similar outcomes compared to usual care.

Coles N, Comeau I, Harrington J, Mendoza R, Schulze A, Kives S, Kamath B and Hamilton J. Severe Neonatal Cholestasis as an Early Presentation of McCune-Albright Syndrome. *Journal of Clinical Endocrinology*. *J Clin Res Pediatr Endocrinol*. 2018 Jul 11.

Background: McCune-Albright syndrome (MAS) is a rare genetic disorder characterized by café-au-lait macules, polyostotic fibrous dysplasia and multiple endocrinopathies. Liver involvement, although described, is a rare complication.

Methods: We review the case of a child with MAS whose initial presentation was characterized by severe neonatal cholestasis.

Results: The case demonstrates a severe phenotype of persistent cholestasis in MAS requiring liver transplantation, which has been previously considered to be a more benign feature.

Conclusions: This case highlights the importance of consideration of MAS as an uncommon but important etiology of neonatal cholestasis. Early diagnosis may allow for prompt recognition and treatment of other endocrinopathies.

Coles N, Retnakaran R, Hanley A, Birken C and Hamilton J. Evaluation of Anthropometric Measures for Assessment of Cardiometabolic Risk in Early Childhood. Accepted for publication in Public Health Nutrition.

Objective: Waist to height ratio has been shown to be an important indicator of cardiometabolic risk. There are few studies evaluating this measure against existing measures of adiposity and cardiometabolic markers in early childhood. The objectives were (i) to determine in young children the ability of waist to height ratio, BMI z score, weight for length and sum of skin fold thickness to predict cardiometabolic risk and (ii) to examine this association at ages one, three and five years.

Design: Prospective cohort study

Setting: University hospital in Toronto, Ontario

Participants: Infants born to mothers with and without gestational diabetes at ages one year (n=406), three years (n=112) and five years of age (n=94).

Results: Weight for length and BMI z score demonstrated the strongest correlations with biochemical measures when compared to waist to height ratio, including leptin (at five years, weight for length z score $\rho=0.65$, $p<0.001$ and BMI z score $\rho=0.67$, $p<0.001$) and measures of insulin resistance (at three years, weight for length z score $\rho=0.25$, $p=0.02$ and BMI z score $\rho=0.24$, $p=0.02$). The magnitude of the associations between the anthropometric measures and biochemical measures strengthened over time. Weight for length and BMI z score were moderately correlated with overall measures of fat mass as measured by dual energy X-ray absorptiometry ($\rho=0.65$, $p=0.00$ and $\rho=0.61$, $p=0.01$).

Conclusions: Waist-to-height ratio was not superior to existing measures in predicting cardiometabolic risk in young children. BMI z score is a preferred measure of adiposity between birth and five years of age

Poster Abstracts

Determinants of Insulin Resistance in Infants Exposed to Gestational Diabetes In Utero. Pediatric Endocrine Society. May 2018. Toronto, Ontario, Canada. Presenters: Coles, N and Hamilton J. (*Poster*)

Background: Maternal gestational diabetes (GDM) results in exposure to hyperglycemia in utero which has been associated with increased adiposity and diabetes in the offspring later in life. The timing and evolution of these changes during early childhood are not well understood.

Objective: To evaluate the impact of exposure to GDM in utero on insulin resistance in childhood.

Design/Methods: A prospective, observational cohort of infants born to mothers with GDM and without GDM underwent anthropometric and metabolic characterization between birth and 3 years of age. Associations between anthropometric measures and insulin resistance (HOMA-IR) were evaluated over time.

Results: A total of 84 infants (38 GDM; 46 non-GDM) had fasting blood work and anthropometry at 3 years of age. Infants born to mothers with GDM were born earlier (38.4 ± 1.3 vs. 39.0 ± 1.3 weeks, $p < 0.0001$), at a lower birth weight (3302 ± 389 vs. 3464 ± 441 g, $p < 0.0001$) and were less likely to be exclusively breastfed (39.73% vs. 51.95% , $p = 0.006$).

At 3 months of age, GDM offspring weighed less when compared to unexposed infants (6.24 ± 0.84 vs 6.44 ± 0.96 kg, $p = 0.0082$). After early infancy, there were no significant differences in anthropometric measures or HOMA-IR between the two groups to age 3 years. Multiple regression analysis of insulin resistance at 3 years of age demonstrated different determinants of HOMA-IR in infants born to women with and without GDM. After adjusting for maternal obesity, 1 kg of offspring weight gain in early childhood predicted a 12% higher HOMA-IR at 3 years of age ($p = 0.0164$) in children born to women without GDM. Whereas, in offspring exposed to GDM, a 1 unit increase in maternal insulin sensitivity predicted a 22% decrease in HOMA-IR ($p = 0.0003$).

Conclusion(s): At 3 years of age, there are no appreciable differences in the growth parameters or insulin resistance of children with or without GDM exposure during pregnancy. However, maternal insulin sensitivity independently predicts HOMA-IR in children exposed to GDM whereas post-natal infant weight gain is significantly associated with HOMA-IR in the offspring of non-GDM pregnancies. These findings suggest that pathways to the development of IR are different in GDM vs non-GDM offspring.

Evaluation of Obesity and Body Composition in a Genetically Diverse Cohort of Children with Osteogenesis Imperfecta. Pediatric Endocrine Society. May 2018. Toronto, Ontario, Canada. Presenters: Coles N, Alsubaihin A, Howard A, Sochett E and Harrington J. (*Poster*)

Background: A small number of studies have described increased prevalence of obesity in OI, particularly among those with OI Type-III. Little is known about body composition in children with rare, autosomal recessive forms of OI.

Objective: To describe the prevalence of obesity in a genetically diverse cohort of children with OI and to understand the differences in body composition in patients with OI according to disease severity, mobility and genotype.

Design/Methods: Retrospective review of 109 patients with OI followed at the Hospital for Sick Children from 1998 to 2017. Anthropometric and body composition data derived from dual energy X-ray absorptiometry scan were collected from the most recent clinic visit and analyzed cross-sectionally.

Results: These results are derived from a preliminary analysis of 57 patients. The prevalence of children with overweight and obesity was 43.9% in children 5 to 18 years, as defined by BMI z score. Increasing age was correlated with higher BMI z scores ($r^2 0.17$, $p = 0.019$) and higher percent fat mass z scores

(PFM) ($r^2=0.053$, $p=0.001$). BMI z scores were associated with PFM z scores ($r^2=0.661$). Overall height, weight and lean mass index (LMI, lean mass/height²) z scores in the cohort were lower compared to the normal population (-1.95 ± 3.02 , $p<0.0001$, -0.73 ± 1.43 , $p<0.0001$ and -1.09 ± 1.31 $p<0.001$). Overall PFM z scores were higher (0.43 ± 1.17 , $p=0.016$) with no difference in BMI z scores (0.33 ± 1.40 $p=0.084$). PFM, LMI and BMI z score were higher among those patients with more significant disease severity and non-ambulatory status ($p=0.001$, $p=0.003$; $p=0.005$, $p=0.01$) but no differences were observed between different OI genotypes. While, patients with non-COL1A1/COL1A2 mutations had lower height and weight z scores ($p=0.003$, $p=0.008$), there was no differences in their body composition measures when compared with patients with COL1A1/COL1A2 mutations.

Conclusion(s): Obesity is more prevalent among children with OI, with increasing BMI and PFM z scores over time. Higher disease severity and physical impairment are more significantly associated with adiposity than any particular genotype. Caution must be exercised when interpreting BMI z scores in patients with OI, particularly among those with more severe disease phenotypes.