Center for Endocrinology, Diabetes, and Metabolism Research  
Jacksonville, Florida  
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The Center for Endocrinology, Diabetes, and Metabolism Research has concentrated on studies in diabetes and disorders of growth and puberty.

“Statins in children with type 1 diabetes: effects on metabolism, inflammation and endothelial function” (N Mauras – PI) (JA Canas, Samuel Gidding, Robert Mason – Project Directors; J Ross, J Bell, M Taboada, M McCulloch – co-investigators). Funded by the Nemours Research Programs through the Cluster Grant mechanism established. This grant proposal encompasses three separate, yet interrelated, projects addressing different aspects of cardiovascular disease risk in children with type 1 diabetes. Project #1 (in collaboration with Dr. JA Canas): a randomized controlled trial on the safety and efficacy of statins in children with diabetes and elevated LDL-C. Besides changes in lipoprotein particles, we will measure changes in concentration of inflammatory markers (hsCRP) and for the first time, correlate levels of these markers with changes in the mean amplitude of glycemic excursions measured by continuous glucose sensors. Project #2 (in collaboration with Dr. Rob Mason): a laboratory project to investigate gene expression and concentration of key molecules that participate in the inflammatory cascade and atheromatous plaque formation. Toll-like receptors (TLRs) are modulated by statins and receptors for advanced glycated end products (RAGE) by glycemic excursions. These may prove to be important biomarkers to monitor the effect of statins on CVD progression in type 1 diabetes patients. Expression levels in children with type 1 diabetes will be compared with those in healthy controls for the first time. Project #3 (in collaboration with Dr. Samuel Gidding): to examine the use of abdominal aortic MRI to measure subclinical atherosclerosis and vascular stiffness in children with type 1 diabetes and healthy age-matched controls. The feasibility of cross-campus MRI calibration and reproducibility of the technique will also be established. Drs. Ross, Schiffman, Taboada, and Bell are also co-investigators. The study is ongoing and the first abstract of the baseline data will be presented at the American heart Association Meetings in November 2012.

“A randomized controlled trial of the use of aromatase inhibitors, alone and in combination with growth hormone (GH), in adolescent boys with idiopathic short stature” (N Mauras – PI) (J Ross, V Mericq, P Gagliardi, M Yu - co-investigators). Funded by the Thrasher Research Fund. This study examines the role of aromatase inhibitors in enhancing growth in adolescent boys with significant short stature. There are three arms: GH alone, aromatase inhibitors alone, and the combination for 2 years with an added year of follow up. We have recruited 75 study subjects thus far. The study is ongoing with recruitment sites in Jacksonville, FL, Philadelphia, PA and Santiago, Chile.

“Hypoglycemia in children and adolescents with type 1 diabetes: mechanisms and prevention: the Diabetes Research in Children Network (DirecNet)” (N Mauras – PI) – National Institutes of Health. This is a five-center consortium of clinical pediatric endocrinology centers plus a coordinating center. Dr. Mauras is also the chair of the protocol development committee for a protocol entitled, “Brain anatomy and function: relation to glycemia in young T1DM children.” This is an ambitious study performing brain magnetic resonance imaging (unsedated) and neurocognitive testing in young kids with diabetes and findings correlated with extensive measures of dysglycemia using continuous glucose monitoring (CGM). Important differences between the brain of children with type 1 diabetes and the non-diabetic group are being observed as well as a strong relationship with measures of glycemia. Drs. Larry Fox in Endocrinology and Allison Cato in Neuropsychology are co-investigators and collaborators. Three abstracts were presented at the ADA and PAS meetings in 2012 and 5 manuscripts are in preparation.
As part of the same NIH-funded study (Mauras – PI), we have been conducting two other studies. One is: “Relationship between loss of β-cell function and loss of the α-cell response to hypoglycemia early in type 1 diabetes.” These are a complex series of metabolic studies assessing the dysregulation of the α-cells in type 1 diabetes, performing mixed meal tolerance tests and hypoglycemic insulin clamps in kids with type I diabetes. All recruitment has been completed, and the first installment of analysis being performed is to be presented at the ADA in June 2012. Another study, also funded by the NIH (N Mauras – PI), is entitled: “A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children (4- to 9-year-olds).” Here, we investigated the usefulness of CGM technology in the youngest children with type 1 diabetes. We have observed no improvement in glucose control in this cohort, despite specific insulin-adjusting algorithms, and despite a great deal of satisfaction with the devices used over six months. A paper was published in Diabetes Care in 2012 as well as a review paper in Endocrine.

Effects of therapeutic intervention on cardiovascular risk markers, insulin resistance, and intra-hepatic fat contents in obese children at risk for metabolic syndrome (syndrome X) (N Mauras – PI), was also funded by the Thrasher Research Fund, and all recruitment and data analysis are completed. One paper has been published in the Journal of Clinical Endocrinology and Metabolism in 2010 showing that in simple obesity (i.e., without associated glucose, lipids or blood pressure abnormalities), there is already a state of increased inflammation and prothrombosis. This is evident even in prepubertal children. Data from the follow up randomized clinical trial using diet, exercise, and Metformin for six months in patients showing these marked elevations in these markers were published in the Journal of Pediatric Endocrinology & Metabolism in 2012 and the results from the exercise and aerobic fitness work were published in Medicine and Science, Sports & Exercise in 2012.

Another grant, titled “Estrogen dosing in Turner syndrome: pharmacology and metabolism” (N Mauras- PI), is being completed with funding from the Genentech Foundation for Clinical Research in Endocrinology. The principal aim is to further define whether oral and transdermal estrogen work differently on body composition and metabolism in girls with Turner syndrome. The study also aims to better understand whether titration of the dose of estrogen can be done using sensitive estradiol assays during treatment. Dr. Martha Taboada, our former fellow, as well as Dr. Judith Ross in Philadelphia and Dr. Veronica Mericq in Chile, are co-investigators in this work. Our new fellow, Dr. Lournaris Torres, is now actively involved in the conduct of this study as well. The full PK/PD paper was just published in November 2011 in the Journal of Clinical Endocrinology & Metabolism. Data were presented at the Endocrine Society meetings in June 2012 by Dr. Lournaris Torres, one of the endocrine fellows and awarded one of the best society abstracts presented by a fellow. A manuscript is now in preparation.

A grant entitled “Dietary amino acids and insulin sensitivity in children with type 1 diabetes” (D Darmaun, N Mauras - Co-PIs) is funded by the Nemours Research Programs and received a career development award from the Thrasher Research Fund for Dr. Lournaris Torres to conduct a series of studies on the effect of the amino acid glutamine on insulin sensitivity. These are complex CRC-based studies being conducted at the Children’s Hospital CRC.
An industry-sponsored study, entitled “An open-label non-comparative, multicenter study to assess the efficacy and safety of bicalutamide when used in combination with anastrozole for the treatment of gonadotropin-independent precocious puberty in boys with testotoxicosis,” was completed in 2010. Dr. Maura was one of the authors of the completed work, published in the Journal of Pediatric Endocrinology & Metabolism in October 2010, that examines this condition. A Nemours patient with testotoxicosis is still receiving bicalutamide, a drug that blocks the virilizing effects of testosterone (the principal male hormone), and anastrozole, a drug that blocks the conversion of androgens to estrogens, hence slowing down the closure of the growth plates.

Another study funded by Abbott is titled, “A phase 3, randomized, multicenter, open-label study to evaluate the efficacy and safety of leuprolide acetate 11.25 mg and 30 mg formulation in children with central precocious puberty” (N Maura - PI, P Gagliardi- Co-I). The study was completed in 2010, and only long-term follow up is active. The paper was written, co-authored by Dr. Maura, and has just been published in the Journal of Clinical Endocrinology & Metabolism for 2012.

Dr. Fox is the PI of a study funded by the National Institutes of Health entitled: “A pilot study assessing the use of real-time continuous glucose monitoring (CGM) in adolescents with poorly-controlled type 1 diabetes mellitus.” This study assesses the safety and benefit of CGM use in adolescents and pre-teens with type 1 diabetes under poor control. Recruitment is ongoing.

Dr. Fox is also the local PI for the Type 1 Diabetes Exchange, a recently-developed national registry for patients of all ages with type 1 diabetes. This project is funded by the Leona Helmsley Foundation. This multicenter project is a national registry and will collect core clinical and laboratory data on children, adolescents, and adults with type 1 diabetes. The overall objective of the network is to improve the care of persons with type 1 diabetes by sharing best practices using a common data repository. Sub-studies that are objective-directed are being developed for various populations of participants within the Type 1 Diabetes Exchange Network. Close to *** patients have been enrolled at Nemours; approximately 20,000 participants have been enrolled nationally.

“A pilot study of the effect of continuous subcutaneous insulin infusion (CSII) in adolescents with newly-diagnosed type 1 diabetes on insulin resistance, beta-cell function and the honeymoon period” (L Fox - PI). This study was funded originally by the Nemours Research Programs and presently by development funds. The study evaluates how insulin pump therapy compares with multiple daily injections in affecting the time of onset and duration of the honeymoon period, a transient period of remission after the diagnosis of type 1 diabetes. The study also assesses whether differences in the honeymoon period are related to changes in insulin sensitivity and beta-cell function. Ten patients have been enrolled: 6 to the MDI group and 4 to the CSII group. Two more will be enrolled.

A new study (LA Fox – PI) has been recently approved and funded by the Nemours Research Programs titled “Treatment of dysglycemia using sitagliptin in adolescents with cystic fibrosis”. It will compare oral glucose tolerance tests with mixed meal tolerance tests as diagnostic tools in evaluating the abnormal glucose tolerance in adolescents with cystic fibrosis (CF). Furthermore, the project assesses whether sitagliptin, a DPP-4 inhibitor, can safely improve beta-cell function and lower postprandial glycemic excursions in children and adolescents with CF and glucose intolerance but not yet CF-related diabetes.
“Effects of a fruit and vegetable juice concentrate (FVJC) in vivo on retinol binding protein 4 and antioxidant capacity in lean and overweight boys: a pilot randomized, placebo-controlled study,” funded by the Nemours Research Programs (JA Canas - PI). This is a study of the role of natural antioxidants in childhood obesity. The study found that 6-month supplementation with FVJC in the presence of nutritional counseling was associated with an increase in serum beta-carotene concentrations and a reduction in adiposity in conjunction with an improvement in insulin resistance in overweight boys. Five abstracts and 1 paper published in The Journal of Pediatrics have resulted from this work.

“A Family Based Partial Hospitalization Program for Obese Children. A Pilot Study.”
The study was funded by an unrestricted grant from The Players Center for Child Health at Wolfson Children's Hospital. (JA Canas - co-PI). This is a randomized placebo controlled study which aims to investigate the effects of carotenoid supplementation on Omega 7 fatty acids and their binding proteins (C16:1n7-palmitoleate and FABP4) in obese children treated with an intense lifestyle intervention for a period of 6 months. The study will compare changes in abdominal fat mass measured by MRI and DEXA before and after the intervention. Acute changes in fatty acid macrophage gene expression will be assessed after 21 days of carotenoid exposure.

Robert Olney, M.D., is the PI of a study entitled: “Pharmacodynamics of C-type natriuretic peptide during growth hormone treatment in children: a potential biomarker of efficacy,” funded by Novo Nordisk and being conducted in collaboration with Children’s Hospital of Los Angeles. Early identification of patients who do not respond to growth hormone therapy could prevent unneeded cost and exposure to adverse effects. The amino-terminal propeptide of C-type natriuretic peptide (NTproCNP) is a new biomarker of growth plate activity that may fulfill this need. Previous studies have shown that NTproCNP levels correlate with height velocity in healthy children and are increased in children during growth hormone therapy. The goal of the study is to identify the ideal timing for determining NTproCNP levels after starting growth hormone therapy. We are studying children with growth hormone deficiency and idiopathic short stature who are about to initiate growth hormone treatment. Subjects are followed for one year, with frequent sampling of NTproCNP and other biomarkers of growth. The study is ongoing.

Dr. Olney is also the PI of another study, entitled “C-Type natriuretic peptide and achondroplasia,” funded by development funds. This study is being performed collaboration with the Skeletal Dysplasia Clinic at Nemours/Al duPont Hospital for Children in Delaware. Achondroplasia and hypochondroplasia are the most common forms of dwarfism. Recent studies have shown that a small hormone called C-type natriuretic peptide (CNP) is an important regulator of linear growth. We believe that genetic abnormality that causes achondroplasia and hypochondroplasia also disrupts CNP signaling, which may contribute to the growth problem. CNP has been suggested as a possible treatment for achondroplasia as well. The investigators propose to look at levels of this and other closely related hormones in children and adults with achondroplasia or hypochondroplasia to see if they are different from levels in healthy people. By studying the potential role of the CNP system in people with achondroplasia or hypochondroplasia, they hope to learn what role this hormone plays in these syndromes. Understanding this role is important if CNP is to be used as a treatment for these patients.
Dr. Olney also completed 3 projects in 2011. The study, “Amino-terminal propeptide of C-type natriuretic peptide levels in healthy children” (R. Olney - PI), funded by Quest Diagnostic Laboratory and Nemours Research Programs, measured levels of C-type natriuretic peptide (CNP) and its aminoterminal propeptide NTproCNP in a large group of healthy children to see if NTproCNP correlates with growth velocity and to define its reference range. Data confirmed that NTproCNP is the only biomarker known that correlates with height velocity in healthy children. This test may be an important new tool for the evaluation of growth and overall health in children. The study is completed, and 258 children were studied. This study is complete and was published in Clinical Endocrinology.

The study, “C-Type natriuretic peptide and skeletal growth: impact of thyroid dysfunction in prepubertal children” was run by Dr. Mitch Geffner at Children’s Hospital of Los Angeles (R. Olney – Co-I), and it was funded as an investigator-initiated project by Pfizer, Inc. It is another study of blood levels of CNP and NTproCNP in children with abnormal rates of growth due to thyroid dysfunction. They determined that these blood levels correlated with growth rates in children with thyroid disorders during treatment. This study is complete and was published in Clinical Endocrinology.

Vitamin D deficiency is a common problem, even in developed countries. In infants, it can lead to rickets, poor growth, and skeletal deformities. Dr. Matthew Benson, a Fellow in the Division of Endocrinology, in collaboration with Dr. Olney, performed a study to look at a simple urine test to screen for vitamin D deficiency in at-risk infants and toddlers. “Utility of the urine calcium-to-creatinine ratio as a screening tool for vitamin D deficiency in infants and toddlers” (R. Olney – PI, M. Benson – Co-I), was funded by the Nemours Research Programs. The study determined that urine calcium levels are too variable in healthy infants in toddlers to serve this purpose. The study is complete, and a manuscript has been published in Pediatrics & Therapeutics.

This summary does not include the Division of Endocrinology’s collaboration with other groups. It represents solely the work originated in this division at Nemours.

The success of much of the work is due in great part to the amazing contributions of our former and present fellows, Drs. Taboada (former), Dr. Benson (former), and Drs. Torres, Sarma and Dussan, as well our team of nurses, Kim Englert, Joe Permuy, Shiela Smith, Kaitlin Sikes, dietician – Emilie Balkman, and research assistants – Ms Tina Ewen and Katie Black, as well as by the Biochemical Analysis Laboratory, with the technical support of Shawn Sweeten, Carl Mann and Astride Altomare (Dr. Balagopal, Director). We also thank the talented nursing staff of the Clinical Research Center at Wolfson Children’s Hospital.

Publications

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Olney RC, Prickett TC, Espiner EA, Ross JL. C-type natriuretic peptide (CNP) levels are altered in boys with Klinefelter syndrome. J Clin Endocrinol Metab. 2012 Sep 7. [Epub ahead of print]


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