Multi-pronged Approach to Combating Type 1 Diabetes

Despite active research, efforts to prevent or completely alleviate type 1 diabetes mellitus (T1DM) have been unsuccessful, and the incidence of the disease continues to rise. At MassGeneral Hospital for Children (MGHfC), clinical and laboratory scientists engage in diverse studies designed to improve existing treatments and develop new approaches so that children with T1DM can live unencumbered and symptom-free lives. These efforts are conducted as part of MGHfC’s comprehensive Pediatric Endocrinology Program and Diabetes Center, an international referral center for the diagnosis and treatment of all endocrine-related conditions in infants, children and adolescents.

Safer Artificial Beta Cells with Viral-free Vectors

One research approach to a permanent cure of T1DM involves re-creating, regenerating or expanding the population of islet beta cells destroyed by the immune system. These cells are highly specialized and must be capable of manufacturing, transporting and releasing insulin in response to glucose. Studies have helped elucidate the mechanisms of action in these cells, including work by Lynne L. Levitsky, MD, chief of the Pediatric Endocrinology Program and Diabetes Center at MGHfC, and her collaborators at MGH/C and Harvard University.

These studies have helped clarify the role of some critical transcription factors for pancreas and liver development. One transcription factor, hepatocyte nuclear factor 4 alpha (HNF4alpha), functions in islet beta cells to maintain glucose homeostasis.1 Dr. Levitsky’s lab has designed ways to augment the activity of the HNF4alpha promoter to engineer an HNF4alpha replacement gene to help convert cognate cells into beta cells. The technique, which is being patented, has the ultimate goal of using the patient’s own cells to stimulate this activity, thereby avoiding the use of viral vectors in the delivery of transcription factors necessary to reprogram beta cells.

Bihormonal Closed-loop System Offers Better Control

The feasibility of a bionic pancreas system has been documented in adults and children, but researchers continue to search for an automated closed-loop system that safely and effectively regulates blood glucose with minimal human intervention. Physician scientists at MGH/C and bioengineers at Boston University are collaborating on just such a system. This work, involving MGH/C pediatric endocrinologist Manasi Sinha, MD, MPH, and led by Mass General adult endocrinologist Steven Russell, MD, PhD, and Boston University bioengineer Ed Damiano, PhD, focuses on a fully closed-loop bihormonal system capable of delivering insulin and glucagon based solely on sensor glucose levels. The system uses wireless communications and automated data transfer to monitor glucose levels every five minutes. It then automatically delivers proper levels of insulin to lower blood glucose, as well as glucagon to raise it in case of insulin overdelivery or delayed insulin absorption. The system contains a patient-controlled meal announcement feature.

Following inpatient testing of the bionic pancreas,2 the research group conducted two outpatient studies of the device. The first study examined the efficacy of the device in patients in a supervised outpatient environment for five days. In the second, children from 12 to 20 years old wore the bionic pancreas for five days during all activities at a summer camp. Both studies yielded improvement in blood glucose control with a decline in glycemic excursions and a decrease in hypoglycemia.

In a clinical trial currently underway, Drs. Sinha and Russell are studying absorption rates of different insulin analogs. More rapid insulin absorption would decrease the delay between control algorithm action and blood glucose response in the context of closed-loop blood glucose control, thereby improving mean blood glucose and reducing the risk of insulin stacking (piggyback doses administered before the previous bolus has finished working) and hypoglycemia. Therefore, closed-loop control might be facilitated by changing the insulin analog if significant differences exist in the absorption by analog within individuals. For additional information about this trial, see bionicpancreas.org or contact Kerry B Grennan, NP (email: kgrennan@partners.org or call 617-724-7700).
Multi-pronged Approach to Combating Type 1 Diabetes

Finding the Right Drug Combinations for Immune Therapy
Nicole Alice Sherry, MD, director of the MGH/C Diabetes Center, and her collaborators are building on immune therapy approaches to combating T1DM to find ways to regenerate beta cells in the absence of active autoimmune destruction and/or to preserve beta cells that continue to exist even after diagnosis. Immune modulators can arrest the loss of insulin secretion in T1DM, but they have not led to permanent disease remission nor to restored normal insulin secretion.

Building on small studies suggesting that short treatments with the anti-CD3 antibody teplizumab in patients with recent-onset T1DM preserved beta cells and decreased insulin needs, Dr. Sherry led MGH/C’s portion of the phase 3 Protégé trial, a double-blind, placebo-controlled, multicenter international study of safety and efficacy of teplizumab in patients with new-onset T1DM. The Protégé investigators recently announced that teplizumab reduced the loss of C-peptide and exogenous insulin needs at two years compared to placebo. They detected no new safety or tolerability issues.3

Also underway are studies of different approaches that target other immunologic processes in T1DM. Among these studies are the phase 1 RETAIN study, which is evaluating the anti-inflammatory protein alpha-1 antitrypsin in recently diagnosed T1DM patients, and the phase 2 T1DAL study, which is studying the immunosuppressive drug alefacept. Dr. Sherry is lead investigator for both studies at Mass General and MGH/C.

Type 2 Diabetes: A Disorder of Adolescence
As many as 20% of new diagnoses of diabetes in young people less than 18 years of age at MGH/C are actually of type 2 diabetes (T2DM). Dr. Levitsky and her collaborators have concluded the TODAY trial of T2DM treatment regimens in adolescents at a number of United States sites and are now moving ahead to new long-term follow-up studies of this cohort. In collaboration with MRI specialists at Brigham and Women’s Hospital, the researchers have identified cardiac fibrosis in obese adolescents with T2DM. Whether these changes can be reversed with careful control is not yet known.

Seamless Transition to Adult Care in Diabetes
The transition from pediatric to adult care is a critical time for patients with chronic diseases, as studies have shown that many patients have interruptions in care and experience worsening of disease during this period. In addition, as children with chronic conditions move from one developmental stage to another, they may face new challenges coping with and managing their disease. Under the leadership of Takara Stanley, MD, MGH/C’s Pediatric Endocrinology Program and Diabetes Center helps patients with T1DM experience a smooth transition through the developmental stages of childhood and into adulthood. The approach recognizes the unique strengths of each patient and focuses on patient-identified issues or skills. Physicians, nurses and social workers then work individually with patients and family members on these areas to provide care that is appropriate to the child’s developmental stage and that includes planning for the future.

MassGeneral Hospital for Children (MGH/C) provides multidisciplinary, personalized care for infants, children and adolescents with ambiguous genitalia in the Disorders of Sexual Development Clinic. Because MGH/C is a distinct, yet integral, part of Massachusetts General Hospital, patients with these conditions can transition seamlessly to adult care providers who know their medical history and who can easily communicate with any member of the pediatric health care team. Girls and young women with Turner syndrome, although cared for by many of the same providers, are seen separately in the Turner Syndrome Clinic.

Disorders of sexual development are rare—the most common of these disorders, congenital adrenal hyperplasia, occurs in approximately one in 15,000 live births worldwide—but high patient volumes, focused research and longevity of the MGH/C program have allowed MGH/C surgeons experience that leads to improved outcomes and that provides insight for pediatric urologists and surgeons across the country. MGH/C’s excellence in disorders of sexual development dates to the late 1960s, when William H. Hendren, MD, chief of pediatric surgery; John Crawford, MD, chief of pediatric endocrinology; and Patricia Donahoe, MD, chief of the pediatric surgery research laboratories, began focusing on surgical techniques, medical treatment and research to improve the management of patients with disorders of sexual development.

Currently these operations are performed by Rafael Pieretti, MD, chief of pediatric urology at MGH/C, who has more than 35 years of experience in pediatric surgery and pediatric urology. Lynne L. Levitsky, MD, chief of the Pediatric Endocrinology Program and Diabetes Center at MGH/C, oversees management of these conditions with her colleagues in endocrinology, genetics and psychiatry. The surgical goal of treatment is to provide each patient with normal-looking exterior genitalia and optimal sexual function with normal sensation; the medical goal is to help each family and each patient make the best possible life and gender decisions based upon previous knowledge of adult outcomes.

Adapted from Pediatric Surgery, 7th edition, Pieretti R and Donahoe P. 1

Physician scientists in the Pediatric Endocrinology Program and Diabetes Center at Mass General Hospital for Children (MGHfC) are studying the full range of neuroendocrine/bone alterations in conditions spanning the spectrum of nutritional disorders in adolescents and in type 1 diabetes (T1DM) in an attempt to identify therapies to optimize bone health. More recently, researchers in the laboratory of Madhusmita Misra, MD, have expanded their work to young athletes to define the impact of subtle energy deficit on the hypothalamic-pituitary-gonadal axis and on bone. These studies are enhanced by the high-resolution peripheral quantitative computed tomography (HR-pQCT) core at Mass General. This technology measures the microscopic internal structure of bone in the distal radius and tibia and uses mathematical modeling to assess biomechanical properties that are indicators of fracture risk. This information cannot be determined using more widely available clinical imaging techniques. Many of the group’s findings in anorexia nervosa are being incorporated into clinical practice guidelines, and investigators are working with the Female Athlete Triad Coalition to develop a position statement for return to play guidelines in amenorrheic athletes.

**Transdermal Estrogen Increases Bone Mass Accrual, Reduces Anxiety in Anorexia Nervosa**

Although data are limited regarding long-term repercussions of eating disorders on bone health, some studies have shown that bone density is lower in women who develop anorexia nervosa in their teenage years when compared to women who develop the disease as an adult, even when the duration of amenorrhea is comparable. Of concern, this condition is associated with an increased risk of fractures, both in adults and in teenagers. Dr. Misra’s lab has shown that even a year after girls with anorexia nervosa recover weight and periods, they continue to lag behind their healthy peers in bone mass accrual, indicating that some hormonal aberrations may persist despite recovery. Because the use of oral estrogen in girls with anorexia nervosa is not effective in increasing bone density, likely because oral estrogen suppresses insulin-like growth factor 1 (IGF-1), a hormone important for increasing bone formation that is already low in girls with anorexia nervosa, Mass General researchers conducted a randomized, controlled study using a transdermal estrogen patch (with cyclic progesterone) instead of oral estrogen. Unlike oral estrogen, transdermal estrogen does not suppress IGF-1. The study found that this method of estrogen delivery was effective in increasing bone mass in girls with anorexia nervosa, and the rate of increase was similar to the rate seen in normal-weight, healthy girls. This was the first study to demonstrate efficacy of a treatment strategy in increasing bone mass in teenagers with this condition. However, girls with anorexia nervosa did not completely overcome their initial bone deficit, likely because other hormonal alterations continued. Transdermal estrogen replacement also resulted in a significant reduction in trait anxiety, a common comorbidity in anorexia nervosa, and prevented the increase in body dissatisfaction observed with weight gain in those who...
received placebo. In additional studies, the group is investigating the effect of adding IGF-1 replacement to treatment with the estrogen transdermal patch; they have also studied the impact of anorexia nervosa on bone health in boys and men.

Studies Seek Solution to Bone Disorders in Amenorrheic Athletes

In 2011, Dr. Misra and her colleagues published a study that showed that the bone microarchitecture of adolescent amenorrheic athletes is impaired compared to eumenorrheic athletes. This effect is observed even in normal weight amenorrheic athletes. Abnormal bone microarchitecture is an independent determinant of fracture risk that has not been assessed previously in young athletes and nonathletes. In ongoing studies, the Misra lab is examining the mechanism of action of various hormones involved in menstrual disruption and their impact on bone density and strength, and is using the capabilities of the HR-pQCT and mathematical modeling to further characterize the phenotype of young amenorrheic athletes compared to their eumenorrheic and non-athlete peers. She is currently conducting a randomized, controlled trial of estrogen replacement (as the estrogen patch vs. the pill) on bone density and structure in normal-weight amenorrheic athletes to differentiate between the effect of athletic activity and the effect of amenorrhea on bone.

Pathogenesis of Type 1 Diabetes-associated Osteoporosis

T1DM is linked to low peak bone density and puts adults with this disease at increased risk for osteoporosis and fracture. To date, however, the pathogenesis of T1DM-associated bone fragility remains unclear, and little research attention is directed toward skeletal health during the pediatric years, a critical time for bone mineral accrual. In a clinical trial currently recruiting girls ages 10 to 16, MGH/Imperial endocrinologist Deborah Mitchell, MD, and her colleagues are using both conventional and advanced imaging techniques to longitudinally assess bone mineral content and microarchitecture in individuals with T1DM and in healthy controls. The study will also investigate how glycemic control and the hormonal environment impact bone growth and mineral accrual among patients with T1DM.

Turner Syndrome Clinic Offers a Lifetime of Coordinated Multispecialty Care

Opened in October of 2011 under the leadership of medical geneticist Angela Lin, MD, and Lynne L. Levitsky, MD, chief of pediatric endocrinology at MassGeneral Hospital for Children (MGHfC) and joined by reproductive endocrinologist Frances Hayes, MD, in 2013, the Turner Syndrome Clinic at MGHfC provides comprehensive evaluation and individualized care for newborns, toddlers and adolescents with Turner syndrome. This care brings together the specialists and subspecialists needed for each patient’s care and continues across the life span, as pediatric specialists work with adult colleagues at Mass General to ensure a comfortable transition through adolescence and into adulthood. The clinic—one of only a handful in the country to provide care across the lifespan—stresses that girls and women with Turner syndrome are healthy individuals with ongoing medical needs and provides patients with a supportive “medical home” for issues relating to Turner syndrome. The clinic’s doctors work with patients’ primary care providers to identify specialty needs and to coordinate care to improve outcomes. Individuals who do not have Turner syndrome but have been diagnosed with a disorder of sexual differentiation are seen in a separate clinic. For more information, please see massgeneralforchildren.org/TurnerSyndrome

Neuroendocrine Service Provides State-of-the-art Diagnosis and Management

MGHfC neuroendocrinologists work closely with specialists and subspecialists throughout the Mass General system to provide individualized, coordinated diagnosis, treatment planning and management of children of all ages with pituitary tumors and disorders of the hypothalamus and pituitary. Among the program’s distinguishing features are:

- The Francis H. Burr Proton Therapy Center at Massachusetts General Hospital, where radiation oncologists have long-term experience treating pediatric patients
- Transphenoidal pituitary surgery in children as young as 4 years of age and open surgery when necessary by internationally recognized surgeons including Brooke Swearingen, MD
- Seamless transition of care from pediatric to adult providers at Mass General capable of addressing the needs of each patient, including subspecialists in thyroid disease, neuroendocrinology, reproductive endocrinology, calcium disorders and other disciplines
- Community-based care for patients in locations throughout Massachusetts and in southern New Hampshire
- Clinical research designed to improve treatments, including current retrospective and prospective trials to determine the endocrine sequelae of proton beam therapy in an effort to establish testing and management guidelines for hormone deficiencies for patients who have received proton beam therapy

- For information on the long-term results of retinoblastoma patients treated with proton radiation study, please contact Madhusmita Misra, MD, MPH (mmisra@partners.org)
- For information on the endocrine dysfunctions following proton beam radiation in children and young adults with brain tumors study, please contact Rose Marino, MD (617-726-2909)
Combined Expertise of Pediatric and Adult Surgeons Improves Thyroid Surgery Outcomes in Children

The Pediatric Thyroid Surgery Program at MassGeneral Hospital for Children (MGH/C)—one of only a few such programs in the United States—is dedicated exclusively to children with thyroid conditions such as Graves’ disease, Hashimoto’s thyroiditis, hyperthyroidism, thyroid cancer, or with thyroid nodules that may require surgery. Treatment planning and clinical care includes pediatric and adult specialists from endocrinology, oncology, surgery, pathology and radiology.

Research has demonstrated that individual surgeon experience and high patient volumes are linked to improved clinical outcomes for patients with thyroid disease, including reduced incidence of injury to the recurrent laryngeal nerves and the parathyroid glands.1 While thyroidectomy is a common procedure for adult surgeons, pediatric surgeons may see only a handful of these patients during their career. This fact may impede the ability of pediatric surgeons within stand-alone pediatric hospitals to achieve the level of experience necessary for optimal outcomes.

According to the co-leaders of the program, endocrine surgeon Antonia E. Stephen, MD, and pediatric surgeon Peter Masiakos, MD, children and adolescents receiving thyroid surgery at MGH/C benefit from the combined abilities of pediatric and adult surgeons who operate from both sides of the table, thus combining the skills of practitioners with in-depth experience caring for children with those of dedicated adult thyroid surgeons who perform hundreds of these procedures each year. Advantages of this paradigm extend into post-operative care as well, because children are generally hospitalized following thyroidectomy for monitoring of calcium metabolism and to optimize pain management in a family-centered and child-friendly environment.

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THINGS TO KNOW ABOUT TURNER SYNDROME

**What Is Turner Syndrome?**

Turner syndrome is a chromosomal condition caused by the loss of an entire sex chromosome (X or Y) or a portion of the X or Y chromosome in all or some cells in the body.

**Who Has Turner Syndrome?**

Only girls and women have Turner syndrome, and it occurs in approximately one in every 2,500 female births.

**Health Concerns Associated with Turner Syndrome**

- >90% absence of normal ovarian function
- >75% frequent ear infections in childhood
- >30% congenital heart issues (bicuspid aortic valve; coarctation of the aorta)
- 30% thyroid issues (hypothyroidism)
- High blood pressure
- Diabetes
- Celiac disease
- Hearing loss
- Growth issues that may require growth hormone treatment

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**At MassGeneral Hospital for Children, surgery and post-operative care for pediatric thyroid conditions such as the thyroid nodule shown in this neck ultrasound (see arrow), combines the expertise of pediatric surgeons and adult surgeons specializing in thyroidectomies. This integrated approach leads to optimal outcomes.**
In This Issue:
Updates in Pediatric Endocrinology and Diabetes

This issue of Cascades summarizes current and ongoing studies within the Pediatric Endocrine Program and Diabetes Center at MassGeneral Hospital for Children (MGHfC). Physicians within this international referral center specialize in the diagnosis and treatment of all endocrine-related conditions of infants, children and adolescents, and are dedicated to working collaboratively with primary care physicians, other specialty caregivers, and patients and families to deliver the highest quality of care.

Clinical and laboratory research efforts within the Pediatric Endocrine Program and Diabetes Center are aimed at improving treatments for disorders of sexual development, growth, calcium and bone metabolism, puberty and disorders of the thyroid and pituitary, as well as for diabetes. Current clinical and research highlights in these areas include:

- Outpatient testing of a fully closed-loop biohormonal "bionic pancreas" and advances in β-cell re-creation and immune therapy in type 1 diabetes
- Bone density and fracture risk assessment using HR-pQCT technology available at Mass General in children with type 1 diabetes, nutrition disorders ranging from anorexia nervosa to obesity, and in amenorrheic athletes
- A dedicated wellness center for girls and young women with Turner syndrome
- Integrated adult and pediatric surgical teams to address the surgical and post-operative needs of children and adolescents requiring surgery for thyroid conditions
- Unique, comprehensive, state-of-the art care for pediatric patients needing pituitary surgery, including proton beam therapy and transphenoidal pituitary surgery for children as young as 4 years of age