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An Update from the Division of Pediatric Endocrinology, Diabetes, and Metabolism

About the Division

The Division of Pediatric Endocrinology, Diabetes, and Metabolism at Children's Hospital of Pittsburgh of UPMC provides diagnostic and therapeutic services for children with diabetes mellitus, hypoglycemia, and disorders of physical growth, sexual maturation, thyroid function, pituitary function, and calcium and phosphorous metabolism, as well as other gender disorders. Patients are evaluated in collaboration with multi-disciplinary teams to come to a unifying diagnosis and provide the best outcomes for patients and families.

For a referral or consultation, please contact us at 412-692-5170. Visit us online at **CHP.edu/diabetes**.

Children's Hospital of Pittsburgh of UPMC

Total Pancreatectomy and Islet Auto Transplant (TPIAT)

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Introduction

Chronic pancreatitis in children is an inflammation of the pancreas that becomes worse over time. It is rare in the pediatric age group, and it is often hereditary in nature. It is a devastating disease. Affected patients suffer recurrent episodes of abdominal pain and gastrointestinal symptoms that usually require multiple hospitalizations, endoscopic GI procedures, and narcotics to control the pain. Chronic pancreatitis greatly impairs the quality of life for children and their families. Additionally, a subset of children with chronic pancreatitis have malabsorption, which may adversely affect growth and weight gain. Diabetes mellitus, liver dysfunction, and (though very rare in pediatrics) pancreatic cancer can complicate the course of the disease.

Currently, there are no known medications that can cure chronic pancreatitis. Surgery (total pancreatectomy) is the only effective treatment for pain relief, but it results in insulin-dependent, brittle diabetes mellitus. Preservation of the insulin-producing islets (endocrine pancreas) has thus been sought to prevent a lifetime of insulin dependence. The Transplant Program at Children's Hospital of Pittsburgh of UPMC is one of a handful of pediatric centers in the United States and around the world that offers total pancreatectomy with islet cell autologous transplant (TPIAT), a procedure that aims at resolution of the chronic pain with preservation of the endocrine function of the beta cells that secrete insulin. The TPIAT program, started in 2009 at Children's, is thoroughly integrated across disciplines — Endocrinology, Gastroenterology and Transplantation — which allows for close collaboration and individualized plans of care for the patients. As many of the patient candidates often travel from great distances (See Figure 1 on Page 5) the program

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TPIAT (Continued from Page 1)

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integration between specialties allows the child to be seen and evaluated by the entire team on one or consecutive days as a matter of convenience. The procedure requires careful planning, surgical technique, and postsurgical monitoring to ensure that specific steps occur (see Table 1 on Page 5.)

Case Study

A 5-year-old boy who presented initially with abdominal pain, nausea, vomiting, and weight loss was initially diagnosed with pancreatitis at a local children's hospital. An abdominal CT scan during that admission showed a dilated main pancreatic duct and mild dilation of the common bile duct, that were consistent with chronic pancreatitis. The patient returned for an Endoscopic Retrograde Cholangio-Pancreatography (ERCP) a few months later, which showed pancreas divisum — an anatomical abnormality involving the pancreatic ducts that predisposes individuals to recurrent pancreatic duct stones and secondary chronic inflammation in the pancreas. Several small calcium stones were removed from the pancreatic ducts, and a temporary stent was placed in the sphincter of Oddi during this procedure. The patient did well for almost a year, when he again presented with abdominal pain and vomiting. A second ERCP was performed, along with pneumatic sphincteroplasty, stone extraction, and stent placement. Two months later, and every two to three months thereafter, he returned with the same symptoms and required multiple stent replacements or the removal of ductal stones. After several months, during which he endured recurrent episodes of abdominal pain and nausea of variable intensity between admissions and procedures, in late 2011 the family traveled to Children's Hospital of Pittsburgh of UPMC to be evaluated for a second opinion by the Division of Pediatric Gastroenterology, Hepatology and Nutrition. The family was counseled regarding the option of total pancreatectomy with islet cell auto transplant (TPIAT).

As the episodes of abdominal pain and pancreatitis became more frequent in the following six months, and the need for narcotics continued to escalate, the family agreed to proceed with the TIPIAT procedure. A preoperative evaluation in the endocrine clinic was reassuring for normal hemoglobin A1c and normal glucose response to a mixed meal tolerance test, which suggested good islet cell function. The surgery was performed at Children's Hospital by Abhinav Humar, MD,

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New Programs Improving Diabetes Care for Adolescents and Young Adults

Adolescents and young adults with type 1 diabetes (T1D) experience significant physical, psychological, and situational demands. They seek independence from their parents who have been helping to manage their diabetes, and also must negotiate variables such as driving, drinking alcohol, and the loss or absence of support from family and friends when leaving home for college or other endeavors. This is the time in their lives when they must become responsible for their own diabetes care, including yearly screenings for complications. Below are details of several recent philanthropic initiatives developed in partnership with the Children's Hospital of Pittsburgh Foundation that are allowing the Division of Pediatric Endocrinology, Metabolism, and Diabetes to improve the care it provides to adolescents and young adults living with type 1 diabetes.

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My 1 Friend Initiative

Education of family and peers of individuals with TID about the signs and symptoms of hypoglycemia is incredibly important in order for them to be able to provide treatment if and when needed. Patients can also wear a diabetes medical ID bracelet at all times to help improve the outcome of a severe diabetes-related hypoglycemia episode. The ***My 1 Friend Initiative Fund***, created by a former patient who was diagnosed with T1D at 13 years of age, supports education and safety initiatives to improve the care of youth with T1D by providing a better understanding of how to recognize when patients need help and how to provide this help. Ensuring that every teenager and young adult wears a medical alert bracelet is part of the mission of the *My 1 Friend Initiative Fund* and is assisting the division with funding to help provide this to its patients.

Fraternal Order of Eagles Initiative

Life expectancy for children with T1D has increased dramatically, however they still face the risk of chronic kidney, eye, and cardiovascular complications. The ability to screen for early markers of complications is crucial in order to prevent their occurrence and progression as best as possible. ***The Fraternal Order of Eagles*** is supporting research in the division to identify novel biomarkers of chronic complications. Among these markers, alpha-klotho (α-klotho), an obligate co-receptor molecule for FGF23 function, expressed in the distal convoluted tubules of the kidneys, has been shown to have decreased expression in chronic kidney disease, particularly in diabetic nephropathy. It also has shown to have significant correlation with albuminuria in adults with T1D. Recent work within the division has shown that alpha-klotho correlated significantly with HbA1c levels and diabetes duration which are among the most important risk factors considered for development of complications and may reflect early changes at the renal level. These findings could ultimately lead to effective prevention, earlier interventions, and significant reduction in the prevalence of complications.

The Beckwith Institute Clinical Transformation Program

Children and adolescents with T1D are at a high risk of developing vision-threatening diabetic retinopathy. Although the American Diabetes Association recommends annual screenings beginning at age 10, many children and their families fail to follow through. Improving patient and parent understanding of the benefits of self-management and good diabetes control in the prevention of future

vision complications is imperative, as is the convenience of screenings. With funding from ***The Beckwith Institute***, the division has developed and tested an age-appropriate shared decision making tool — My Eyes and Diabetes. The tool is centered on the relationship between early screening to prevent diabetic retinopathy, self-management, and glycemic control. In addition to the tool the division has collaborated with the Division of Pediatric Ophthalmology to introduce retinopathy screening at the same time as routine follow up visits for patients with T1D. This initiative is leading to increased compliance, particularly with the patient population most at risk for developing complications.

David Paul Diabetes Transition Care Research Initiative: The PREP U Program

Adolescents and young adults with diabetes must navigate the transition from pediatric to adult health care services. Unfortunately, clinic attendance has been reported to drop during this shift with many young people lost to follow-up at a time when they are also experiencing high rates of hypoglycemia and diabetic ketoacidosis. Poor glycemic control, all too common in this age group, is closely associated with chronic complications. For these reasons, national organizations recommend preparing young people for the transition process. Yet, a persistent need remains for clinical programs that take into account the specific needs and interests of adolescents and young adults with diabetes.

The recently established Diabetes Transition Program at Children's Hospital of Pittsburgh of UPMC fulfills a need for programs to equip adolescents and young adults with diabetes with confidence, knowledge, and support that can foster successful lifelong disease management. Supported by the ***David Paul Diabetes Transition Care Research Initiative Fund***, the goals of this program are to provide the best care, and find through research initiatives the best ways to support and guide a successful transition for young patients and their parents. The program utilizes a multidisciplinary team approach to diabetes care involving physicians, nurse practitioners, diabetes educators, dietitians, psychologists, and consultants.

Patients attend four sessions in a one-year period, each of which includes a routine clinic appointment plus a group discussion led by diabetes educators and other health care professionals. Group discussions focus on issues relevant to teenagers within the context of diabetes. Moderators utilize evidence-based approaches and strategies to encourage participants to become increasingly engaged in making informed decisions about their diabetes care. Program participants also learn about resources that directly connect them to adult care services to help prepare them and their families for a smooth transition to adult care services. By meeting with the same group of peers every three months, the intention is that patients serve as their own support group.

For more information about the Prep U Program, please call 412-692-6862.

To learn more about these new programs, please contact the Division of Pediatric Endocrinology, Diabetes, and Metabolism at 412-692-6993.

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clinical director of the Thomas E. Starzl Transplantation Institute. At the time of surgery, the patient was 8 years old.

In the complex operation, which included pancreatectomy with choledochal-duodenostomy and gastrojejunostomy, islet cells were isolated from the pancreas and were then reinfused in the portal vein to be implanted in the liver. The patient did well without any postoperative complications, was transferred from the Pediatric Intensive Care Unit to the floor after three days, and was discharged 16 days after surgery. He received an insulin infusion for tight glycemic control in the first of five days, after which he was switched to insulin injections. His pain improved dramatically, and he was weaned off narcotics, requiring only acetaminophen for postoperative pain by the fifth day following the surgery.

Figure 1. Patients are referred to Children's Hospital of Pittsburgh of UPMC for the TPIAT procedure from across the country.

When the patient returned for follow-up two months later, he had no pain, and he was euglycemic on 0.5 units of long-acting insulin at night. As his hemoglobin A1c was normal at 5.5%, and his blood glucose records were within normal limits, the insulin was discontinued completely. During the following four years, he returned for annual evaluations in combined endocrine, GI, and transplant clinic appointments. He remained pain free and euglycemic without insulin. His hemoglobin A1c and mixed meal tolerance tests remained normal. Both his height and weight parameters improved dramatically in the years following surgery, and he was able to normalize his body mass index, which was very low before surgery.

TABLE 1: Critical TPIAT Surgical and Postsurgical Steps

- Maintain the vascular flow and viability of the (endocrine) pancreas as long as possible during surgery
- Isolation of the islet cell from the exocrine pancreas in a specialized laboratory
- Infusion of the islet cell suspension into the portal vein so that these cells lodge in the liver and start to make insulin in their "new organ"
- Strict control of glucose levels by hourly adjustment of an insulin infusion for several days after surgery, as the transplanted beta cells do not start to work immediately and are damaged by elevated glucose levels
- Continue close monitoring of glucose levels and insulin dosing until the patient is able to be off insulin completely or on a stable insulin dose

TABLE 2: TPIAT Postsurgical Highlights

Discontinuation of pain medications within 3 months of surgery	77%*
Patients on no insulin or low dose basal insulin only	61%*

*n=13

Conclusion

Thirteen patients underwent TPIAT at Children's Hospital between 2009 and 2016.

This procedure has proven to be an effective treatment for chronic pancreatitis in children and adolescents, as it allows substantial or complete pain relief, along with good glycemic control. Ten of the 13 patients (77%) were able to discontinue pain medication within three months of surgery. Eight of the 13 patients (61%) were able to maintain excellent glucose levels on no insulin or low dose basal insulin only. (Table 2)

TPIAT is a promising procedure that offers a great hope of cure for those who suffer from chronic pancreatitis, while preventing severe, insulin-dependent diabetes in most patients. In the future, studies will need to be undertaken to follow patients to understand what the long-term implications of the procedure are, five, ten, or even 25 years postsurgery.

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About Children's Hospital of Pittsburgh of UPMC

Regionally, nationally, and globally, Children's Hospital of Pittsburgh of UPMC is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists. With generous community support, Children's Hospital has fulfilled this mission since its founding in 1890. Children's is named consistently to several elite lists of pediatric hospitals, including ranking No. 9 in the prestigious *U.S. News & World Report* annual Honor Roll of America's Best Children's Hospitals for 2017–2018 and ranking 10th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2016).

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