Penn Medicine

CLINICAL BRIEFING™

Penn Endocrinology, Diabetes and Metabolism • Rodebaugh Diabetes Center

Enrolling Clinical Studies in Automated Insulin Delivery for Type 1 Diabetes

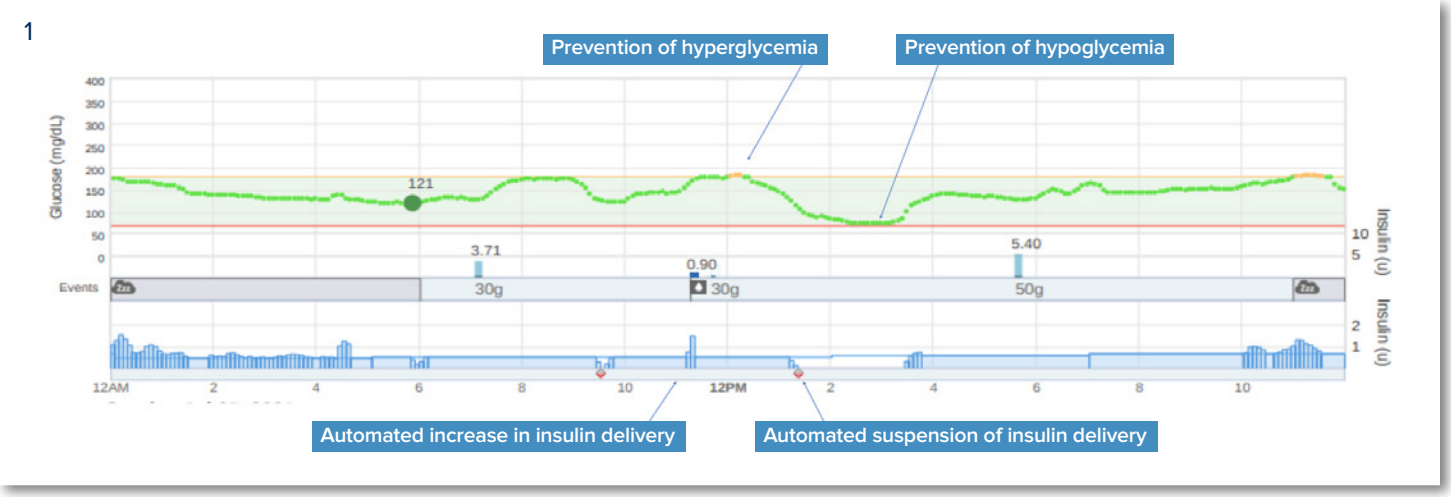

Figure 1: Continuous glucose monitoring profile (top) with sensor communicating insulin pump automating insulin delivery (bottom) by increasing insulin delivery for predicted hyperglycemia (red diamonds). User input is required for estimated carbohydrate intake to provide prandial insulin boluses (middle) and can be added for sleep (Zzz) and exercise (not shown).

Researchers at the Penn Rodebaugh Diabetes Center are conducting an enrolling clinical trial to assess the safety and efficacy of both hybrid closed-loop control and predictive low-glucose insulin suspension technology on hypoglycemia and other glycemic outcomes, quality of life (QOL), and usability compared with sensor-augmented pump therapy in older adults with type 1 diabetes (T1D).

Current Diabetes Technologies

The introduction of insulin pumps, continuous glucose monitoring sensors and their combination (sensor-augmented pumps), hold great promise for the improvement of glycemic control for patients with type 1 diabetes (T1D) and advanced type 2 diabetes (T2D). However, despite the wide adoption of these technologies, a 2019 report found that only 21% of American adults with diabetes had achieved the American Diabetes Association HbA1c goal of <7.0% (53 mmol/mol), and that 7% of adults report having experienced a severe hypoglycemic episode resulting in seizure or loss-of-consciousness in the previous three months.

Automated closed-loop systems (known informally as artificial pancreas systems) offer a further step towards reducing the burden of diabetes management. The object of closed-loop systems is to replicate the physiology of the pancreas while requiring less input from the patient for insulin dosing decisions than is required with open-loop control. These systems have three interconnected components: a real-time continuous glucose monitoring sensor; a control algorithm device (or CAD); and an insulin pump directed by the dosing control algorithm.

In closed-loop mode, the insulin pump uses the control algorithms to respond to measured glucose levels, decreasing insulin delivery when a patient's sensor glucose is predicted to be low and increasing insulin delivery when a patient's sensor glucose is predicted to be high. Closed-loop systems can be designed to deliver insulin alone, or insulin and glucagon or another hormone (dual hormone systems), and are classified as "hybrid" when basal insulin delivery is automated, but user input is required to bolus for carbohydrate intake or administer additional corrective insulin doses. Hybrid closed-loop (HCL) systems have been in development for more than a decade, but it is not yet known whether their complexity provides additional glycemic benefit for individuals with hypoglycemia unawareness or older adults, populations with T1D at greatest risk for experiencing life-threatening episodes of severe hypoglycemia. Moreover, problems with mechanical insulin delivery and variability of insulin absorption present challenges to closed-loop control of blood glucose.

Critical Research Needs in the T1D Population

Older adults with recent severe hypoglycemia (SH) have a remarkably high prevalence of hypoglycemic unawareness (the loss of physiological symptoms associated with low blood glucose). In addition, aging is associated with normative decline in cognitive functioning that may impact diabetes self-management and contribute to hypoglycemia risk. Among much else, hypoglycemia unawareness is associated with a 20-fold increased risk for experiencing life-threatening hypoglycemia.

Continued on back

Studies suggest that for those with SH within the prior year, 58% have hypoglycemic unawareness, compared to 25% in those with no SH in the prior 3 years.

To date, studies of automated insulin delivery technologies have not included older adults in sufficient numbers to allow for focused evaluation of efficacy and QOL impacts that may differ from those observed in younger age groups.

In persons with long-standing T1D, impaired glucose counterregulation when combined with hypoglycemic unawareness may substantially increase the risk for severe hypoglycemia. Glucose counterregulation is the body's physiologic response to restore normal glucose in the wake of hypoglycemia and becomes progressively impaired with longer duration of T1D and with more frequent exposure to even mild degrees of hypoglycemia.

Individuals with impaired glucose counterregulation and hypoglycemic unawareness are perhaps most in need of new therapeutic strategies. However, in automated insulin delivery, sensor overestimation of blood glucose may be a concern for older persons, since the patient's awareness of hypoglycemia would then be dependent upon his or her capacity to recognize low blood glucose. Thus, it is critical to understand the effects of hybrid closed-loop insulin delivery on physiologic defense mechanisms against the development of low blood glucose before fully closed-loop control may be acceptable in this population.

CLINICAL STUDIES AT PENN MEDICINE

Currently, the Penn Rodebaugh Diabetes Center is enrolling patients for a clinical study in older adults with type 1 diabetes that is evaluating automated insulin delivery in the context of hypoglycemia and other glycemic outcomes. This study is being sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health.

Automated Insulin Delivery in Elderly Patients with Type 1 Diabetes (AIDE T1D):
The primary objective of this study in older adults (>65 years) with T1D is to assess the safety and effectiveness of a 12-week period of HCL technology use and a 12-week period of predictive low-glucose insulin suspension (PLGS) on hypoglycemia and other glycemic outcomes, QOL and usability in comparison to a 12-week period of sensor-augmented pump (SAP) therapy. Secondary objectives include identifying participant characteristics associated with optimal outcomes with and preference for SAP therapy, HCL technology or PLGS during a 12-week patient preference extension period. During all four 12-week study periods participants will receive a Tandem (t:slim) insulin pump and Dexcom (G6) continuous glucose monitoring system.

Enrollment information for this trial can be obtained by contacting:
Cornelia V Dalton Bakes at **215.746.2085** or **corneliv@pennmedicine.upenn.edu.**

Additional clinical studies can be found listed here:
www.med.upenn.edu/idom/trials

ABOUT THE PENN RODEBAUGH DIABETES CENTER

The Penn Rodebaugh Diabetes Center at the Hospital of the University of Pennsylvania is a state-of-the-art facility dedicated to the treatment and prevention of diabetes. The Center, unique to the Philadelphia region, provides comprehensive care exclusively for patients with type 1 diabetes, type 2 diabetes, pancreatogenic diabetes, hypoglycemia disorders, and related metabolic diseases.

For more information about the Penn Rodebaugh Diabetes Center, please visit:
https://www.pennmedicine.org/practices/rodebaugh-diabetes-center

ACCESS

Penn Rodebaugh Diabetes Center
Perelman Center for Advanced Medicine
West Pavilion, 4th Floor
3400 Civic Center Boulevard
Philadelphia, PA

CLINICAL RESEARCH TEAM

Michael R. Rickels, MD, MS
Willard and Rhoda Ware Professor in Diabetes and Metabolic Diseases
Clinical Science Director, Endocrinology, Diabetes and Metabolism

Mark H. Schutta, MD
G. Clayton Kyle Associate Professor in Diabetes
Medical Director, Penn Rodebaugh Diabetes Center

Ilona S. Lorincz, MD
Associate Professor of Clinical Medicine
Director of Quality, Endocrinology, Hospital of the University of Pennsylvania

Anastassia Amaro, MD
Associate Professor of Clinical Medicine
Medical Director, Penn Metabolic Medicine

Serena Cardillo, MD
Professor of Clinical Medicine
Fellowship Program Director, Endocrinology, Diabetes and Metabolism

Rahaf Sultan, MD
Assistant Professor of Clinical Medicine

CLINICAL RESEARCH COORDINATORS AND SUPPORT

Paola Alvarado, CCRC

Cornelia Dalton-Bakes, CCRC, MA

Patti Bourne, BSN

Eileen Markmann, BSN

Amy J. Peleckis, CNRP

Huong-Lan Nguyen, BS

RECENT RESEARCH PUBLICATIONS INVOLVING PENN MEDICINE PATIENTS WITH T1D (2020-2021):

Riddell MC, Li Z, Beck RW, Gal RL, Jacobs PG, Castle JR, Gillingham MB, Clements M, Patton SR, Dassau E, Doyle FJ, Martin CK, Calhoun P, Rickels MR: More time in glucose range during exercise days than sedentary days in adults living with type 1 diabetes. Diabetes Technology and Therapeutics 23(5): 376-383, May 2021. PMCID: PMC Journal - In Process

Carlson AL, Kanapka LG, Miller KM, Ahmann AJ, Chaytor NS, Fox S, Kiblinger L, Kruger D, Levy CJ, Peters AL, Rickels MR, Salam M, Shah VN, Young LA, Kudva YC, Pratley R; WISDM Study Group: Hypoglycemia and glycemic control in older adults with type 1 diabetes: baseline results from the WISDM study. Journal of Diabetes Science & Technology 15(3): 582-592, May 2021. PMCID: PMC Journal - In Process

Markmann JF, Rickels MR, Eggerman TL, Bridges ND, Lafontant DE, Qidwai J, Foster E, Clarke WR, Kamoun M, Alejandro R, Bellin M, Chaloner K, Czarniecki CW, Goldstein JS, Hering BJ, Hunsicker LG, Kaufman DB, Korsgren O, Larsen CP, Luo X, Naji A, Oberholzer J, Posselt AM, Ricordi C, Senior PA, Shapiro AMJ, Stock PG, Turgeon NA; Clinical Islet Transplantation Consortium: Phase 3 trial of human islet-after-kidney transplantation in type 1 diabetes. American Journal of Transplantation 21(4): 1477-1492, April 2021. PMCID: PMC Journal - In Process

Malone SK, Peleckis AJ, Grunin L, Yu G, Jang S, Weimer J, Lee I, Rickels MR, Goel N: Characterizing glycemic control and sleep in adults with long-standing type 1 diabetes and hypoglycemia unawareness initiating hybrid closed loop insulin delivery. Journal of Diabetes Research 6611064: 1-8, February 2021. PMCID: PMC7896863

Gillingham MB, Li Z, Beck RW, Calhoun P, Castle JR, Clements M, Dassau E, Doyle FJ, III, Gal RL, Jacobs P, Patton SR, Rickels MR, Riddell M, Martin CK: Assessing mealtime macronutrient content: patient perceptions versus expert analyses via a novel phone app. Diabetes Technology & Therapeutics 23(2): 85-94, February 2021. PMCID: PMC7868577

Casu A, Kanapka LG, Foster NC, Hirsch IB, Laffel LM, Shah VN, DeSalvo DJ, Lyons SK, Vendrame F, Aleppo G, Mastrandrea LD, Pratley RE, Rickels MR, Peters AL; T1D Exchange Clinic Network: Characteristics of adult- compared to childhood-onset type 1 diabetes. Diabetic Medicine 37(12): 2109-2115, December 2020

Sherk VD, Vigers T, Pyle L, Snell-Bergeon JK, Nadeau KJ, Rickels MR, Miller K, Greenbaum CJ, Shah VN: Acute hyperinsulinemia alters bone turnover in women and men with type 1 diabetes. JBMR Plus 4(9): e10389, August 2020. PMCID: PMC7507374

Agarwal S, Kanapka LG, Raymond JK, Walker A, Gerard-Gonzalez A, Kruger D, Redondo MJ, Rickels MR, Shah VN, Butler A, Gonzalez J, Verdejo AS, Gal RL, Willi S, Long JA: Racial-ethnic inequity in young adults with type 1 diabetes. Journal of Clinical Endocrinology & Metabolism 105(8): e2960-e2969, August 2020. PMCID: PMC7457963

Pratley RE, Kanapka LG, Rickels MR, Ahmann A, Aleppa G, Beck R, Bhargava A, Bode BW, Carlson A, Chaytor NS, Fox DS, Goland R, Hirsch IB, Kruger D, Kudva YC, Levy C, McGill JB, Peters A, Philipson L, Philis-Tsimikas A, Pop-Busui R, Shah VN, Thompson M, Vendrame F, Verdejo A, Weinstock RS, Young L, Miller KM; Wireless Innovation for Seniors with Diabetes Mellitus (WISDM) Study Group: Effect of continuous glucose monitoring on hypoglycemia in older adults with type 1 diabetes. JAMA 323(23): 2397-2406, June 2020. PMCID: PMC7298607

Hermann JM, Miller KM, Hofer SE, Clements MA, Karges W, Foster NC, Fröhlich-Reiterer E, Rickels MR, Rosenbauer J, DeSalvo DJ, Holl RW, Maahs DM; T1D Exchange Clinic Network and the DPV Initiative: The Transatlantic HbA1c gap: differences in glycaemic control across the life-span between the US T1D Exchange and German/Austrian DPV registries. Diabetic Medicine 37(5), May 2020

Rickels MR, Evans-Molina C, Bahnson HT, Ylescupidez A, Nadeau KJ, Wei Hao W, Clements MA, Sherr JL, Pratley RE, Hannon TS, Shah VN, Miller KM, Greenbaum CJ; T1D Exchange B-Cell Function Study Group: High residual C-peptide likely contributes to glycemic control in type 1 diabetes. Journal of Clinical Investigation 130(4): 1850-1862, April 2020. PMCID: PMC7108933

Mishra R, Åkerlund M, Cousminer DL, Ahlqvist E, Bradfield JP, Chesi A, Hodge KM, Guy VC, Brillon DJ, Pratley RE, Rickels MR, Vella A, Ovalle F, Harris RI, Melander O, Varvel S, Hakonarson H, Froguel P, Lonsdale JT, Mauricio D, Schloot NC, Khunti K, Greenbaum CJ, Yderstræde KB, Tuomi T, Voight BF, Schwartz S, Boehm BO, Groop L, Leslie RD, Grant SFA: Genetic discrimination between LADA and childhood-onset type 1 diabetes within the MHC. Diabetes Care 43(2): 418-425, February 2020. PMCID: PMC6971787

Miller KM, Hermann J, Foster N, Hofer SE, Rickels MR, Danne T, Clements MA, Lilienthal E, Maahs DM, Holl RW; T1D Exchange and DPV Registries: Longitudinal changes in continuous glucose monitoring use among individuals with type 1 diabetes: international comparison in the German and Austrian DPV and US T1D Exchange Registries. Diabetes Care (letter) 43(1): e1-e2, January 2020. PMCID: PMC7881298