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Closed-Loop Insulin Therapy in Young Children

Written by Phil Vinall

Glycemic control is difficult to maintain in children with diabetes aged <7 years for several reasons. Children of this age are at increased risk of hypoglycemia (particularly at night), and there is the potential for hypoglycemia-related neurocognitive outcomes. In addition, at this age, children often have unpredictable eating patterns and variable levels of activity. Closed-loop insulin delivery is a recent medical innovation that aims to achieve tight glucose control while reducing the risk of hypoglycemia, but it has not been tested in young children. Andrew Dauber, MD, Boston Children's Hospital, Boston, Massachusetts, USA, presented data from the Closed-Loop Insulin Delivery in Children <7 years of Age Study that showed how closed-loop therapy (CLT) has the potential to improve diabetes care in young children [NCT01421225].

CLT combines glucose-sensing and insulin-delivery components with real-time glucose-responsive insulin administration. A disposable sensor measures interstitial glucose levels, which are fed automatically into an algorithm that is used to control the delivery of a rapid-acting insulin analog into the subcutaneous tissue by an insulin pump. This was a randomized crossover trial that compared CLT with standard (open-loop) pump therapy (SPT) in children aged <7 years who were diagnosed with type 1 diabetes for more than 6 months and had been treated with insulin pump therapy for more than 6 weeks. Study participants (n=10) had a mean age of 5.1 years (range 2.0 to 6.8 years) with a mean duration of diabetes of 2.1 years (range 0.5 to 4.7 years). Mean HbA1C was 8.1% (range 7.1% to 8.9%), and the average daily insulin dose was 0.72 units/kg (range 0.61 to 1.0 units/kg). All subjects had fasting c-peptide levels <0.1 ng/mL.

In this study, glucose values were transmitted from 2 Freestyle Navigator® sensors (one placed in each thigh) to a bedside receiver. The values were retrieved from the receiver and entered manually into a control algorithm to calculate insulin recommendations. The control algorithm was a physiological insulin delivery algorithm, developed by one of the investigators, that utilized proportional-integral-derivative terms that were modified by insulin feedback. All recommendations generated by the algorithm were approved by the physician and then entered into the Animus OneTouch® Ping® insulin pump remote, which transmitted the insulin order to the insulin pump attached to the patient. There were 2 periods of control: overnight (10:00 PM to 8:00 AM) when basal rates were adjusted every 20 minutes based on sensor readings, and daytime (8:00 AM to noon), when mini-boluses of insulin in increments of 0.05 units were given up to every minute, based on sensor readings. Target blood sugars were 150 mg/dL during the night and 120 mg/dL during the day.

Subjects were admitted to the clinic for 48 hours. Meals and snacks were provided on a regular schedule. Participants were free to choose from a standardized menu but received the identical meals/snacks on Days 1 and 2. All meals were weighed pre- and post-consumption. The Freestyle sensors were placed on the morning of admission. That afternoon patients were switched to the study insulin pump. An intravenous line was also placed to allow for frequent blood sampling. The study period began at 10:00 PM and ran until noon the following day. During that time, subjects were randomized to receive either CLT or SPT. From noon until 10:00 PM, subjects received their standard therapy. At 10:00 PM on the second evening, subjects were randomized to the opposite therapy from the prior night.

Time at overnight target was increased with CLT but was not significantly different from SPT; however, time in extreme hyperglycemia was significantly reduced as was the total glycemic excursion overnight. There was no difference in the number of interventions for hypoglycemia or in daytime peak postprandial glucose (despite the absence of a pre-meal bolus), while the pre-lunch was significantly decreased (Table 1).

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Table 1. Outcomes.

Outcome Measure	SPT	CLT	p value
Time in target (110-200 mg/dL overnight; hours)	3.20±0.77	5.30±0.66	0.12
Time >300 mg/dL overnight (hours)	1.30±0.42	0.18±0.08	0.035
AUC >200 mg/dL overnight (mg/dL*hours)	384±84	162±40	0.049
Number of interventions for hypoglycemia	4.0	5.0	1.0
Peak postprandial glucose (mg/dL)	353±24	367±23	0.71
12:00 PM glucose (mg/dL)	273±24	189±18	0.009

CLT maintained tight glucose control without increasing the incidence of hypoglycemia and improved pre-lunch blood sugars, leading the investigators to conclude that it has the potential to improve diabetes care for very young children.

The Precocious "AGE'ing" Effect of Type 1 Diabetes in Children

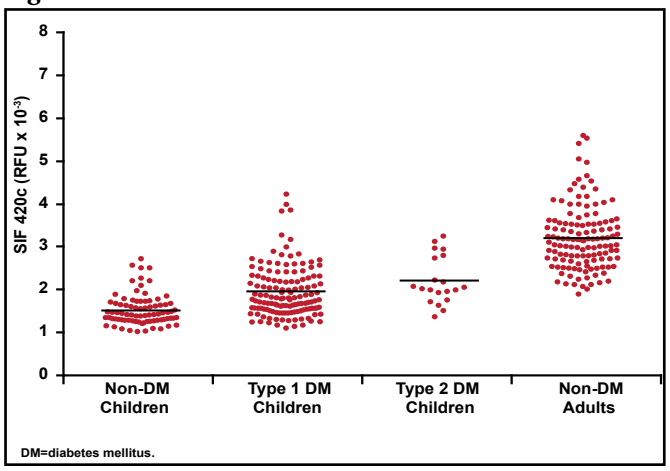
Written by Phil Vinall

Type 1 diabetes mellitus increases the formation of long-lived complexes, known as advanced glycation endproducts (AGEs), which can contribute to the development of complications in patients with diabetes [Genuth S et al. *Diabetes* 2005]. AGEs accumulate naturally in tissues over time, and tissue burden is a function of chronological age. Shreepal Shah, MD, Louisiana State University, New Orleans, Louisiana, USA, presented results of the "The Precocious "AGE'ing" Effect of Type 1 Diabetes in Children" study, which examined the relationship between chronological age and type 1 diabetes on skin AGEs in children. The study results indicated that a large proportion of children with type 1 and type 2 diabetes have precocious accumulation of skin AGEs, as estimated by skin-intrinsic fluorescence (SIF), compared with children and adults without diabetes.

The study was conducted in children with established type 1 (n=133; mean age 13 years) and type 2 diabetes (n=20; mean age 15 years) and healthy children (n=91; mean age 10 years) and adults (n=129; mean age 40 years) without diabetes. The mean duration of diabetes was 6 years for patients with type 1 diabetes and 4 years for those with type 2 diabetes. History of, or current smoking was cause for exclusion. Skin AGEs were estimated noninvasively by measuring SIF using a Scout DS® device using procedures previously described by Felipe et al. [Felipe DL et al. *Diabetes Care* 2011]. The goal of the study was to assess accumulated skin AGEs, estimated from SIF, from children with diabetes compared with individuals who did not have diabetes.

In individuals without type 1 diabetes, SIF, stimulated at 420λ (SIF 420c), increased with chronological age. When adjusted for chronological age and gender, SIF 420c was higher in children with type 1 and type 2 diabetes compared with children without diabetes (Figure 1). Forty-three percent of children with type 1 diabetes and 55% with type 2 diabetes had SIF values that were comparable with those of the adults (who were approximately 27 years older) without diabetes. SIF was associated with HbA1C or hemoglobin glycation index in the children with diabetes, but mean blood glucose levels were not.

Figure 1. SIF 420c.



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Many children with type 1 and type 2 diabetes have estimated skin AGE levels that are comparable with those that would be observed naturally only in adults aged 20 to 40 years. The investigators estimated that 4 to 6 years of diabetes duration is comparable with ~30 years of chronological aging. The authors speculated that factors that predispose individuals to precocious accumulation of skin AGEs may also predispose them to precocious development of diabetes complications.

Abatacept in Patients with New-Onset Type 1 Diabetes: One-Year Follow-Up

Written by Phil Vinall

Type 1 diabetes mellitus (T1DM) is an autoimmune disease that is driven by activated T-lymphocytes. To be fully active, immune T-cells need a costimulatory signal in addition to the main antigen-driven signal. A previous study showed that abatacept, a costimulation modulator that prevents full T-cell activation, slowed reduction in