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REVIEW ARTICLE

Diabetes Research in Children Network: Availability of Protocol Data Sets

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Abstract

The Diabetes Research in Children Network (DirecNet) was established in 2001 by the National Institute of Child Health and Human Development and the National Institute of Diabetes and Digestive and Kidney Diseases through special congressional funding for type 1 diabetes research. The network consists of five clinical centers, a coordinating center, and a central laboratory. Since its inception, DirecNet has conducted nine protocols, resulting in 28 published manuscripts with an additional 2 under review and 5 in development. The protocols have involved evaluation of technology available for the treatment of type 1 diabetes, including home glucose meters (OneTouch Ultra, FreeStyle, and BD Logic), continuous glucose monitoring systems (GW2B, CGMS, FreeStyle Navigator, and Guardian RT), and hemoglobin A1c (HbA1c) devices (DCA 2000 and A1cNow). In addition, the group has conducted several studies evaluating factors affecting hypoglycemia, including exercise and bedtime snack composition. The data sets that have resulted from these studies include data from the devices being evaluated, central laboratory glucose, HbA1c and hormone data, clinical center glucose and HbA1c data, accelerometer data, and pump data depending on the procedures involved with each protocol. These data sets are, or will be, available at no charge on the study group's public Web site. Several psychosocial questionnaires developed by DirecNet are also available.

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Introduction

The Diabetes Research in Children Network (DirecNet) was established in 2001 through funding from the National Institute of Child Health and Human Development and the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (NIH). DirecNet was established as part of the funds earmarked by Congress for research in type 1 diabetes.

The network consists of five clinical centers and a coordinating center that were selected after responding to a request for applications from the NIH. The five clinical centers are at the Barbara Davis Center of the University of Colorado, Nemours Children's Clinic in Jacksonville, Florida, Stanford University, the University of Iowa, and Yale University; the coordinating center is

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Abbreviations: (CGMS) continuous glucose monitoring system, (CRC) clinical research center, (CSII) continuous subcutaneous insulin infusion, (DCCT) Diabetes Control and Complications Trial, (DirecNet) Diabetes Research in Children Network, (HbA1c) hemoglobin A1c, (HGM) home glucose meters, (NIH) National Institutes of Health, (PC) personal computer, (T1D) type 1 diabetes

Keywords: continuous glucose sensors, data sets, type 1 diabetes

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at the Jaeb Center for Health Research in Tampa, Florida. A central laboratory was established at the University of Minnesota.

A primary goal of DirecNet has been to investigate the potential use of glucose monitoring technology to improve the management of type 1 diabetes (T1D) in children and to develop a better understanding of hypoglycemia and its prevention. DirecNet exemplifies the economy of scale and other benefits of a well-functioning, highly productive network. It has rapidly initiated and conducted multiple protocols and analyzed and published their results. This has been possible principally because of the effective interactions between highly motivated and dedicated investigators and staff at the coordinating center and clinical centers and because of the use of informatics to enhance efficiency in conducting clinical trials. An extensive Web site is used for virtually all network operations. The use of touch-screen tablet computers for real-time data capture enhances not only the efficiency of the data collection process but also the quality of data by the many measures that can be implemented on the Web site to assure the verity of data and adherence to the protocol.

In its first 6 years of existence, the network has conducted nine protocols and numerous ancillary studies as part of these protocols. All protocols have included children with type 1 diabetes. Protocols have evaluated the accuracy of several continuous glucose monitors—the GlucoWatch® G2 Biographer (GW2B; Cygnus, Inc., Redwood City, CA) and the Continuous Glucose Monitoring System® (CGMS; Medtronic MiniMed, Northridge, CA), the FreeStyle Navigator continuous glucose monitor (Navigator; Abbott Diabetes Care, Alameda, CA), and the Guardian RT (Medtronic MiniMed, Northridge, CA); several home glucose meters (HGM)—the OneTouch Ultra® (LifeScan, Inc., Milpitas, CA), FreeStyle (Abbott Diabetes Care, Alameda, CA), and the BD® Logic (Becton Dickinson, Franklin Lakes, NJ); one point of service hemoglobin A1c (HbA1c) device—the DCA 2000®+ analyzer (Siemens Medical Solutions Diagnostics, Tarrytown, NY); and one home HbA1c meter—the A1cNow® (Metrika, Inc., Sunnyvale, CA). Outpatient use of the GW2B and the Navigator has been evaluated. Other studies have evaluated the effect of exercise on nocturnal hypoglycemia, the effect of insulin pump discontinuation during exercise on the development of hypoglycemia, the effect of high-fat versus low-fat snacks on nocturnal hypoglycemia, and a comparison of the counterregulatory hormone response to hypoglycemia in younger versus older children. The protocols have resulted in 28 manuscripts published or in press, with another 2 submitted for publication and 5 in preparation. A number of presentations of study results have been made at meetings of the American Diabetes Association; the Diabetes Technology Society, which has been a strong supporter of DirecNet; and other national and international meetings.

Data sets for each of these protocols have already been placed in the public domain or will be available during 2007–2008. The purposes of this article are to summarize the studies that DirecNet has conducted and to provide details regarding the available data sets, as well as questionnaires for assessing satisfaction with the use of continuous glucose monitors and with algorithms for applying glucose data to daily management.

Summaries of Protocols and Available Data Sets

The protocols with available data sets are listed in **Table 1** and are detailed here. All protocols except where noted included children with T1D.

Protocol A: An Assessment of the Accuracy of GW2B and CGMS in Diabetic Children[1–8]

The study included 89 subjects (mean age 9.9 years, range 3.5 to 17.7) who were hospitalized for approximately 26 hours. Each subject wore two GW2B sensors and one or two CGMS sensors, one of which was initiated either 2 days prior, 1 day prior, or on the day of admission. Samples were drawn for reference blood glucose measurements every 60 minutes during the day and every 30–60 minutes overnight, with additional measurements every 5 minutes for 90 minutes during an insulin-induced hypoglycemia test and every 5 minutes for 60 minutes during a meal-induced hyperglycemia test. The OneTouch Ultra meter was used for calibrating sensors and for monitoring blood glucose. During the insulin-induced hypoglycemia test, additional glucose measurements were also made with a Beckman, Yellow Spring Instrument, or I-Stat.

Protocol B: An Assessment of the Accuracy of GW2B and CGMS in Nondiabetic Children[9]

The study evaluated the accuracy of the CGMS and the GW2B in normal children while examining the 24-hour pattern of glucose concentrations. Fifteen healthy children 9–17 years of age (11 boys/4 girls) with no family history of type 1 diabetes and normal body mass index were admitted to a clinical research center (CRC) for approximately 24 hours. Each subject wore one or two GW2B and one or two CGMS sensors. Samples

Table 1.
DirecNet Protocols and Available Data

Protocol [a]	# of subjects/ type	Age range (years)	Study type	Devices with data	Other available data
A	89/T1D	3 to <18	Inpatient	GW2B, CGMS, Ultra	Glucose measurements from central lab, Yellow Spring Instrument, Beckman, I-Stat, DCA 2000 A1c
B	15/nondiabetic children	9 to <18	Inpatient	GW2B, CGMS, Ultra	Glucose measurements from central lab, DCA 2000 A1c
C	15/T1D	7 to <18	Outpatient	GW2B, Ultra	Central lab A1c, DCA2000 A1c
D	200/T1D	7 to <18	Outpatient	GW2B, CGMS, Ultra Smart	Central lab A1c, DCA 2000 A1c, accelerometer
E	50/T1D	11 to <18	Inpatient	CGMS, Ultra, FreeStyle HGM, BD Logic	Glucose measurements from central lab, DCA 2000 A1c
F	57/T1D	3 to <18	Inpatient/ outpatient	CGSM, FreeStyle Navigator, FreeStyle HGM	Glucose measurements from central lab, DCA 2000 A1c, pump data
G	49/T1D	8 to <18	Inpatient	CGMS, FreeStyle HGM	Glucose measurements from central lab, central lab A1c, DCA 2000 A1c, AtcNow, pump data
H	30/T1D	3 to <7 and 12 to <18	Inpatient	Guardian RT, Ultra	Glucose measurements from central lab, DCA 2000 A1c, pump data
I	10/T1D	4 to <18	Outpatient	FreeStyle Navigator, FreeStyle HGM	Pump data

[a] Protocol A: An assessment of the accuracy of the GW2B and CGMS in diabetic children.
Protocol B: An assessment of the accuracy of the GW2B and CGMS in nondiabetic children.
Protocol C: A pilot study to evaluate outpatient use of the GW2B.
Protocol D: A randomized trial to assess the effectiveness of the GW2B.
Protocol E: The effect of exercise on the development of nocturnal hypoglycemia.
Protocol F: A pilot study to evaluate the FreeStyle Navigator.
Protocol G: The effect of continuing versus discontinuing basal insulin on the development of hypoglycemia during exercise.
Protocol H: A comparison of the counterregulatory hormone response to insulin-induced hypoglycemia in younger and older children with T1D.
Protocol I: A pilot study to compare high-fat versus low-fat bedtime snacks to prevent nocturnal hypoglycemia.

were drawn for reference blood glucose measurements every 60 minutes during the day and every 30 minutes overnight. The OneTouch Ultra meter was used for calibration of the sensors.

Protocol C: A Pilot Study to Evaluate Outpatient Use of the GW2B

This 3-month pilot study was conducted to assess the feasibility of using a personal computer (PC) in the home for computer-based data acquisition and transmission in a larger 12-month study. Fifteen subjects with type 1 diabetes mellitus (age range 7.3–17.9 years) were provided with a GW2B and a OneTouch Ultra meter along with a personal computer and software for downloading glycemic data for each device. The PC was also used weekly to complete a questionnaire regarding hypoglycemia and problems with using the GW2B. Patients were able to view Ultra and GW2B data at any time on the PC. Each week, data were uploaded to the study coordinating center and made available to the clinical centers on a secure Web site. Therapeutic changes were based on downloads, hypoglycemia questionnaires, and telephone contacts with clinical centers. Quality of life, diabetes self-management behaviors, and satisfaction with GW2B use were measured.

Protocol D: A Randomized Trial to Assess the Effectiveness of GW2B[10–18]

The study included 200 subjects who were randomized to either the GW2B or to usual care. Subjects assigned to the GW2B group were instructed to use it a minimum of two times (with at least 1 day and 1 night of sensor wear) per week. Each subject was provided with a PC for downloading of GW2B and HGM and to serve as a

resource for diabetes self-management. Follow-up visits were performed at 3 and 6 months and phone contacts at 1, 2, and 4 weeks and then every 4 weeks. The Ultra meter was used for home glucose monitoring. At baseline and after 3 and 6 months, a CGMS was used for 3 days and eight-point blood glucose testing was performed for 2 of those days using an Ultra meter. Primary outcomes were a change in HbA1c and frequency of hypoglycemia from baseline to 6 months. Quality of life, diabetes self-management behaviors, and satisfaction with GW2B use were also measured. As part of this study, accuracy of the DCA 2000 was evaluated. At the randomization visit of this trial at each center, HbA1c was measured from a finger stick blood sample with the DCA 2000, following the manufacturer's guidelines. At the same visit, an additional finger stick blood sample was obtained, refrigerated, and within 7 days shipped as whole blood to the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications laboratory.

Protocol E: Effect of Exercise on the Development of Nocturnal Hypoglycemia[19–23]

The study included 50 subjects, aged 11 to 17 years, who were studied in a clinical research center on 2 separate days. On both days, a CGMS was inserted at the time of admission. During 1 of the 2 days (ordered through randomization), a structured exercise protocol was completed in the late afternoon. On the other day, the subjects did not exercise. The exercise session consisted of 15 minutes walking on a treadmill at a heart rate of approximately 140 beats/minute followed by a 5-minute rest period. This cycle was repeated three more times for a total of four 15-minute exercise periods with 5-minute rest periods in between (75 minutes total). Glucose measurements were made from venous blood at a central laboratory as well as on a OneTouch Ultra meter prior to starting the exercise, during each of the three rest periods, immediately following the exercise session, and at 15-minute intervals for 1 hour following completion of the exercise. Subsequent glucose measurements were made every half-hour from 10:00 PM to 6:00 AM. At times when samples were collected for glucose measurements, samples were also collected for assessment of counterregulatory hormones. Concurrent glucose measurements were made using the OneTouch Ultra meter, BD Logic meter, and FreeStyle Flash meter to coincide with measurements made by the central laboratory. As part of this study, accuracy of the A1cNow was assessed. HbA1c was measured four times using the A1cNow, twice by the subject or parent at home, and twice the following day by site staff at a DirecNet study visit. At the study visit, HbA1c was measured using the DCA 2000, and a finger stick blood sample was obtained, frozen at –70°C, and shipped to the DCCT/DirecNet central laboratory.

Protocol F: A Pilot Study to Evaluate the FreeStyle Navigator[24–26]

The study included 57 subjects, 30 using continuous subcutaneous insulin infusion (CSII) therapy and 27 using multiple daily injection therapy with insulin glargine (Lantus) combined with short-acting insulin injections. Subjects wore the Navigator for 1 week blinded to the sensor glucose values. Subjects on CSII therapy then returned for a 24-hour CRC admission for an assessment of accuracy of the device, which included following a meal and during a structured exercise session. During the outpatient phase, subjects were instructed to use the device daily and were provided with instructions (algorithms) for making management decisions based on the sensor glucose values. Follow-up visits were performed at 1, 3, 7, and 13 weeks and phone contacts at 3 days and then at 2, 4, 8, and 10 weeks. Subjects were given the option at the 13-week visit to continue wearing the Navigator; if they agreed, subjects were seen every 3 months. The FreeStyle meter built into the Navigator was used for home glucose monitoring. HbA1c was measured at baseline, 7 and 13 weeks, and at each visit thereafter for those who agreed to continue the study. Satisfaction with Navigator use was measured at 13 weeks and each subsequent visit for those who continued the study.

Protocol G: Effect of Continuing versus Discontinuing Basal Insulin on the Development of Hypoglycemia during Exercise[27,28]

The study included 49 subjects age 8 to 17 years using CSII therapy. Subjects were seen during two outpatient visits each with a structured exercise session in the late afternoon. Each exercise session consisted of four 15-minute treadmill cycles at a target heart rate of 140 beats/minute interspersed with three 5-minute rest breaks for a total of 75 minutes. The basal insulin rate from the subject's insulin pump was continued during the exercise on one exercise day. On the other exercise day, the basal rate was discontinued at the start of exercise and was not restarted until the end of the 45-minute postexercise observation period. Glucose measurements were made from venous blood at a central laboratory sample and used a FreeStyle Flash meter prior to starting the exercise, during each of the three rest periods, immediately following the exercise

session, and at 15-minute intervals for 45 minutes following completion of the exercise. At each of these times, samples were also collected for the measurement of counterregulatory hormones. Samples were collected for the measurement of adiponectin prior to starting exercise and immediately following the exercise session. A CGMS was used on both exercise days, and subjects had the option of continuing to wear the CGMS sensor following each visit.

Protocol H: A Comparison of the Counterregulatory Hormone Response to Insulin-Induced Hypoglycemia in Younger and Older Children with T1D[29,30]

The study included 30 subjects using CSII therapy, 15 in the age range of 3 to <7 years and 15 in the age range of 12 to <18 years. Subjects wore a Guardian RT for 1 week and then returned for an 18-hour overnight CRC admission. Some subjects had a second Guardian RT inserted at the time of admission. The OneTouch Ultra meter was used for calibration of the sensors. Samples were drawn for reference blood glucose measurements every 30 minutes during the admission, every 15 minutes following dinner for an assessment of accuracy of the Guardian RT, and at prespecified intervals the next morning during an insulin-induced hypoglycemia test. During this procedure, hypoglycemia was induced by increasing the basal insulin rate on the pump. Blood samples were collected for laboratory determination of glucose and hormone concentrations at baseline (before increasing the insulin infusion) and when the glucose levels were <90, <80, <70, and <60 mg/dl as determined by the OneTouch Ultra meter.

Protocol I: A Pilot Study to Compare High-Fat versus Low-Fat Bedtime Snacks to Prevent Nocturnal Hypoglycemia

The pilot study included 10 subjects age 4 to 18 years (mean age 12.4 years) who were using the FreeStyle Navigator. Subjects completed a questionnaire on the study Web site on 12 nights and were instructed to consume a primarily carbohydrate (low fat) snack on 6 nights and a carbohydrate plus fat (high fat) snack on the other 6 nights. Using a minimization algorithm the Web site provided the bedtime snack type to be consumed on each night, balancing on self-reported presnack glucose level and amount of activity during the day. For each study night, glucose levels were obtained from the Navigator.

Questionnaires[16, 18, 26]

The following questionnaires were developed and validated in DirecNet studies and are available for public use.

Continuous Glucose Monitor Satisfaction Scale

This questionnaire was designed to measure the impact of using a CGM on family diabetes management, general family relationships, and individual emotional, behavioral, and cognitive reactions to use of the device. The initial 37 item scale used in Protocols C and D was expanded to 44 items following those studies. Internal consistency and parent–youth agreement are acceptable, and the scale has demonstrated sensitivity to different CGM devices. The scale was completed by parents/caregivers and children with diabetes who were at least 11 years old.

Insulin Dose Adjustment Guidelines Satisfaction Questionnaire

This questionnaire was developed to measure the frequency, convenience of use, and perceived effectiveness of study-developed algorithms and satisfaction with use of the algorithms in conjunction with HGM and CGM data. The questionnaire was completed by parents/caregivers and children with diabetes who were at least 11 years old.

How to Obtain Data Sets

The DirecNet study group strongly supports NIH's data-sharing principles and has shared data with several outside investigators over the past 6 years. Data sets are or will be available for all completed studies on the DirecNet Web site (http://public.direc.net). Additional information can be obtained by contacting Roy W. Beck, M.D., Ph.D. (rbeck@jaeb.org). We encourage all investigators who might benefit from data that DirecNet has generated to utilize this Web site.

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