A Randomized Multicenter Trial Comparing the GlucoWatch Biographer With Standard Glucose Monitoring in Children With Type 1 Diabetes

THE DIABETES RESEARCH IN CHILDREN NETWORK (DIRECNET) STUDY GROUP

OBJECTIVE — This study assesses whether use of the GlucoWatch G2 Biographer (GW2B) in addition to standard glucose monitoring lowers HbA_{1c} and reduces hypoglycemia compared with standard glucose monitoring alone.

RESEARCH DESIGN AND METHODS — In all, 200 subjects aged 7 to <18 years with type 1 diabetes were randomly assigned at five centers to standard glucose monitoring (usual care) or standard glucose monitoring plus GW2B use for 6 months. Study outcomes included HbA_{1c} values obtained at 6 months and occurrence of severe hypoglycemia.

RESULTS — The mean HbA_{1c} at baseline was 8.0% in both groups; at 6 months, HbA_{1c} was 7.9% in the usual care group and 8.1% in the GW2B group (95% CI for mean reduction in the GW2B group compared with the usual care group −0.4 to 0.1%; $P = 0.15$). A decrease in HbA_{1c} of ≥0.5% was achieved in 21% of the usual care group and 28% of the GW2B group ($P = 0.29$). Severe hypoglycemia events occurred in 7% of the GW2B group and in 2% of the usual care group ($P = 0.10$). In the GW2B group, sensor use declined throughout the study from a mean value of 2.1 times/week in the 1st month to 1.5 times/week in the 6th month. Reasons given for declining use included skin irritation (76%), frequent skips (56%), excessive alarms (47%), and inaccurate readings (33%).

CONCLUSIONS — Use of the GW2B in addition to standard glucose monitoring did not improve glycemic control or reduce the frequency of severe hypoglycemia. Skin reactions and other problems led to decreasing sensor use over time.

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Despite the results of the Diabetes Control and Complications Trial demonstrating the importance of lowering HbA_{1c} levels as close to normal as possible in children and adults (1), management of type 1 diabetes in childhood remains suboptimal with only ~30% of youth having HbA_{1c} values <8% (2–5). Moreover, the incidence of severe hypoglycemia is higher in adolescents than adults (6,7). Estimated prevalence of nocturnal hypoglycemia in children ranges from 36 to 58% with ~50% of these episodes being symptomatic (8,9). Fear of hypoglycemia is a major deterrent to attaining good glycemic control (10). Consequently, the introduction of a near-continuous glucose monitoring device, the GlucoWatch G2 Biographer (GW2B) (Cygnus, Redwood City, CA), with real-time glucose values and alarms for high and low glucose levels, offers the potential to lower both HbA_{1c} levels and frequency of severe hypoglycemia in children with type 1 diabetes.

The GW2B, which is shaped like an enlarged watch, adheres to the skin of an extremity and extracts interstitial fluid from which the glucose level is measured and displayed every 10 min for up to 13 h (11). In a prior inpatient study of pediatric patients with type 1 diabetes, our study group found that the accuracy of the GW2B, although substantially lower than the accuracy of home glucose meters, was sufficient to presume that use of the device could improve management of type 1 diabetes in children (12,13). Results of a small single-center 3-month randomized trial suggested that GW2B use reduced HbA_{1c} and improved hypoglycemia detection in youth with type 1 diabetes (14). Because a larger, more definitive study was needed, we conducted a multicenter randomized trial to determine the effectiveness of the GW2B in children with type 1 diabetes.

RESEARCH DESIGN AND METHODS

The study was conducted by the Diabetes Research in Children Network (DirecNet), funded by the National Institutes of Health. The DirecNet Data and Safety Monitoring Board and the institutional review boards at each center approved the study protocol. A parent or guardian gave written consent, and each subject gave written assent.

Eligibility criteria included *1*) age of 7–18 years, *2*) type 1 diabetes with use of insulin for at least 1 year, *3*) HbA_{1c} level 7.0–11.0% inclusive, *4*) a stable insulin regimen (either a pump or at least two injections/day) for the prior 2 months with no plans to switch modality of insulin administration during the next 6 months, *5*) no prior home use of a GlucoWatch Biographer, *6*) no corticosteroid use in the previous 6 months, and *7*) no

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Abbreviations: CGMS, continuous glucose monitoring system; DirecNet, Diabetes Research in Children Network; GW2B, GlucoWatch G2 Biographer.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

history of cystic fibrosis or another chronic illness that might affect study participation. Eligible subjects needed to successfully complete home glucose monitoring using both an UltraSmart Meter (at least three measurements/day for 4–14 days) and a continuous glucose monitoring system (CGMS) (Medtronic MiniMed, Northridge, CA) (at least 48 h of CGMS use) to be enrolled.

Each subject was randomly assigned with equal probability to either the GW2B group or the usual care group. Randomization was accomplished by study personnel at each clinical center on the study's web page using a permuted-blocks design stratified by clinical center and age-group (7 to <12 and 12 to <18 years).

Home procedures

Subjects in the GW2B group were provided with a GW2B and an unlimited number of sensors. They were encouraged to use sensors as often as desired and instructed to use a minimum of four sensors during the 1st week and then at least two sensors a week thereafter, with at least one weekly use overnight. Subjects in the usual care group were offered a GW2B after the completion of the 6-month follow-up period. Subjects in both groups were provided with a One Touch UltraSmart Meter (Ultra; Lifescan, Milpitas, CA) and an unlimited number of test strips and were asked to measure finger-stick blood glucose levels at least four times a day (i.e., before each meal and bedtime).

Subjects in both groups were given a personal computer for home use to download Ultra and GW2B glucose data and view glucose results on a weekly basis. Subjects were compensated $5 for each on-time download and $2 for each late download. All subjects used the computer to complete a weekly questionnaire on episodes of symptomatic hypoglycemia. The GW2B group was also asked to report any problems that were encountered with use of the device.

At 3 and 6 months, a CGMS sensor was inserted at the clinical center and used by the subject for a minimum of 48 h. The CGMS is a nonviewable continuous glucose monitor that records subcutaneous interstitial glucose values every 5 min (15). The CGMS data were transmitted directly to the coordinating center and not viewed by the clinical center staff or the subjects.

Clinical center procedures

An effort was made to handle subjects in both groups as similarly as possible. Consequently, the study protocol included for both groups follow-up visits at 3 and 6 months and phone contacts after 1, 2, and 4 weeks and then monthly through 6 months to review diabetes management. For the GW2B group, at each visit an assessment of skin reaction was made using a modified Draize scale (16). At the 6-month visit, a satisfaction scale consisting of 37 questions (1–5 Likert scale, with a higher score indicating greater satisfaction) related to use of a continuous glucose monitor was completed by parents of subjects in the GW2B group and by subjects in the GW2B group who were at least 11 years old. The Diabetes Worry Scale (17), a measure of diabetes-related anxiety among parents and youths, Diabetes Self Management Profile (18), a measure of treatment adherence, and PedsQL Diabetes Module (19), a measure of children's diabetes-related quality of life, were also completed at baseline and 6 months.

Laboratory procedures

At baseline and the 3- and 6-month visits, a finger-stick blood sample was sent to the DirecNet Central Laboratory at the University of Minnesota where HbA_{1c} was measured by the Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer method using cation-exchange high-performance liquid chromatography methodology (20).

Statistical methods

The sample size of 200 was selected to have 90% power to detect a mean difference in HbA_{1c} between groups of 0.5%, assuming a standard deviation of 1.0, $\alpha = 0.05$, and 10% losses to follow-up. The primary analysis, which followed the "intent-to-treat" principle, was a treatment group comparison of HbA_{1c} values obtained 6 months after randomization and adjusted for the baseline HbA_{1c} value in an ANCOVA model. As a preplanned secondary analysis, the proportion of patients in each group whose HbA_{1c} level improved from baseline by at least 0.5% were compared using logistic regression controlling for baseline HbA_{1c}. The number of subjects experiencing at least one severe hypoglycemia episode, defined as loss of consciousness or seizure, was compared between groups using Fisher's exact test.

RESULTS — Between July 2003 and January 2004, 200 subjects entered the trial (40 at each of the five clinical centers), with 99 randomly assigned to the GW2B group and 101 to the usual care group. The baseline characteristics of the two groups were similar (Table 1).

All but one subject completed all study visits. The GW2B group had more unscheduled visits (mean per subject 0.2 vs. 0.1 visits, $P = 0.02$) and phone contacts (mean per subject 3.6 vs. 1.9 contacts, $P < 0.001$) than did the usual care group, mostly related to use of the GW2B. The two groups were comparable for weekly computer questionnaire completion (75 vs. 76%, $P = 0.81$) and CGMS usage at 3 months (77 vs. 82%, $P = 0.49$) and 6 months (82 vs. 83%, $P = 0.85$). Home glucose monitoring with the Ultra meter averaged 5.3 ± 1.6 times/day in the GW2B group and 5.0 ± 1.6 times/day in the usual care group ($P = 0.15$); 79 and 75% of the GW2B and usual care groups, respectively, averaged at least four measurements per day ($P = 0.62$).

GW2B use

During the 1st month, the number of sensors used averaged 2.1 ± 0.8 per week, whereas the number of sensors with at least 8 h of use averaged 1.2 ± 0.7 per week. Only 16% of the subjects averaged at least 2.0 uses of ≥8 h/week, and none averaged at least 4.0 uses per week. By the 3rd month, 7 (7%) of the 99 subjects reported discontinued use of the GW2B; by the 6th month, 27 (27%) of the 99 subjects had discontinued use. Among those still using the sensor at 6 months, the number of sensors placed during the last month of the study averaged 1.5 ± 0.6 per week, whereas the number of sensors with ≥8 h of use averaged 0.7 ± 0.5 per week. There were no subjects averaging >3.0 uses/week. The frequency of sensor use was similar across the five clinical centers.

Metabolic control

Mean HbA_{1c} levels were 8.0% at baseline in both groups and did not change significantly during the course of the study (mean HbA_{1c} reduction from baseline to 6 months in GWB group minus that in the usual care group was −0.2% [95% CI

Table 1—*Baseline characteristics by treatment group*

	Usual care	GW2B	All patients
n	101	99	200
Female	47 (47)	45 (45)	92 (46)
Age (years)	12.7 ± 2.9	12.3 ± 2.7	12.5 ± 2.8
Race/ethnicity			
White	85 (84)	84 (85)	169 (85)
Hispanic or Latino	3 (3)	2 (2)	5 (3)
African American	7 (7)	6 (6)	13 (7)
Multiple	5 (5)	4 (4)	9 (5)
Asian	1 (<1)	2 (2)	3 (2)
Unknown/not reported		1 (1)	1 (<1)
Duration of diabetes (years)	5.4 ± 3.1	5.3 ± 3.4	5.4 ± 3.3
Insulin route			
Pump	47 (47)	46 (46)	93 (47)
Injection	54 (53)	53 (54)	107 (54)
Baseline HbA_{1c}	8.0 ± 0.9	8.0 ± 0.9	8.0 ± 0.9
<8.0%	54 (53)	58 (59)	112 (56)
≥8.0%	47 (47)	41 (41)	88 (44)
BMI percentile (%)	66 ± 24	70 ± 23	68 ± 24

Data are *n* (%) or means ± SD.

−0.4 to +0.1]) (Table 2). At 6 months, HbA_{1c} was improved by ≥0.5% in 28% of the GW2B group versus 21% in the usual care group ($P = 0.29$). Analyses in subgroups based on baseline HbA_{1c}, insulin route, age, sex, BMI, and clinical center produced results similar to the overall analysis. CGMS estimates of glycemic control did not differ significantly between groups during the study (Table 2). Among the 72 subjects in the GW2B group who were still using the sensor after 6 months, mean HbA_{1c} was 8.1 compared with 8.0 at baseline; the magnitude of change was similar to that found in the usual care group ($P = 0.16$).

In both groups, the total daily insulin dose increased slightly (mean change from baseline to 6 months was 0.1 ± 0.2 units in the GW2B group and 0.1 ± 0.2 units in the usual care group, $P < 0.001$ in each group by Wilcoxon's signed-rank test). Changes in insulin dosages over the 6 months were made with similar frequency in the GW2B and usual care groups (79% in both groups). The most frequent change was in basal or intermediate-acting insulins (54 and 47%, respectively). Changes in premeal rapid acting insulin were made in 10 and 15% of the two respective groups. A change in HbA_{1c} from baseline to 6 months was not associated with the average number of UltraSmart meter glucose checks per day (Spearman correlation −0.13, $P = 0.19$ in the GW2B group and −0.06, $P = 0.53$ in the usual care group).

Hypoglycemia

Severe hypoglycemia events occurred in seven (7%) subjects (one subject with three events and six subjects with one event) in the GW2B group and in two (2%) subjects (one subject with two events, one with one event) in the usual care group ($P = 0.10$). The number of episodes of symptomatic hypoglycemia reported on the weekly computer questionnaires during the 6 months of the study was slightly higher in the usual care group; this difference was less apparent for data collected on phone calls and at visits (Table 2). The numbers of hypoglycemic episodes per 24 h defined by the CGMS (see Table 2 for definition) were similar in the two groups at 3 and 6 months.

Skin reactions

Skin irritation from wearing the GW2B was reported at least once during the 6-month follow-up period by all 99 subjects either on the weekly computer questionnaire, during a phone contact, or at a visit. One subject's skin reaction was judged to be severe on examination, and 48 subjects (48%) were documented to have moderate reactions. At the 6-month visit, 54 (55%) of the 98 subjects were considered to have acute changes reflective of GW2B use (mild in 36%, moderate in 19%, and severe in 0%), and 50 subjects (51%) were considered to have nonacute changes such as scabbing, dry skin, hypopigmentation, hyperpigmentation, or scarring.

Questionnaires

There were no differences between the two groups at baseline or 6 months on the Diabetes Worry Scale (17), Diabetes Self Management Profile (18), or the Peds QL Diabetes Module (19). Parents' total scores on the Diabetes Self Management Profile, a measure of treatment adherence, declined slightly for both groups from baseline to 6 months; the drop in scores was marginally less for the GW2B group than for the usual care group (1.3 ± 6.6 and 3.4 ± 7.0, respectively, $P = 0.03$). Within the GW2B group, scores on these measures were not correlated significantly with frequency of GW2B use or with change in HbA_{1c} or frequency of hypoglycemia during the study.

At the 6-month visit, the reasons most frequently given for either not still using the GW2B or not using it more often (more than one reason per subject possible) included skin irritation (76%), skips too frequently (56%), alarms too frequently (47%), and does not provide accurate readings (33%). On the satisfaction scale, the mean of the item scores was 2.7 ± 0.7 for subjects and 2.7 ± 0.6 for parents, with 30 of 37 items (81%) for subjects and 27 of 37 items (73%) for parents averaging <3.0 ("neutral"). The items for which the response most often was "agree" or "agree strongly" included "is uncomfortable or painful" (child 76%, parent 77%); "interferes a lot with sports, playing outside, etc." (child 67%, parent 72%); "is more trouble than it is worth" (child 67%, parent 59%); "causes too many interruptions" (child 64%, parent 56%); "makes it harder to sleep" (child 62%, parent 60%); "skips too many readings to be useful" (child 61%, parent 67%); "is too hard to get it working right" (child 59%, parent 60%); "has been harder or more complicated than expected" (child 52%, parent 68%).

CONCLUSIONS — Previously, we evaluated the accuracy of the GW2B by comparing sensor glucose values with frequently sampled reference serum glucose levels in an inpatient setting in youth with

Table 2—*Summary of major study results*

Outcome	Usual care	GW2B	*P* value
n	101	98*	
HbA_{1c} (%)			
Baseline	8.0 ± 0.9	8.0 ± 0.9	
3 months	7.9 ± 0.8	7.9 ± 1.0	
6 months	7.9 ± 0.9	8.1 ± 1.1	
Change from baseline to 6 months	0.0 ± 0.8	0.1 ± 0.8	0.15†
CGMS glucose level (mg/dl)‡			
Baseline	183 ± 39	183 ± 40	
3 months	178 ± 40	178 ± 43	
6 months	182 ± 33	178 ± 36	
Change from baseline to 6 months	−1 ± 46	−4 ± 38	0.34†
Hypoglycemia			
Subjects with severe episode of hypoglycemia (%)§	2	7	0.10‖
Episodes of symptomatic hypoglycemia per week			
Weekly questionnaires¶	2.5 ± 1.6	2.0 ± 1.6	0.03#
Protocol scheduled phone calls	2.2 ± 1.0	2.0 ± 1.0	0.19#
3-month visit	2.2 ± 1.5	1.8 ± 1.4	0.06#
6-month visit	2.2 ± 1.5	2.0 ± 1.5	0.49#
Episodes of hypoglycemia defined by the CGMS per 24 h‡**			
Baseline	1.0 ± 0.9	0.9 ± 0.7	
3 months	0.9 ± 0.9	1.1 ± 1.0	
6 months	0.9 ± 0.8	1.0 ± 0.9	
Change from baseline to 6 months	−0.1 ± 1.0	0.1 ± 0.9	0.27†

Data are means ± SD unless otherwise noted. *Excludes one subject who dropped out of the study post-randomization; †ANCOVA model controlling for baseline value; ‡analysis restricted to subjects who completed ≥40 h of CGMS use averaging ≥3 calibrations per 24 h at baseline ($n = 96$ usual care, $n = 97$ GW2B), 3 months ($n = 85$ usual care, $n = 85$ GW2B), and 6 months ($n = 85$ usual care, $n = 86$ GW2B). Calculation of change from baseline to 6 months is restricted to subjects meeting these CGMS criteria at both time points ($n = 82$ usual care, $n = 85$ GW2B); §defined as seizure or loss of consciousness, anytime from baseline to 6 months. ‖Fisher's exact test; ¶excludes one subject in the usual care group who did not complete any of the weekly questionnaire; #Wilcoxon rank-sum test; **CGMS episode of hypoglycemia defined as at least two values ≤60 mg/dl with no intermediate values >70 mg/dl. Distinct episodes were required to be separated by at least 30 min.

type 1 diabetes (12,13). Although the accuracy of individual glucose measurements, particularly for hypoglycemia, was not high enough to make real-time management decisions without a confirmatory home glucose meter measurement, the sensor glucose trends in that study generally paralleled the reference glucose values. These observations served as the rationale for the current study. We hypothesized that the added data from day and nighttime GW2B tracings could improve glycemic control in children and adolescents with type 1 diabetes compared with standard diabetes management.

To test this hypothesis, we carried out a parallel group randomized clinical trial involving 200 youngsters between 7 and 18 years of age with type 1 diabetes. We found that use of the GW2B in addition to standard blood glucose monitoring did not result in an improvement in glycemic control or a reduction in the frequency of severe hypoglycemia compared with the usual care control group.

The treatment groups were well balanced at baseline with respect to clinical characteristics, and the follow-up rate in the trial was very high; all but one of the randomized subjects completed the trial. The large sample size and low dropout rate provided the trial with sufficient power to detect a meaningful difference in HbA_{1c} levels between the two groups had such a difference existed. However, the incidence of severe hypoglycemia in the usual care group was so low (2%) that the trial had little ability to determine whether use of the GW2B could reduce this incidence. Personnel staffing the five clinical centers in the DirecNet Study Group have considerable expertise in the management of type 1 diabetes in children. All personnel had experience with the use of the GW2B before the start of the study, and similar results were achieved at each center. Thus, failure to show an effect of the GW2B cannot be attributed to a lack of experience with the use of the device at the centers involved in the study.

The failure to observe a significant effect of the GW2B on overall metabolic control of diabetes may be due to the failure of subjects to use the sensor frequently enough to affect their diabetes management. At the start of the study, subjects and their parents were given the device and offered an unlimited supply of sensor pads at no cost, and they received encouragement during scheduled telephone contacts to use the GW2B as often as possible. Despite these efforts, no subject averaged ≥4 days/week of GW2B use of at least 8 h, even during the 1st month. In contrast, the subjects were remarkably conscientious in following recommendations regarding performance of at least four UltraSmart meter tests per day. Therefore, the failure to demonstrate a benefit of the GW2B cannot be explained by the enrollment of children who were generally noncompliant with their diabetes treatment regimen. Use of the GW2B appeared to have little if any effect on the psychosocial measures that were obtained. A negligible difference in deterioration of treatment adherence during the study favoring the GW2B group was the only such effect that was observed. The absence of effects on quality of life and other dimensions of adjustment to diabetes is not surprising given the low and declining frequency of GW2B use and the absence of substantial glycemic effects. Similarly, satisfaction with use of the GW2B was generally negative for both subjects and parents. The reasons varied for not using the GW2B more frequently, but skin irritation was most commonly cited. Inability of the families to use the sensor data effectively may be a reason why the sensors were not used more often and why their use did not improve glycemic control. The staff at the clinical centers only reviewed the sensor data at the specified times (for phone calls and visits). Whether or not more intensive review of the data with the families (e.g., weekly for the duration of the study) could have had a greater impact on glyce-

mic control cannot be ascertained. However, it is unrealistic to expect that the degree of involvement between the diabetes team and patients in clinical practice could be any greater than what it was in the study.

Our findings differ from those of a previous randomized trial of the GW2B in 40 children with type 1 diabetes (14). In that study, HbA_{1c} levels were decreased more in subjects using the GW2B versus those receiving usual care; hypoglycemia detection was also reported to be enhanced with GW2B use, which averaged 3.5 times/week (about twice the average in the current study). In the prior study, the GW2Bs were brought to a clinic each week where the glucose data were downloaded and analyzed by a physician. In contrast, in the current study GW2B data were reviewed with the family by phone with a nurse-coordinator rather than a physician at less frequent intervals with the intent to have the families learn to use the data in their home for better diabetes management. The previous study required HbA_{1c} ≥8.0% for study eligibility (compared with ≥7.0% in the current study); however, the results of the current study showed no difference in HbA_{1c} outcome between treatment groups when the analysis was limited to subjects with a HbA_{1c} level of at least 8.0%.

Our results raise issues that apply generally to continuous glucose monitors. The ultimate goal for this technology is to have a device that is accurate and easy enough to be used on a daily basis, without the need for a home glucose meter other than for calibration purposes. A continuous glucose monitor that is used for only a small portion of the week may have limited use as a real-time device because daily management must still depend on frequent glucose measurements with a home glucose meter. For patients to accept such a device, the perceived benefit from the device must outweigh side effects such as skin irritation and inaccuracies. Much still needs to be learned about algorithms that can be used to assist patients and clinicians in optimal use of real-time continuous glucose monitor data for diabetes management.

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APPENDIX

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