Evaluation of an Algorithm to Guide Patients With Type 1 Diabetes Treated With Continuous Subcutaneous Insulin Infusion on How to Respond to Real-Time Continuous Glucose Levels

A randomized controlled trial

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OBJECTIVE — To evaluate an algorithm guiding responses of continuous subcutaneous insulin infusion (CSII)–treated type 1 diabetic patients using real-time continuous glucose monitoring (RT-CGM).

RESEARCH DESIGN AND METHODS — Sixty CSII-treated type 1 diabetic participants (aged 13–70 years, including adult and adolescent subgroups, with A1C ≤9.5%) were randomized in age-, sex-, and A1C-matched pairs. Phase 1 was an open 16-week multicenter randomized controlled trial. Group A was treated with CSII/RT-CGM with the algorithm, and group B was treated with CSII/RT-CGM without the algorithm. The primary outcome was the difference in time in target (4–10 mmol/l) glucose range on 6-day masked CGM. Secondary outcomes were differences in A1C, low (≤3.9 mmol/l) glucose CGM time, and glycemic variability. Phase 2 was the week 16–32 follow-up. Group A was returned to usual care, and group B was provided with the algorithm. Glycemia parameters were as above. Comparisons were made between baseline and 16 weeks and 32 weeks.

RESULTS — In phase 1, after withdrawals 29 of 30 subjects were left in group A and 28 of 30 subjects were left in group B. The change in target glucose time did not differ between groups. A1C fell (mean 7.9% [95% CI 7.7–8.2to 7.6% [7.2–8.0]; $P < 0.03$) in group A but not in group B (7.8% [7.5–8.1] to 7.7 [7.3–8.0]; NS) with no difference between groups. More subjects in group A achieved A1C ≤7% than those in group B (2 of 29 to 14 of 29 vs. 4 of 28 to 7 of 28; $P = 0.015$). In phase 2, one participant was lost from each group. In group A, A1C returned to baseline with RT-CGM discontinuation but did not change in group B, who continued RT-CGM with addition of the algorithm.

CONCLUSIONS — Early but not late algorithm provision to type 1 diabetic patients using CSII/RT-CGM did not increase the target glucose time but increased achievement of A1C ≤7%. Upon RT-CGM cessation, A1C returned to baseline.

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Real time-continuous glucose monitoring (RT-CGM) can be integrated with a continuous subcutaneous insulin infusion (CSII) device (1,2). Interstitial glucose readings, with direction and rate of change, are displayed and linked to low and high glucose alarms. Data can be uploaded and reviewed retrospectively. Apart from recent devices with automatic shutoff for low glucose, RT-CGM cannot initiate insulin delivery. Insulin changes must be initiated by the patient or caregiver. Continuous glucose monitoring (CGM) data interpretation can be difficult, and advice guiding insulin or lifestyle change may enhance benefits (3).

In this study, we tested the glycemia effects of an algorithm guiding responses to RT-CGM in CSII-using type 1 diabetic subjects. We also evaluated whether glucose changes persisted after RT-CGM withdrawal and whether late algorithm introduction improved glycemia.

RESEARCH DESIGN AND METHODS

— The study was an ethics committee–approved randomized controlled trial at three adult and two pediatric Australian centers. Written informed consent was obtained, including guardian consent for pediatric participants.

Participants were recruited in pairs matched for age (within 5 years), sex, and A1C (within 1%). Inclusion criteria were age >13 years, type 1 diabetes duration >1 year, >3 months CSII with bolus calculator use, A1C ≤9.5%, self-monitoring

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of blood glucose ≥4 times daily, Internet access, and willingness to use RT-CGM for 6 of each 7 days for the study duration. Exclusion criteria were physical or intellectual limitations, renal impairment (estimated glomerular filtration rate <60 ml/min), using or likely to require steroid therapy, gastroparesis, untreated celiac or thyroid disease, hemoglobinopathies, regular blood transfusions, current or planned pregnancy, and breast-feeding.

No data were available regarding glycemia after RT-CGM initiation at time of study design. The only CGM data available were retrospective continuous glucose monitoring system (Medtronic, Northridge, CA) traces recorded within 3 months after CSII commencement (without RT-CGM) in 40 patients at one adult center, which demonstrated a 33% increase in 4–10 mmol/l time to 58% (17%) and mean ± SD A1C reduction from 7.9 ± 1.4 to 7.1 ± 1.0%. A between-group difference in the target glycemia time increment of 25% was chosen for the study because the impact of RT-CGM and the algorithm was expected to be less than that of CSII initiation. Thirty participants in each (algorithm and nonalgorithm) group had >99% power to detect a 25% difference between groups at the 0.05 significance level. Corresponding power for 18 adults and 12 adolescents per group was >95 and >90%, respectively.

Protocol

A history was obtained, physical examination was performed, and blood and urine were collected. BMI SD score was calculated for adolescents (4). All participants were provided with and educated in operation of the MiniMed MMT 722 Paradigm Real-Time system and web-based CareLink software (Medtronic) for glucose and pump parameter review (1,2). A prerandomization 6-day masked CGM device (Guardian System; Medtronic) was worn without wearer access to real-time glucose information, and data were uploaded by users. Real-time sensor function was not activated until randomization.

Phase 1

Participant pairs were computer-randomized centrally to receive the algorithm (group A) or no further RT-CGM interpretation guidelines (group B) for 16 weeks. All participants were requested to wear the sensor, which was to be changed every 3 days, for 6 of 7 days. All were instructed to upload to Carelink, review their RT-CGM data every 1–2 weeks, and alter their insulin delivery accordingly. One week before the end of phase 1, the 6-day masked CGM device was worn along with the unmasked Paradigm device, with both linked to a single transmitter.

Phase 2

Group A participants returned to usual care (CSII without RT-CGM) and were followed for a further 16 weeks. Group B participants continued CSII/RT-CGM, were provided the algorithm, and were followed for 16 weeks. One week before the end of phase 2, the 6-day masked CGM device was again worn.

All participants received routine care from their own health professionals with no additional clinician visits. A safety-monitoring team, not involved in participant care, accessed uploaded CGM data, which were only made available to care providers if the individual was judged to be at risk of severe hypoglycemia or ketoacidosis.

Algorithm

A two-part (reactive and proactive) algorithm advising responses to RT-CGM was devised by physicians and certified diabetes nurse educators (DNEs) with input from CSII-using (nonstudy participant) patients. (Supporting information is found in supplementary Appendix A, available at http://care.diabetesjournals.org/cgi/content/full/dc09-1481/DC1. This includes the wallet card [reactive algorithm], wall chart [proactive algorithm], and teaching manual.) The algorithm was to guide immediate responses to glucose levels and trends, as well as proactive changes to pump basal insulin settings, insulin to carbohydrate ratios, and correction factors. Participants assigned to receive the algorithm in phase 1 (group A) received education, averaging 90 min, either on a one-to-one basis or in pairs. They were provided with paper and electronic versions of the algorithm, a wallet card summarizing reactive guidelines, and a wall chart summarizing proactive changes to assist RT-CGM upload review (available at http://www.diabetesccre.unimelb.edu.au). In response to phase 1 (group A) comments, phase 2 (group B) participants were also given a handset summarizing the reactive algorithm. After entering the glucose level, number and direction of arrows, and time since food and relation to bedtime, the suggested algorithm response would appear on-screen. The participant entered whether he or she agreed or disagreed. Handset interactions were automatically transmitted to a remote database. Site uniformity was ensured by a prestudy group meeting of DNEs to review the education document and the lead site DNE observing each site's algorithm teaching.

Glycemia

Six-day masked CGM data at baseline and study end were used to quantify percent time in target (4.0–10.0 mmol/l), low (≤3.9 mmol/l), and high (≥10.1 mmol/l) glucose ranges. Glycemic variability was estimated by mean amplitude glycemic excursion (MAGE) (5). A1C (baseline, 16 weeks, and 32 weeks) was quantified by an independent Diabetes Control and Complications Trial–accredited laboratory (Primus CLC330 affinity high-pressure liquid chromatography analyzer). Phase 1 primary outcome was the difference between algorithm and nonalgorithm groups in target glucose time. Secondary outcomes were differences in A1C, time in low and high glucose ranges, and MAGE derived from CGM traces. Phase 2 outcomes were glycemia as above, comparing 32 weeks with 16 weeks and baseline.

Statistics

SAS (version 9.1.3; SAS Institute, Cary, NC) was used. For continuous data (percent target, high and low glucose time, A1C, and MAGE), two-way repeated-measures ANOVA was used. Models included tests of time, algorithm use, and the interaction term for time by algorithm use. Count data (percentage with A1C ≤7%) used Fisher's exact test for between-group comparisons and the McNemar test for paired proportions. Correlations are Spearman correlations. Significance was taken at $P < 0.05$.

RESULTS — Of 60 recruits (from 68 patients approached), 57 (95%) returned for the phase 1 end visit, with withdrawals as noted in Fig. 1. Fifty-six commenced phase 2 as 1 (group B) adult discontinued because of severe skin reactions to adhesives. One group A adult was lost to follow-up (Fig. 1). Masked 32-week CGM data were unavailable for four (three group A and one group B) participants (two declined to wear the device, one device failed to record, and one device failed to upload). Baseline characteristics are shown in Table 1.

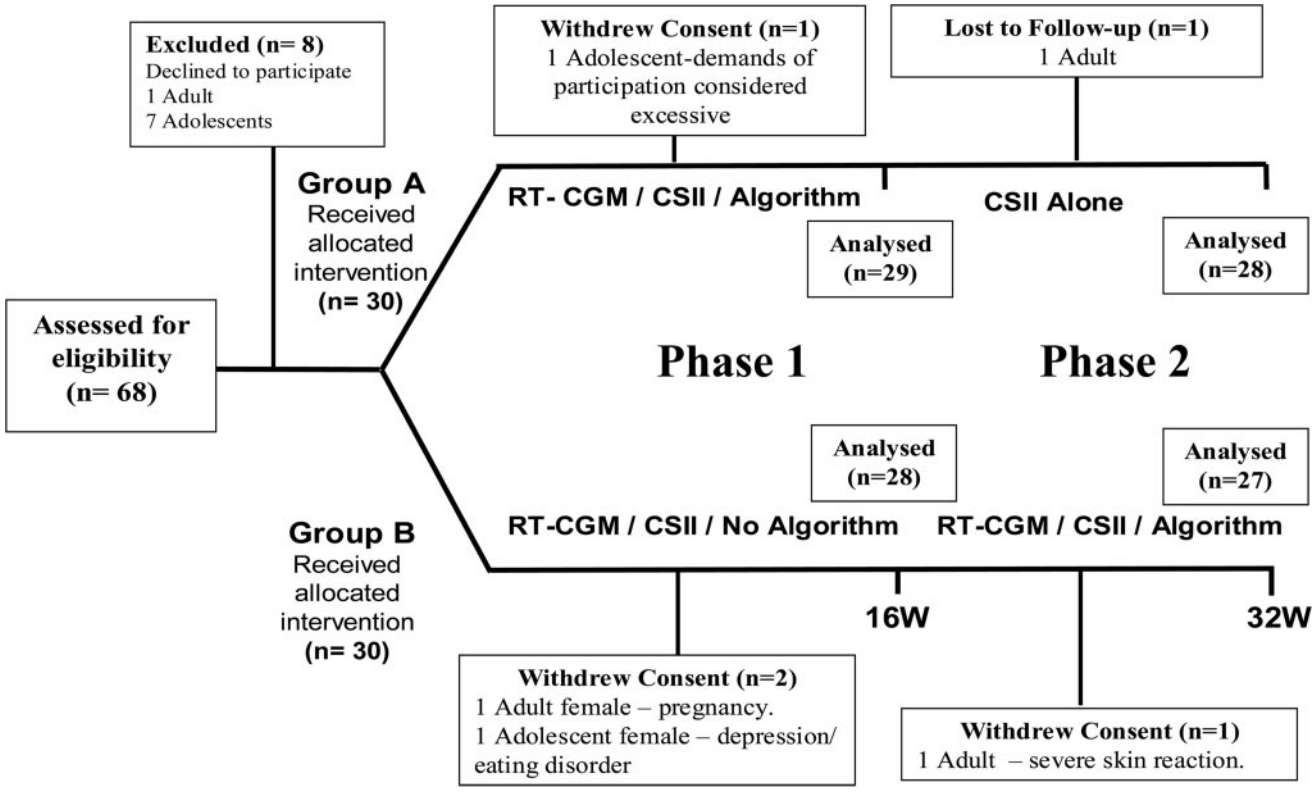

Figure 1—*Flow of participants through the study.*

Sensor use

Mean ± SD sensor use in phase 1 was 4.5 ± 1.3 days/week and did not differ between subjects provided versus not provided the algorithm (4.7 ± 1.0 vs. 4.4 ± 1.5 days). Sensor use was greater in adults than in adolescents (4.8 ± 1.3 vs. 4.1 ± 1.0 days; $P = 0.02$). Sensor use by group B in phase 2 (4.3 ± 1.5 days) did not differ from that in phase 1.

Glycemia

Phase 1. There were no statistically significant differences in target glucose time changes in group A or B nor any difference by algorithm assignment. A1C decreased in group A ($P = 0.03$) but not in group B (Fig. 2*A*). A1C change did not vary significantly by algorithm assignment. More participants in group A than in group B achieved A1C ≤7.0% ($P = 0.015$). In both groups, MAGE and low glucose time did not change significantly (Table 2).

A1C for group A adults decreased ($P < 0.001$). The difference between groups A and B approached significance ($P = 0.08$) (Fig. 2*B*). More group A adults achieved A1C ≤7.0% (2 of 18 at baseline and 13 of 18 at 16 weeks) than group B adults (4 of 17 at baseline and 6 of 17 at 16 weeks; $P = 0.0045$). A1C did not change in adolescents (Fig. 1*C*) nor vary by algorithm assignment. A1C change differed between algorithm-assigned adults and adolescents by 0.77% (0.62 ± 0.43% reduction in adults vs. 0.15 ± 0.99% increase in adolescents; $P = 0.032$).

The association of A1C (16 weeks) with sensor use time, age-group, and (time using sensor × age-group) interac-

Table 1—*Baseline clinical characteristics of adult and adolescent CSII-RT-CGM users randomized to group A or group B who returned for the 16-week visit*

	All subjects		Adult subjects		Adolescent subjects	
	Group A	Group B	Group A	Group B	Group A	Group B
Subjects (male/female)	11/18	11/17	6/12	6/11	5/6	5/6
Age (years)	30.3 ± 14.8	29.7 ± 14.0	37.7 ± 12.0	39.1 ± 12.5	16.7 ± 1.2	16.7 ± 1.6
Diabetes duration (years)	14.6 ± 10.1	15.4 ± 10.4	18.7 ± 10.0	18.7 ± 11.4	7.8 ± 5.5	10.1 ± 6.4
CSII (years)	2.6 ± 1.7	2.5 ± 1.6	2.6 ± 1.9	2.7 ± 1.8	2.4 ± 1.6	2.3 ± 1.1
Total insulin (units/kg/day)	0.68 ± 0.15	0.74 ± 0.29	0.64 ± 0.12	0.62 ± 0.24	0.76 ± 0.16	0.93 ± 0.27
BMI (kg/m^2)	NA	NA	27.5 ± 3.1	28.5 ± 7.0	1.71 ± 0.45	1.26 ± 0.75
Macrovascular disease	0/29	2/28	0/18	2/17	0/11	0/11
Neuropathy	2/29	1/28	1/18	1/17	1/11	0/11
Retinopathy	1/29	2/28	1/18	2/17	0/11	0/11
Nephropathy	2/29	0/28	1/18	0/17	1/11	0/11

Data are expressed as *n* or means ± SD. Adolescent subjects results are expressed as BMI SD scores (4). NA, not applicable.

Table 2—*Glycemia variables before and after intervention*

Parameter	Baseline*	16 weeks	32 weeks	Phase 1 P_{time} (baseline–16 weeks)	Phase 1 $P_{interaction}$	Phase 2 P_{time} (16–32 weeks)	P_{time} (baseline–32 weeks)
n		57†	55†				
Target range (% time)							
Group A	55.2 (49.5–60.0)	55.1 (48.2–62.0)	53.4 (46.6–60.3)	0.9062	0.3077	0.4442	0.5864
Group B	61.0 (56.2–65.9)	56.8 (49.4–64.1)	58.9 (53.0–66.8)	0.1235		0.3830	0.6351
A1C (%)							
Group A	7.9 (7.7–8.2)	7.6 (7.2–8.0)	8.1 (7.6–8.6)	0.0305	0.3488	0.0196	0.4792
Group B	7.8 (7.5–8.1)	7.7 (7.3–8.0)	7.7 (7.4–8.1)	0.3639		0.5191	0.5918
A1C ≤7.0%							
Group A	2/29	14/29	5/28	0.0005	0.0148	0.0114	0.0833
Group B	4/28	7/28	7/27	0.2568		1.0000	0.1573
Low range (% time)							
Group A	4.8 (2.1–7.4)	4.5 (2.3–6.7)	4.1 (2.3–5.9)	0.8787	0.2920	0.5919	0.6298
Group B	4.5 (2.8–6.1)	2.1 (0.86–3.4)	3.3 (1.9–4.7)	0.0301		0.1786	0.0855
MAGE (mg/dl)							
Group A	103.3 (93.8–112.8)	100.5 (89.0–112.1)	106.9 (95.3–118.6)	0.6498	0.2651	0.6929	0.4750
Group B	104.1 (92.8–115.4)	92.1 (85.1–99.1)	98.6 (88.4–108.9)	0.0605		0.2986	0.4895

Data are means (95% CI) or *n*. *Baseline parameters are provided for those participants who returned for the 16 week visit. †Guardian CGM data were available for 56 participants at 16 weeks and 51 participants at 32 weeks.

tion was determined by linear regression. A1C was inversely associated with sensor use time ($B = -0.025$, $P = 0.028$) and adulthood ($B = -2.03$, $P = 0.014$). The inverse association of A1C with sensor use time was similar in adults and adolescents (P for interaction term = 0.248).

The phase 1 mean ± SD number of pump-setting (basal rate and insulin-to-carbohydrate ratio) changes was greater in the algorithm group than in the no algorithm group (12.7 ± 11.6 vs. 6.3 ± 6.5 changes; $P = 0.0164$) and was similar in adults and adolescents (11.3 ± 11.3 vs. 7.1 ± 6.8; $P = 0.14$). A trend was observed between the number of pump-setting changes and (16 weeks) A1C in algorithm users ($r = -0.35$; $P = 0.07$) but not in those without the algorithm ($r = 0.08$; $P = 0.7$).

Phase 2. In group A, A1C at 32 weeks was higher than that at 16 weeks and similar to baseline (Fig. 2*A*) for the whole group, driven by the adults (Fig. 2*B*). A1C in adolescents did not change significantly (Fig. 2*C*). There were no significant changes in target or low glucose time or MAGE.

In group B, there were no significant changes in target or low glucose times, A1C, or MAGE at 32 weeks versus baseline or 16 weeks. Handset use was greater in adults versus adolescents (mean 118 [range 0–434] vs. 50 [0–260] interactions; $P = 0.05$). Users disagreed with algorithm-handset advice on 1.6 ± 2.3% interactions, being similar in adults and adolescents (1.7 ± 2.4 vs. 1.5 ± 2.2%; $P > 0.5$). The number of handset interactions correlated with percent target range time ($r = 0.4$; $P = 0.04$) and A1C at 32 weeks ($r = -0.5$; $P = 0.009$) and change in A1C between 16 and 32 weeks ($r = -0.4$; $P = 0.04$). More than 80% of handset interactions occurred within the first month (Fig. 2*D*).

Adverse events

One phase 1 group B female adolescent developed depression and an eating disorder. One group A male adult had severe skin reactions to sensor adhesives. Another group A male adult experienced a sensor insertion site infection requiring outpatient antibiotics. One male adolescent and one female adult, both group A, experienced two severe hypoglycemic episodes in phase 1, attributable to guideline breaches (sensor alarms turned down, inappropriate sensor calibration, bolus administration without bolus calculator use, and deliberate entry of inaccurate data into the bolus calculator). In phase 2 one group A female adult experienced a severe hypoglycemic episode. Four participants had pump malfunctions requiring replacement.

CONCLUSIONS — CSII-experienced type 1 diabetic patients commencing RT-CGM provided a decision support algorithm (group A) did not change target glucose time, the primary study end point, but their A1C fell significantly. There was no change in those without the algorithm (group B) and between-group differences were not significant. A significantly greater proportion of patients in group A achieved A1C ≤7.0%, without increased low glucose time.

In the present study, MAGE at baseline was in the range consistent with type 1 diabetes (5,6) and did not improve significantly with RT-CGM use with or without the algorithm. This lack of benefit, in keeping with previous observations (6,7), may represent limitations of both the algorithm itself and the tools used to measure glycemic variability.

No studies (6–12) have examined the glycemia impact of specific education on Rt-CGM outcomes. The Australian Sensor Augmented Pump Study (ASAPS) evaluated naive RT-CGM use (6), comparable to phase 1 group B of this study. In ASAPS, after 12 weeks, 56% RT-CGM users achieved A1C ≤7.0%, with a mean study end A1C of 7.1% and a 0.2% reduction. In comparison, after 16 weeks of unguided sensor use, group B A1C fell by 0.1% to 7.7%, with only 25% achieving the target. Baseline glycemia of ASAPS subjects was lower than that in the present study, suggesting the importance of patient characteristics.

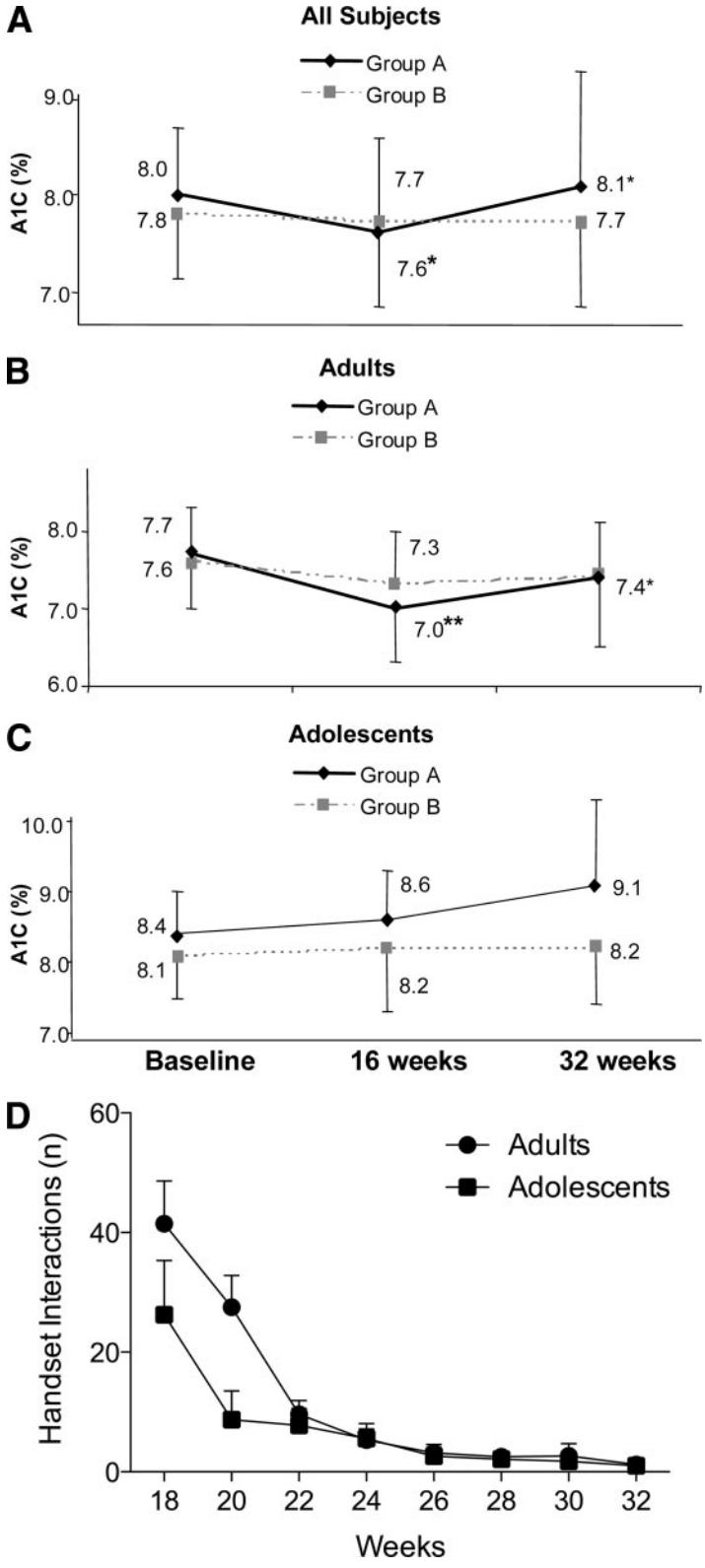

Figure 2—*A1C at baseline, 16 weeks, and 32 weeks according to study group in all participants* (A)*, adult participants* (B)*, and adolescent participants* (C) *who returned for the 32-week visit.* D*: Number of interactions with handsets providing "reactive" guidelines on how to respond to real-time glucose levels.* *P < *0.05, compared with baseline for the 16-week data and compared with 16 weeks for the 32-week data.* **P < *0.0001, 16 weeks compared with baseline.*

In other studies (7,9), instructions and guidance regarding responses to RT-CGM were provided, although protocols were not structured to determine education impact. Thus, the relative contributions of health caregiver guidance versus that initiated by patients cannot be discerned. In our study health caregivers could not access RT-CGM information; thus, we can examine the benefit of patient education alone.

Intensive diabetes management with frequent follow-up has clear benefits (13,14) but requires substantial staff and financial resources (15). Some RT-CGM studies followed participants at intervals of 2–3 weeks (7,9) in person or by telephone (I. Hirsch, MD, University of Washington, personal communication), although recent evidence suggests a benefit for RT-CGM in conventional clinical settings (16). The additional (~90 min) algorithm education in this study is less burdensome on the limited resources that characterize many health care systems.

The timing of algorithm provision relative to CSII/RT-CGM commencement may have an impact on outcome. When the algorithm and ongoing RT-CGM were provided after 16 weeks naive CSII/RT-CGM use, glycemia was unchanged. Perhaps during the initial unguided 16 weeks, RT-CGM participants developed their own responses, which could not then be modified by a relatively short teaching session. In contrast, at baseline when RT-CGM was novel, participants would have had no preconceived ideas and may have more readily used the algorithm provided.

During phase 1 it was not known whether subjects consulted the algorithm. Indirect evidence supporting the proactive instruction use may be the greater number of pump-setting changes made by the algorithm-provided group. The handsets incorporated into phase 2 documented consultation of the reactive algorithm. Despite lack of A1C reduction after algorithm provision, the number of handset interactions correlated inversely with target glucose time, 32-week A1C, and A1C changes between 16 and 32 weeks. The observed initial intensive handset interaction, which then declined, may indicate that patients incorporate the reactive changes with time. This is the first time that such technology has been used to document patient behavior.

By follow-up of (group A) participants initially allocated the algorithm, we determined whether RT-CGM benefit

continues after its cessation. Sixteen weeks after reversion to usual care with CSII alone, A1C returned to baseline, indicating that ongoing RT-CGM use is required to maintain A1C improvements. This finding supports previous data relating sensor use time with glycemia (6–9), although we believe this is the first study to formally examine RT-CGM withdrawal.

The challenges of glycemic control in adolescents with type 1 diabetes, including those using CSII is recognized (17–22). Our findings complement those of the Juvenile Diabetes Research Foundation (JDRF) study in which 15–24 year olds assigned RT-CGM had a A1C fall of only 0.18% from a baseline of 8.0% (7). In contrast, ASAPS (6) demonstrated an A1C benefit in adolescents. Baseline glycemia of ASAPS adolescents was better than that of the JDRF cohort (7) or that in the present study, and the time for which the sensor was used was greater in ASAPS than in this study, both of which may have influenced outcome.

Despite the observed A1C benefit, baseline and 16-week masked CGM data in algorithm users did not increase target glucose time. Lack of concordance between A1C and CGM data is not unique (6). Subject numbers could limit statistical power to detect modest differences in glycemia reflected by CGM. Another contributor may be differences between glycemia assessments of 6 days (CGM) and 3 months (A1C). However, analysis of phase 1 CGM uploads (not shown) regarding target glucose time did not suggest an early impact of the algorithm that was later lost. CGM use may also have altered subject behavior, with a greater impact at baseline when it was novel than at 16 and 32 weeks when it was routine.

Despite more algorithm-assigned adults reaching target A1C ≤7%, the prestated primary end point, target glycemia time, was not met, and the difference in A1C change between groups did not achieve statistical significance. It may be that these established CSII-using patients already had sufficient diabetes-related education, with addition of the algorithm resulting in minor benefit. Inherent bolus calculator limitations may have also affected outcome. Finally, at algorithm formulation time, there was limited experience with RT-CGM data usage. We acknowledge that the algorithm requires refinement. For example, based on glucose trend arrow information, it did not suggest increments in premeal insulin doses above that recommended by the bolus calculator, nor were changes in premeal bolus timing suggested.

A remaining question is whether the adult A1C benefit 16 weeks after RT-CGM and algorithm provision is maintained over an extended time. Exploration of glycemia benefit durability is particularly important in light of a DirecNet Study report of declining sensor use between 13 and 26 weeks and rising A1C, despite initial improvement (23). There is a technology-associated burden, indicated by our observation that even without cost barriers most participants chose not to use real-time sensors 100% of their availability. Finally, study participants are generally well-motivated, and the benefit we observed in algorithm-assigned adults may not translate to the general adult type 1 diabetic population.

RT-CGM provides additional information regarding glycemia. Data collection is not an end in itself, rather it is the enactment on the acquired information that is important. An algorithm informing responses of CSII-using type 1 diabetic patients to RT-CGM data has been devised and evaluated. Some benefit in adults has been demonstrated and may be enhanced by algorithm refinement. Adolescent management merits reevaluation.

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