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Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial

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IMPORTANCE Previous clinical trials showing the benefit of continuous glucose monitoring (CGM) in the management of type 1 diabetes predominantly have included adults using insulin pumps, even though the majority of adults with type 1 diabetes administer insulin by injection.

OBJECTIVE To determine the effectiveness of CGM in adults with type 1 diabetes treated with insulin injections.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted between October 2014 and May 2016 at 24 endocrinology practices in the United States that included 158 adults with type 1 diabetes who were using multiple daily insulin injections and had hemoglobin A1c (HbA1c) levels of 7.5% to 9.9%.

INTERVENTIONS Random assignment 2:1 to CGM (n = 105) or usual care (control group; n = 53).

MAIN OUTCOMES AND MEASURES Primary outcome measure was the difference in change in central-laboratory–measured HbA1c level from baseline to 24 weeks. There were 18 secondary or exploratory end points, of which 15 are reported in this article, including duration of hypoglycemia at less than 70 mg/dL, measured with CGM for 7 days at 12 and 24 weeks.

RESULTS Among the 158 randomized participants (mean age, 48 years [SD, 13]; 44% women; mean baseline HbA1c level, 8.6% [SD, 0.6%]; and median diabetes duration, 19 years [interquartile range, 10-31 years]), 155 (98%) completed the study. In the CGM group, 93% used CGM 6 d/wk or more in month 6. Mean HbA1c reduction from baseline was 1.1% at 12 weeks and 1.0% at 24 weeks in the CGM group and 0.5% and 0.4%, respectively, in the control group (repeated-measures model \( P < .001 \)). At 24 weeks, the adjusted treatment-group difference in mean change in HbA1c level from baseline was −0.6% (95% CI, −0.8% to −0.3%; \( P < .001 \)). Median duration of hypoglycemia at less than 70 mg/dL was 43 min/d (IQR, 27-69) in the CGM group vs 80 min/d (IQR, 36-111) in the control group (\( P = .002 \)). Severe hypoglycemia events occurred in 2 participants in each group.

CONCLUSIONS AND RELEVANCE Among adults with type 1 diabetes who used multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA1c level during 24 weeks. Further research is needed to assess longer-term effectiveness, as well as clinical outcomes and adverse effects.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT02282397


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only approximately 30% of individuals with type 1 diabetes meet the American Diabetes Association goal of hemoglobin A1c (HbA1c) level of 7.5% (58 mmol/mol) for children (<18 years) and 7.0% (53 mmol/mol) for adults (≥18 years), indicating the need for better approaches to diabetes management. Continuous glucose monitoring (CGM) with glucose measurements as often as every 5 minutes, plus low and high glucose level alerts and glucose trend information, has the capability of better informing diabetes management decisions than blood glucose meter testing performed several times a day. Randomized clinical trials have demonstrated the benefit of CGM in adults with type 1 diabetes, but not consistently in children, to improve glycemic control as measured by HbA1c level and to reduce hypoglycemia. These previous trials have either completely or predominantly included insulin pump users, although the majority of adults with type 1 diabetes deliver insulin via injections.

Only a small proportion of individuals with type 1 diabetes who inject insulin use CGM, although the limited available observational data suggest that the glycemic benefit may be comparable to that for pump users. In TID Exchange registry 2015 data, mean HbA1c level in the 410 adult insulin injectors using CGM was similar to that in 2316 pump users using CGM (7.6% vs 7.7%, respectively) and lower than mean HbA1c level in the 6222 injection users not using CGM (7.6% vs 8.8%; P < .001).

Whether individuals receiving insulin injections would be willing to regularly wear CGM sensors and would derive glycemic benefits from CGM needs investigation. Accordingly, this randomized multicenter clinical trial was conducted to evaluate the effect of CGM in adults with type 1 diabetes who have elevated HbA1c levels and use multiple daily injections of insulin.

Methods

The trial was conducted at 24 endocrinology practices in the United States (19 community-based and 5 academic centers). The protocol and Health Insurance Portability and Accountability Act–compliant informed consent forms were approved by institutional review boards (central commercial board for 17 sites and local boards for the other 7 sites). Written informed consent was obtained from each participant. The protocol is provided online and the statistical analysis plan is available in Supplement 1.

Study Participants

Major eligibility criteria included age 25 years or older, diagnosis of type 1 diabetes treated for at least 1 year with multiple daily insulin injections, central laboratory–measured HbA1c level of 7.5% to 10.0%, no home use of a personal CGM device in the 3 months before the trial, and a negative pregnancy test for women of childbearing potential (eTable 1 in Supplement 2 has a complete listing of the inclusion and exclusion criteria).

Synopsis of Study Design

Each participant was required to complete a 2-week prerandomization phase using a CGM system that was configured to record glucose concentrations not visible to the participant (referred to as a “blinded” CGM). Eligibility required that the blinded CGM be worn on at least 85% of possible days, the CGM be calibrated at least 2 times per day, and blood glucose meter testing (with a study-provided meter and test strips) be performed at least 3 times daily. Fourteen participants did not meet these criteria and did not continue into the randomized trial (Figure 1). One participant had a sudden death during the prerandomization phase.

On the study website, after verification of eligibility from data entered, each participant was assigned randomly from a computer-generated sequence to either the CGM or control group in a 2:1 ratio, with a permuted block design (block sizes of 3 and 6) stratified by HbA1c level (<8.5% and ≥8.5%). A 2:1 randomization was used rather than 1:1 to provide a larger sample size for a separate follow-on randomized trial assessing glycemic benefits of initiating pump therapy in CGM users using insulin injections.

Participants in the CGM group were provided with a CGM system (Dexcom G4 Platinum CGM System with an enhanced algorithm, software SOS, Dexcom Inc) that measured glucose concentrations from interstitial fluid in the range of 40 to 400 mg/dL every 5 minutes for up to 7 days. Participants in both groups were provided with a Bayer Contour Next USB meter and test strips. The CGM group was instructed to use the CGM daily, calibrate the CGM twice daily, and verify the CGM glucose concentration with the blood glucose meter before injecting insulin (as per the regulatory labeling of the device at the time the trial was conducted). General guidelines were provided to participants about using CGM, and individualized recommendations were made by their clinician about incorporating CGM trend information into their diabetes management. The control group was asked to perform home blood glucose monitoring at least 4 times daily. Participants in both groups were provided general diabetes management education, and clinicians were encouraged to review downloaded glucose data at each visit to inform treatment recommendations, which were at clinician discretion and not prescriptive in the protocol. eTable 2 in Supplement 2 describes the participant education as well as guidelines for clinicians. CGM guidelines for participants are included in Supplement 1.

Key Points

Question For adults with type 1 diabetes who are using multiple daily insulin injections, does continuous glucose monitoring improve hemoglobin A1c (HbA1c) levels compared with self-monitored blood glucose management?

Findings In a randomized clinical trial of 158 adults with type 1 diabetes, there was a significantly greater decrease in HbA1c level during 24 weeks with continuous glucose monitoring vs usual care (-1.0% vs -0.4%).

Meaning Continuous glucose monitoring resulted in better glycemic control compared with usual care, but further research is needed to assess clinical outcomes, as well as effectiveness, in a typical clinical population.
Follow-up visits for both treatment groups occurred after 4, 12, and 24 weeks. The CGM group had an additional visit 1 week after randomization. The control group had 2 additional visits 1 week before the 12- and 24-week visits, at which a CGM sensor in blinded mode was inserted to collect glucose data for 1 week. Telephone contacts for both groups occurred 2 and 3 weeks after randomization.

Hemoglobin A1c level was measured at baseline, 12 weeks, and 24 weeks at the Northwest Lipid Research Laboratories, University of Washington, Seattle, with the Diabetes Control and Complications Trial standardized analyzer (TOSOH, Biosciences Inc).

Outcomes

The primary outcome was change in the central laboratory-measured HbA1c level. Prespecified secondary outcomes included percentage of participants with HbA1c level less than 7.0%; CGM-measured time in range (70-180 mg/dL), duration of hypoglycemia (<70 mg/dL, <60 mg/dL, and <50 mg/dL), duration of hyperglycemia (180 mg/dL, >250 mg/dL, and >300 mg/dL), and glucose variability (coefficient of variation); change in hypoglycemia unawareness; and change in frequency of blood glucose meter testing (longitudinal changes in blood glucose meter testing were not assessed). Prespecified exploratory outcomes included CGM-measured mean glucose concentration and the following binary HbA1c outcomes to assist in translation of the primary HbA1c analysis to a participant level: HbA1c level less than 7.5% and relative HbA1c reduction greater than or equal to 10%. Post hoc outcomes included HbA1c reduction of 1% or more, HbA1c level less than 7.0% or reduction of 1% or more, CGM-measured area above the curve 70 mg/dL and area under the curve 180 mg/dL, change in insulin dose, and change in body weight.

Satisfaction with CGM was assessed by completion at 24 weeks of the CGM Satisfaction Survey (44 items on a 1-5 Likert scale, with the computed score representing the mean of the 44 items and subscales of benefits and lack of hassles). Quality-of-life and health economic outcomes will be reported in separate articles.

Safety outcomes included severe hypoglycemia (defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions), diabetic ketoacidosis, and serious adverse events regardless of causality.

Statistical Methods

A sample size of 147 for the 2:1 randomization was calculated to have 90% power to detect a difference in mean HbA1c level between treatment groups, assuming a population difference of 0.4%, standard deviation of the 24-week values of 0.7 adjusted for the correlation between baseline and 24-week values (based on data from the Juvenile Diabetes Research Foundation CGM randomized trial), and a 2-sided a level of .05. Sample size initially was increased to 169 to account for potential loss to follow-up. When it was recognized by the coordinating center that the trial completion rate was higher than anticipated, the recruitment goal was changed to a minimum of 150, with the approval of the steering committee and the sponsor.

Analyses followed the intent-to-treat principle. The following change was made from the protocol and statistical analysis plan before the data lock: the primary analysis was a treatment group comparison of the change in HbA1c level from baseline to 24 weeks, adjusted for baseline HbA1c level and clinical site as a random effect, in a repeated-measures linear model in the protocol and with analysis of covariance in the statistical analysis plan; both are reported in this article. Confounding was assessed by repeating the analysis, including potential confounding variables as covariates. The Rubin method was used to impute for missing data. Exploratory analyses were conducted to assess for interaction between the treatment effect on the change in HbA1c level from baseline to 24 weeks and baseline factors by including interaction terms in analysis of covariance models.

For CGM outcomes, treatment group comparisons using the CGM data collected in each group for 7 days at 12 and 24 weeks were made with analysis of covariance models based on ranks using van der Waerden scores if the metric was
Glycemic Control and Other Outcomes

Primary Outcome

Mean reduction in HbA1c level from baseline was 1.1% at 12 weeks and 1.0% at 24 weeks in the CGM group and 0.5% and 0.4%, respectively, in the control group (primary analyses with 99% CIs accordingly provided).

Statistical methods for other analyses are described in table footnotes. Standard deviations are reported for means and interquartile ranges (IQRs) for medians where applicable. Reported point estimates are unadjusted unless otherwise noted. Analyses were conducted with SAS version 9.4. All P values are 2 sided. P < .05 was considered significant for the primary analysis and P < .01 for all other analyses to account for multiple comparisons (with 99% CIs accordingly provided).

SI Unit Conversions

Throughout, to convert HbA1c to the SI units of mmol/mol, multiply the HbA1c percentage value × 10.93 and subtract 23.5 from the product. For example, an HbA1c value of 7.0% corresponds to 53 mmol/mol. To convert glucose to mmol/L, multiply the values × 0.0555.

Results

Between October 2014 and December 2015, 158 participants were assigned to the CGM group (n = 105) or control group (n = 53). Mean age was 48 years (SD, 13) (range, 26-73 years, with 34 participants [22%] ≥60 years); 44% were women. Median diabetes duration was 19 years (IQR, 10-31 years), and mean baseline HbA1c level was 8.6% (SD, 0.6%; range, 7.5%-9.9%). Participant characteristics according to randomized group are shown in Table 1.

The 24-week primary study outcome visit was completed by 102 participants (97%) in the CGM group and all 53 (100%) in the control group (Figure 1). Overall visit completion was 99% and 98%, respectively. Three participants in the CGM group (4 total visits) and 3 in the control group (3 total visits) had additional visits, not required in the protocol, for diabetes management.

Among the 102 participants in the CGM group who completed the trial, median CGM use was 7.0 d/wk (IQR, 7.0-7.0) at 4, 12, and 24 weeks; only 2 (2%) discontinued CGM before the 24-week visit. During month 6 (weeks 21-24), CGM use was 6 or more d/wk for 93% of the 102 participants (eTable 3 in Supplement 2). No participant in the control group initiated blinded CGM use before the primary outcome.

According to meter downloads, mean blood glucose self-monitoring was 5.1 tests per day (SD, 1.8) in the CGM group and 5.1 tests per day (SD, 1.4) in the control group during the baseline period of blinded CGM wear and 3.6 tests per day (SD, 1.6) and 4.6 tests per day (SD, 1.6), respectively, at 24 weeks (adjusted mean difference for the change, -1.0; 99% CI, -1.7 to -0.4; P < .001).
Participant are shown in Figure 2A, and the cumulative distribution of the 24-week HbA1c values is shown in Figure 2B.

Secondary, Exploratory, and Post Hoc HbA1c Outcomes
The greater HbA1c improvement in the CGM group also was reflected in multiple participant-level secondary, exploratory, and post hoc HbA1c outcomes (Table 2). There was no significant interaction of the effect of treatment on 24-week HbA1c level according to baseline HbA1c, age, education level, or type of site (eTable 4 in Supplement 2).

Table 2. Primary Outcome and Hemoglobin A1c Outcomes at 12 and 24 Weeks*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>12 Weeks</th>
<th>24 Weeks</th>
<th>Between-Group Differencea,b</th>
<th>P Valuea,b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CGM Group (n = 103)</td>
<td>Control Group (n = 52)</td>
<td>CGM Group (n = 105)</td>
<td>Control Group (n = 53)</td>
</tr>
<tr>
<td>Primary outcome, mean (SD), %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.6 (0.7)</td>
<td>8.1 (0.7)</td>
<td>7.7 (0.8)</td>
<td>8.2 (0.8)</td>
</tr>
<tr>
<td>Change in HbA1c from baseline</td>
<td>−1.1 (0.7)</td>
<td>−0.5 (0.7)</td>
<td>−1.0 (0.8)</td>
<td>−0.4 (0.7)</td>
</tr>
<tr>
<td>Prespecified secondary outcome, No. (%)</td>
<td>14 (14)</td>
<td>2 (4)</td>
<td>18 (18)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>HbA1c &lt;7.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prespecified exploratory outcomes, No. (%)</td>
<td>49 (48)</td>
<td>6 (12)</td>
<td>39 (38)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Relative reduction in HbA1c ≥10%</td>
<td>62 (60)</td>
<td>12 (23)</td>
<td>58 (57)</td>
<td>10 (19)</td>
</tr>
<tr>
<td>HbA1c &lt;7.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post hoc outcomes, No. (%)</td>
<td>55 (53)</td>
<td>12 (23)</td>
<td>53 (52)</td>
<td>10 (19)</td>
</tr>
<tr>
<td>Reduction in HbA1c ≥1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in HbA1c ≥1% or HbA1c &lt;7.0%</td>
<td>57 (55)</td>
<td>12 (23)</td>
<td>53 (52)</td>
<td>11 (21)</td>
</tr>
</tbody>
</table>

Abbreviations: CGM, continuous glucose monitoring; HbA1c, hemoglobin A1c.

SI Conversion: to convert HbA1c to the SI units of mmol/mol, multiply the HbA1c percentage value × 10.93 and subtract 23.5 from the product.

a Mean baseline HbA1c level was 8.6% in each group. For all analyses, missing HbA1c values in which the central laboratory value was missing but the local laboratory value was known were imputed with a regression line based on the site’s local HbA1c measurements (CGM/control: 1/0 at 12 weeks; 1/1 at 24 weeks).

b For the 24-week primary outcome only, the Rubin method was used to impute missing HbA1c values when both the central and local laboratory values were missing (3 in the CGM group and 0 in the control group). For the secondary, exploratory, and post hoc analyses, n = 102.

c For the primary analysis, treatment group comparisons were made with analysis of covariance models, adjusted for baseline HbA1c level and clinical site as a random effect. Model residuals were verified to have an approximate normal distribution.

d For the secondary, exploratory, and post hoc outcomes, treatment group comparisons were made with propensity scores, adjusted for baseline HbA1c level and clinical site. P < .01 was considered significant to account for multiple comparisons (with 99% CIs accordingly provided).
variability favored the CGM group compared with the control group (Table 3, eTable 5 in Supplement 2). In exploratory analyses, hypoglycemia treatment group differences favored the CGM group during both daytime and nighttime, but hyperglycemia treatment group differences favoring the CGM group were present only during the daytime (eTables 6 and 7 in Supplement 2). In exploratory analyses, hypoglycemia treatment group differences favored the CGM group during both daytime and nighttime, but hyperglycemia treatment group differences favoring the CGM group were present only during the daytime (eTables 6 and 7 in Supplement 2).

Other Analyses
At 24 weeks, in post hoc analyses there were no significant differences between the CGM group and control group in median change in total daily insulin dose per kilogram of body weight (-0.02 vs 0.03 U/kg; P = .23), median ratio of long-acting to rapid-acting daily insulin dose (0.9 vs 1.0; P = .54), proportion of participants with an increase in injections of rapid-acting insulin per day (26% vs 26%; P = .90), or mean change in body weight (1.7 vs 0.7 kg; mean difference, 1.0 kg; 99% CI, -0.7 to 2.8; P = .12) (eTable 8 in Supplement 2). Clarke Hypoglycemia Unawareness scores did not differ between groups (mean difference, -0.1; 99% CI, -0.7 to 0.5; P = .64).

Severe Hypoglycemia and Other Adverse Events
Severe hypoglycemic events occurred in 2 participants in each group (P = .67). There were no occurrences of diabetic ketoacidosis. Other serious adverse events, unrelated to the study intervention, occurred in 2 participants in the CGM group and none in the control group (eTable 9 in Supplement 2).

CGM Satisfaction
In the CGM group, satisfaction with use of CGM was high, as indicated by the mean (SD) score of 4.2 (0.4) on the CGM Satisfaction Survey, with mean (SD) scores of 4.2 (0.5) on the benefits subscale and 4.3 (0.5) on the subscale for lack of hassles (eTable 10 in Supplement 2).

Discussion
Among adults with type 1 diabetes using multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA1c level during 24 weeks. The HbA1c benefit in the CGM group was consistently present across the age range of 26 to 73 years, the baseline HbA1c level range of 7.5% to 9.9%, and all education levels. In addition, CGM use was associated with a high degree of participant satisfaction with CGM, increased time with glucose concentrations between 70 and 180 mg/dL, decreased time with glucose concentrations less than 70 mg/dL, and decreased glycemic variability, measured with the coefficient
of variation. The trial was not designed to demonstrate a benefit in reducing clinical severe hypoglycemia events, and the low event rate in the control group precluded a meaningful analysis. However, less biochemical hypoglycemia, as was observed in the trial, has been associated with a lower risk for subsequent severe hypoglycemic events and improved quality of life.

The amount of CGM use by the participants was high (median CGM use 7 d/wk in month 6) despite a protocol approximating usual practice, with only 1 visit after week 4 and no visits or other protocol-specified contacts between 12 and 24 weeks. The amount of use was similar to or greater than the frequency of use in pump-using adults with type 1 diabetes in previous trials and observational studies, which could be related to CGM accuracy being significantly improved from the generation of sensors in previous trials. The observed benefits of CGM occurred despite the CGM group’s having significantly less blood glucose meter testing per day than the control group.

The magnitude of benefit of CGM on HbA1c levels relative to control in this trial of insulin injection users is comparable to the magnitude of benefit of CGM observed in pump users in previous randomized trials. This finding was not a foregone conclusion. Insulin injection users have less flexibility in adjusting their insulin delivery in response to CGM glucose concentrations and trends than do pump users. Basal insulin delivery for pump users is continuous, and can be temporarily changed in response to decreasing glucose concentrations or planned activities such as exercise. In contrast, injection users have fixed basal insulin based on the absorption of their long-acting insulin and can make adjustments only to rapid-acting insulin boluses.

The strengths of the trial included a high retention rate, high adherence to treatment group assignment, central laboratory measurement of HbA1c, a protocol approximating usual clinical practice, and participation in the trial by both community-based and academic sites. Assignment to the CGM and control groups could not be blinded because of the nature of the intervention; however, the groups had a similar number of visits. The 0.4% mean improvement in HbA1c level in the control group likely reflects both a study effect related to clinical trial participation and more structured training in using blood glucose monitoring in adjusting insulin regimens than was occurring for these individuals before the study.

This study also had several limitations. In light of the eligibility criteria, the results may not apply to individuals with type 1 diabetes who are younger than 26 years or have HbA1c levels outside the range of 7.5% to 9.9% and should not be applied to individuals with type 2 diabetes who receive multiple daily injections of insulin. The informed consent process and the run-in phase had the potential to exclude individuals who might be less adherent with CGM than the cohort that was studied.

Conclusions

Among adults with type 1 diabetes who use multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA1c level during 24 weeks. Further research is needed to assess longer-term effectiveness, as well as clinical outcomes and adverse effects.
REFERENCES


