

Emerging Treatments and Technologies

ORIGINAL ARTICLE

Continuous Glucose Monitoring-Guided Insulin Adjustment in Children and Adolescents on Near-Physiological Insulin Regimens

A randomized controlled trial

KYLIE YATES, MBBS, FRACP¹
ABUL HASNAT MILTON, PHD²

KEITH DEAR, PHD³
GEOFFREY AMBLER, MD, FRACP¹

OBJECTIVE — This randomized controlled trial assesses the effect on glycemic control of continuous glucose monitoring system (CGMS)-guided insulin therapy adjustment in young people with type 1 diabetes on intensive diabetes treatment regimens with continuous subcutaneous insulin infusion (CSII) or glargine.

RESEARCH DESIGN AND METHODS — Pediatric subjects were recruited if they had an HbA_{1c} (A1C) <10% and had been on CSII or glargine for at least 3 months. Thirty-six subjects were randomized to insulin adjustment on the basis of 72 h of CGMS every 3 weeks or intermittent self-monitoring of blood glucose (SMBG) for 3 months. A1C and fructosamine were measured at baseline and 6 and 12 weeks. Follow-up A1C was measured at 6 months. Mean baseline A1C was 8.2% (n = 19) in the CGMS group and 7.9% (n = 17) in the control group.

RESULTS — There was a significant improvement in A1C from baseline values in both groups, but there was no difference in the degree of improvement in A1C at 12 weeks between the CGMS (-0.4% [95% CI -0.7 to -0.1]) and the control group (-0.4% [-0.8 to 0.2]). In the CGMS group, improved A1C was at the cost of increased duration of hypoglycemia.

CONCLUSIONS — CGMS is no more useful than intermittent fingerstick SMBG and frequent review in improving diabetes control in reasonably well-controlled patients on near-physiological insulin regimens when used in an outpatient clinic setting.

Diabetes Care 29:1512-1517, 2006

Recent target recommendations for HbA_{1c} (A1C) in children and adolescents with type 1 diabetes are <7.5% (1,2), provided that this can be achieved without excessive hypoglycemia. Even small reductions in A1C have been shown to be beneficial (3,4), and any technique that can aid in improving met-

abolic control will have an impact on the incidence of long-term complications.

Intensive insulin treatment regimens designed to mimic physiological insulin production are beneficial in achieving good metabolic control (5,6). Continuous insulin infusion (CSII) and multiple daily doses of insulin (MDI) given with each

meal have been shown to improve metabolic control in children without an increased rate of adverse events (7). A meta-analysis of studies, mostly in adults, found A1C was 0.5% lower in subjects on CSII compared with insulin injections (8). Glargine is a new insulin analog that has been shown to reduce fasting blood glucose levels (BGLs) without increased hypoglycemia in young people with type 1 diabetes (9). One trial (6) in young people showed marginal superiority of CSII in A1C reduction. Two trials (10,11) in adults had similar reductions in A1C in both glargine and CSII arms.

One of the barriers to better glycemic control is intermittent blood glucose testing, which provides limited blood glucose profiles. Accordingly, devices that continuously monitor glucose levels have been developed to overcome such limitations and improve the ability to assess blood glucose patterns allowing improved adjustment of management. The continuous glucose monitoring system (CGMS) has been shown to be useful in detecting unrecognized hypoglycemia (12,13) and other patterns prompting insulin adjustment that had not been detected with intermittent blood glucose monitoring (14). Early uncontrolled studies (14,15) and a cross-over trial (16) have shown some benefit in improving glycemic control, but larger controlled studies have not repeated the findings (17,18). The use of CGMS requires further evaluation in children and adolescents, particularly with an intermediate frequency of use.

The purpose of this study was to assess the effect on diabetes control of guiding insulin adjustment with four cycles of CGMS over 3 months in children on near-physiological insulin replacement regimen.

RESEARCH DESIGN AND METHODS — Seventy-five eligible pediatric patients of The Children's Hospital, Westmead, the largest pediatric diabetes center in NSW, Australia, were

From the ¹Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Westmead, NSW, Australia; the ²Centre for Clinical Epidemiology and Biostatistics, University of Newcastle, Newcastle, Australia; and the ³National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australia.

Address correspondence and reprint requests to Kylie Yates, MBBS, FRACP, Institute of Endocrinology and Diabetes, The Children's Hospital, Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia. E-mail: kyliey@chw.edu.au.

Received for publication 28 November 2005 and accepted in revised form 16 April 2006.

K.Y. and G.A. have received grant/research support from Medtronic MiniMed.

Abbreviations: BGL, blood glucose level; CGMS, continuous glucose monitoring system; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily doses of insulin; SMBG, self-monitoring of blood glucose.

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

DOI: 10.2337/dc05-2315. Clinical trial no. ISRCTN28387915, clinicaltrials.gov.

© 2006 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Table 1—Baseline characteristics

	CGMS	Control	Refused
n	19	17	36
Male	7 (37)	6 (36)	10 (50)
Age (years)	14.7 (13.6–14.4)	14.1 (12.8–15.3)	15.1 (13.1–16.6)
CSII	9 (47)	8 (47)	8 (22)
Baseline A1C (%)	8.2 ± 0.9	7.9 ± 0.9	8.5 ± 0.7*
Mean A1C in last 12 months	8.4 ± 1.0	8.3 ± 0.7	8.5 ± 0.9
Insulin (dose/kg)	1.1 ± 0.4	0.9 ± 0.3	1.0 ± 0.4
Initial A1C ≤7.5%	6 (32)	6 (35)	1 (3)

Data are means ± SD, n (%), or median (interquartile range). **P* = 0.04.

consecutively approached from May 2004 until 39 patients had agreed to participate. Participation criteria were aged ≤18 years with type 1 diabetes for at least 1 year on either CSII or an MDI regimen that included glargine for at least 3 months. Subjects with known poor compliance or A1C >10% were excluded. Thirty-six declined to participate, usually because of concerns about blood tests or wearing an invasive monitor. Compared with participants, those who refused had a similar mean A1C (8.5%) in the previous year. Glargine users declined to participate more frequently than CSII users. Glargine patients administered short-acting insulin at least three times per day before main meals. All subjects had received education on adjustment of doses for variation in carbohydrate intake, activity, and ambient BGLs. Formalized sliding scales were not used. CSII patients were asked to bolus before all carbohydrate intake using the ratio that had been set by previous contact with the diabetes team. CSII patients had also received education about adjustments for activity and corrections for ambient BGLs outside the target range. Participants were stratified according to treatment regimen and then randomized to CGMS or control arms in equal numbers. Group allocation was blinded with opaque sealed envelopes. Randomization was done by an independent body using biased coin randomization. This study was approved by the ethics committee of The Children's Hospital Westmead. Signed informed consent was obtained from parents and assent obtained from all participants. Verbal or behavioral assent (e.g., holding own arm out for blood collection) was considered acceptable in younger children.

CGMS

The Medtronic CGMS was used as previously described (15,19) and is a system that does not give live readings to subjects. Subjects were asked to enter at least four calibration readings per day and event codes for meals, exercise, and hypoglycemia symptoms. They were not asked to adhere to a special diet or exercise routine but were encouraged to continue their usual behavior.

The CGMS arm had monitoring for 3 days every 3 weeks over a 3-month period in addition to traditional intermittent self-monitoring of blood glucose (SMBG), and the control arm had SMBG four to six times daily. Every 3 weeks, the insulin doses were reviewed and adjusted based on either the CGMS and SMBG or SMBG alone by the principal investigator. BGL targets were set at 4–7 mmol/l before meals, <9 mmol/l 2 h postprandial, 5.5–8 mmol/l at bedtime, and 5–8 mmol/l at 3 A.M. These principles were based on the standards of care at our institution.

Subjects were asked to confirm symptoms of hypoglycemia with SMBG and were asked about episodes of severe hypoglycemia causing coma or seizure at each review. Other than the method of glucose measurement, groups were treated equally. All subjects were educated on appropriate meter use. On enrollment, each subject's existing meter was compared with a single reference meter and accepted if the readings did not differ by >10%.

MiniMed solution software version 3.0B and modified sensors were used. Sensor traces were accepted for pattern recognition and insulin dose adjustment if there were at least two SMBG calibration points in agreement with sensor data. Area under the curve (AUC) for BGL >9

mmol/l (20) and duration of time with BGL <3.9 mmol/l was calculated for the first and fourth cycle for each subject in the CGMS arm of the study using only the data that conformed to the software recommendations (19). Duration of time for events occurring during CGMS are expressed as a percentage of total acceptable hours because of inconsistency in the number of hours each monitor was worn and the need to exclude data not fulfilling accuracy criteria above.

Measurement

Diabetes control was measured using A1C and fructosamine measured at baseline and 6 and 12 weeks. A1C was measured using ion-exchange high-pressure liquid chromatography (Bio-Rad Laboratories), which has a nondiabetic normal range of 4.6–6.5%. A1C values in the 12 months before the study and 6 months after were measured at routine clinic visits using DCA 2000 (Roche Diagnostics), which has a nondiabetic normal range of 4–6%. Fructosamine was measured using Cobras Integras system (normal range 190–285 μmol/l; Roche Diagnostics).

Power calculation

Recruitment of 40 subjects was designed to have 80% power at the 95% confidence level to detect 0.8% difference in mean A1C based on an SD of 0.9 in this population (21).

Statistical analysis

Baseline characteristics are presented as means ± SD unless otherwise indicated. Results are presented as means (95% CI). Significance was set at the 5% level. Continuous variables were compared using a two-sided *t* test or paired *t* test for change within each subject. Univariate ANOVA was used to examine factors that may confound the change in A1C. Stepwise multiple linear regression was used to examine predictors of change in A1C from CGMS data. Friedman test was used for nonparametric data. Data were analyzed using SPSS version 11.5.1

RESULTS — CGMS and control groups were similar for all measured baseline characteristics (Table 1). CSII users had lower insulin doses than glargine users in both CGMS and control arms (*P* = 0.04 and *P* = 0.02). Baseline A1C and mean A1C for the previous 12 months did not differ between CSII and glargine users within each arm. Three glargine users were on a three-injections-per-day regi-

Table 2—Glycemic control by study group

Variable	CGMS	Control	P
A1C (%)			
Baseline	8.2 (7.8–8.8)	7.9 (7.3–8.3)	0.47
6 weeks	8.0 (7.4–8.5)	7.7 (7.3–8.1)	0.37
12 weeks	7.9 (7.4–8.3)	7.6 (7.2–7.8)	0.21
6 months	8.2 (7.5–8.9)	7.8 (7.3–8.2)	0.25
Change (from baseline to 6 weeks)	-0.2 (-0.5 to -0.1)	-0.2 (-0.5 to 0.2)	0.71
Change (from baseline to 12 weeks)	-0.4 (-0.7 to -0.1)	-0.4 (-0.8 to 0.2)	0.83
Change (from baseline to 6 months)	-0.1 (-0.4 to 0.6)	-0.1 (-0.4 to 0.7)	0.87
Fructosamine ($\mu\text{mol/l}$)			
Baseline	397.5 (367.6–427.4)	400.4 (368.5–430.1)	0.88
6 weeks	384.5 (350.7–411.8)	383.5 (363.8–403.5)	0.95
12 weeks	385.7 (353.1–413.9)	369.2 (344.5–389.7)	0.35
Change (from baseline to 6 weeks)	-16.3 (-43.5 to 10.9)	-16.8 (-47.0 to 15.6)	0.98
Change (from baseline to 12 weeks)	-25.8 (-50.7 to -1)	-18.6 (-60 to 23)	0.59
Final A1C $\leq 7.5\%$	10 (53)	8 (47)	0.5
Increase in insulin dose (units $\cdot \text{kg}^{-1} \cdot \text{day}^{-1}$)	0.01	0.03	0.69

Data are means (95% CI).

men, with NPH and regular insulin; the remainder were on at least four injections per day. Two subjects, both on glargine, initially consented and then withdrew before commencing the trial, one from the CGMS arm and one from the control arm. One subject on CSII randomized to CGMS withdrew after 12 h of CGMS because of skin irritation at the sensor site. There were no other withdrawals, and the remaining 36 patients were included in the final analysis.

Metabolic control

Patients who had insulin adjustments made on the basis of CGMS data had a

significant reduction in A1C at 6 weeks compared with baseline values ($\Delta -0.2\%$ [95% CI -0.5 to -0.1]) and at 12 weeks ($\Delta -0.4\%$ [-0.7 to -0.1]). Similar improvements were seen in the control group at 6 weeks ($\Delta -0.2\%$ [-0.5 to 0.2]) and 12 weeks ($\Delta -0.4\%$ [-0.8 to 0.2]). However, there was no significant difference in A1C or fructosamine values between the CGMS and control groups at 6 or 12 weeks. At 6 months, there was no significant difference in A1C from baseline in either group (Table 2). CGMS appears to be of greater benefit in users of glargine than CSII (Fig. 1) but as the broad CIs indicate that there is no significant difference in final

A1C in the CGMS and control groups for either type of insulin therapy.

Adverse events

There were no cases of hypoglycemia causing coma or seizures. One subject in the CGMS group was admitted with ketoacidosis thought to be due to insulin omission, and one subject in the control arm was admitted with suicidal ideation associated with recent onset of depression.

CGMS data

A total of 80 sensors were inserted. One subject only had three cycles of CGMS. In total, 75 traces were available for analysis. Monitors were worn for an average of 74 h (range 42–99). Data accuracy was maintained into the 4th day in subjects who wore CGMS for longer periods.

CGMS sensors were well tolerated, but only 70% of the total hours worn were usable; suboptimal data were usually because of insufficient calibration points. Average number of data points for each subject was 860 ± 109 (range 725–1,202). This equates to 200 glucose readings per day compared with an average of 4.4 SMBGs per day for both CSII and MDI users in the control group.

Common patterns seen were postprandial hyperglycemia, asymptomatic nocturnal hypoglycemia, excessive treatment and rebound after hypoglycemia, erratic response to exercise, and idiosyncratic reaction to certain foods. Specific adjustments for those using glargine included tolerance of lower glucose level at bed time and omitting supper. In three children, glargine was moved from the evening to the morning to avoid a peak effect overnight. Standard compliance problems were also encountered, such as

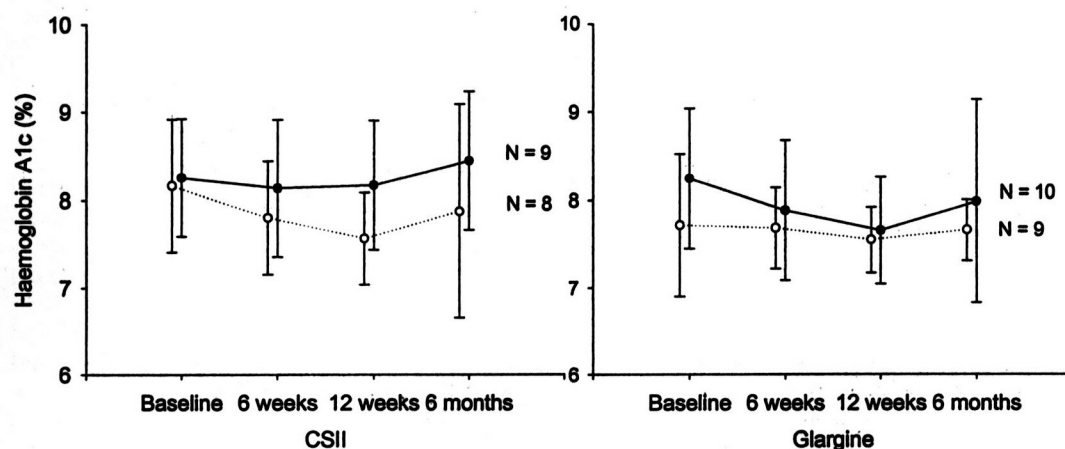


Figure 1—Mean A1C (95% CI) in CGMS (●) and control (○) groups for those on CSII and glargine.

missed boluses and failure to repeat SMBG after hypoglycemia treatment.

$AUC_{>9\text{mmol/l}}$ was weakly associated with initial A1C ($R^2 = 0.4$, $P = 0.098$) and did not significantly change from the first to the last cycle. There was no significant correlation between change in $AUC_{>9\text{mmol/l}}$ and change in A1C ($R^2 = 0.04$, $P = 0.4$). Absolute values and change from cycles one to four for $AUC_{>9\text{mmol/l}}$, percentage of time with hypoglycemia, and nocturnal hypoglycemia were similar in CSII and glargine users.

In the CGMS group, an improvement in A1C was at a cost of an increase in hypoglycemia. For each 1% reduction in A1C, there was a 7% increase in percent of total monitoring period with hypoglycemia ($R^2 = 0.22$, $P = 0.06$) and an 18% increase in the percent of the night with hypoglycemia ($R^2 = 0.2$, $P = 0.08$). Similarly, there was a significant increase in percent of total monitoring period with hypoglycemia in those whose A1C improved by at least 0.5% compared with those whose A1C did not improve ($P = 0.012$).

There were 18 separate nocturnal hypoglycemic events (glucose ≤ 3.9 mmol/l) in 8 of 18 (44%) subjects with usable data. Nocturnal hypoglycemic events ranged from 1 to 7 h. There was no change by the fourth cycle when there were 20 events in 10 subjects (59%). Most events were asymptomatic, except one in the first cycle and five in the fourth cycle. There was no significant change in the percent of nocturnal hours with hypoglycemia between each of the four cycles.

Mild, self-treated symptomatic hypoglycemia was very common in both groups. In the control group, the number of hypoglycemic events recorded with SMBG was 0.3 per day. This increased to 0.7 per day by the fourth cycle. In between CGMS cycles, the mean number of hypoglycemic events recorded by SMBG in the CGMS group did not change from 0.4 per day. Eight control subjects chose to wear CGMS at the end of the study. There was no difference in the duration of hypoglycemia recorded by CGMS between the eight control arm subjects and the CGMS group ($P = 0.19$), but the numbers were small.

CONCLUSIONS— This study shows that in children on intensified insulin regimens there was no additional benefit from CGMS-guided insulin adjustment every 3 weeks for 3 months that could not be achieved by standard intermittent BGL

monitoring and with regular review. The trend to improvement was associated with increased hypoglycemia. We did not find CGMS, in this form, a useful tool in reducing A1C when used in the general clinic setting.

Our findings are similar to those of several recent larger studies in adults (17,18). Tanenberg et al. (18) randomized 128 adults to insulin adjustment on the basis of one cycle of CGMS or frequent SMBG. They found a significant drop in A1C after 3 months but no difference between the intervention and control arms. There was a reduction by half in the duration of hypoglycemic events in the intervention arm when all subjects wore CGMS for a second time 3 months later. We did not test all our control group with CGMS at the end of the study, but in the intervention group we found the opposite, i.e., improved A1C was at the cost of increased hypoglycemia in both groups.

Making appropriate insulin dose adjustments was difficult in the face of large interday variations in glucose readings, which have been previously noted (22). This reflects the daily difficulty young patients face in recognizing the impact of variation in exercise and food intake on their blood glucose levels. Many subjects commented that they found it useful to see a graphical representation of the effect of different activities, but this was not translated into improved management. One of the limitations of CGMS was the high rate of unusable data because of failure to calibrate SMBG readings frequently, and this is a commonly reported issue (16,17,23,24). The same patients who have poor control because of reluctance to perform SMBG may not comply with CGMS.

A1C is a useful measure of glucose exposure that is known to correlate with risk of complications, but it does not give any indication of glucose stability. CGMS graphs give an insight into changes in glycemic profile over the day, and it can reveal rapid changes in glucose levels that do not predict A1C but are associated with increased risk of hypoglycemia (25). We postulated that in some children high $AUC_{>9\text{mmol/l}}$ may be offset by long periods of hypoglycemia. We did not find that high $AUC_{>9\text{mmol/l}}$ and longer duration of hypoglycemia were associated in any individual, only that A1C decreased because of an increase in hypoglycemia without a reduction in $AUC_{>9\text{mmol/l}}$.

One of the well-recognized limitations of CGMS is the high rate of asym-

ptomatic hypoglycemia mostly occurring at night (12,13,26), much of which may be spurious (27–29). Frequent calibration of CGMS at a variety of plasma glucose-to-insulin ratios with SMBG data has been reported to prevent this problem. Most subjects wearing CGMS outside a controlled trial will not wake overnight to enter these additional calibration data points. This limitation has prompted the suggestion that CGMS should be used for pattern recognition and to target high readings in those with poor control (28). In our study, therapy was adjusted to focus primarily on high readings, but there was difficulty in knowing at what level to respond to low CGMS readings. This was especially the case when low readings occurred after recent dose increases, and this limited further dose increases, possibly explaining our failure to reduce $AUC_{>9\text{mmol/l}}$. Hopefully, these limitations will be overcome as sensor reliability improves (28,30).

It is recognized that our study is relatively small and is unable to detect small differences between each group, which may still have clinical significance at a population level. As there is no recognized threshold for an A1C at which there is no increased risk of diabetes complications, any reduction population mean A1C is likely to be beneficial. Recruitment of larger numbers was hampered by adolescents' reluctance to be attached to an external device or additional device in the case of CSII users. New wireless sensors may improve patient acceptability, especially if they do not interfere with bathing, sport, or sleep, the three most common concerns leading to refusal to participate in this study.

Physicians and patients alike hold great hope for new developments in diabetes care, and there is a temptation to regard evolving technology as a panacea for all the limitations of current management techniques. The adoption of new therapies follows a characteristic trajectory of rapid uptake, abandonment as limitations are identified, and then an eventual plateau as appropriate applications are agreed upon. Clinical use of CGMS is still in this first phase and is being tested in a wide range of situations. Our study adds to existing knowledge by demonstrating that the benefits of CGMS are not universal. Subjects willing to undertake this study are likely to be better motivated and more willing to accept the inconvenience of an invasive monitor than the general clinic population. De-

spite this, we were not able to show a benefit that could not be achieved with increased review alone. CGMS may be better suited to patients whose interest in their own diabetes management falls at either end of the normal spectrum rather than a general management tool for the majority of patients. It could act either as a motivational device for those with poor control or to provide additional information for the very diligent who have not been able to fine tune their treatment despite frequent SMBG. Future studies could focus on these populations. Patient readable real-time CGMS devices are likely to be more widely available soon, changing the monitoring and adjustment paradigm for patients. As for currently available CGMS, what must follow is a critical analysis of its performance in different settings and the cost benefits compared with existing methods of monitoring. Ultimately, the most suitable circumstances for CGMS (non-real-time and real-time) will be identified, and it will be able to be used in those settings with acknowledgment of its limitations.

Acknowledgments—CGMS monitors were on loan from Medtronic MiniMed who also donated half the sensors. Novo Nordisk and the Australian Diabetes Society provided research grants. Minimed and grant providers did not have any input into study design or presentation of results.

The authors thank all the participants and their families. They also thank the Endocrine Lab at The Children's Hospital, Westmead, and the Clinical Chemistry Laboratory at Westmead Hospital.

References

- National Institute of Clinical Excellence (NICE): *CG15 Type 1 Diabetes: Diagnosis and Management of Type 1 Diabetes in Children, Young People and Adults: NICE Guideline*. London, NHS, 2004
- Australian Paediatric Endocrine Group: *Clinical Practice Guidelines: Type One Diabetes in Children and Adolescents*. Canberra, Australia, National Health and Medical Research Council, 2005
- The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
- Donaghue KC, Fung AT, Hing S, Fairchild J, King J, Chan A, Howard NJ, Silink M: The effect of prepubertal diabetes duration on diabetes: microvascular complications in early and late adolescence. *Diabetes Care* 20:77–80, 1997
- Alemzadeh R, Ellis JN, Holzum MK, Parton EA, Wyatt DT: Beneficial effects of continuous subcutaneous insulin infusion and flexible multiple daily insulin regimen using insulin glargine in type 1 diabetes. *Pediatrics* 114:91–95, 2004
- Doyle EA, Weinzimer SA, Steffen AT, Ahern JA, Vincent M, Tamborlane WV: A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care* 27:1554–1558, 2004
- Weintrob N, Benzaquen H, Galatzer A, Shalitin S, Lazar L, Fayman G, Lilos P, Dickerman Z, Phillip M: Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: a randomized open crossover trial. *Pediatrics* 112:559–564, 2003
- Pickup J, Mattock M, Kerry S: Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ* 324:705, 2002 [see comments]
- Schober E, Schoenle E, Van Dyk J, Wernicke-Panten K, the Pediatric Study Group of Insulin Glargine: Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 15:369–376, 2002
- Harmel AP, Mathur R: Similar A1C outcomes in type 1 diabetic patients undergoing intensive diabetes management with preprandial rapid acting insulin and either CSII or Glargine (Letter). *Diabetes Care* 27:272–273, 2004
- Lepore G, Dodesini AR, Nosari I, Trevisan R: Effect of continuous subcutaneous insulin infusion vs multiple daily insulin injection with glargine as basal insulin: an open parallel long-term study. *Diabetes Nutr Metab* 17:84–89, 2004
- Kaufman FR, Austin J, Neinstein A, Jeng L, Halvorson M, Devoe DJ, Pitukcheewanont P: Nocturnal hypoglycemia detected with the continuous glucose monitoring system in pediatric patients with type 1 diabetes. *J Pediatr* 141:625–630, 2002
- Boland E, Monsod T, Delucia M, Brandt CA, Fernando S, Tamborlane WV: Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. *Diabetes Care* 24:1858–1862, 2001 [see comments]
- Kaufman FR, Gibson LC, Halvorson M, Carpenter S, Fisher LK, Pitukcheewanont P: A pilot study of the continuous glucose monitoring system: clinical decisions and glycemic control after its use in pediatric type 1 diabetic subjects. *Diabetes Care* 24:2030–2034, 2001
- Bode BW, Gross TM, Thornton KR, Mastrototaro JJ: Continuous glucose monitoring used to adjust diabetes therapy improves glycosylated hemoglobin: a pilot study. *Diabetes Res Clin Pract* 46:183–190, 1999 [erratum in *Diabetes Res Clin Pract* 47:225, 2000]
- Ludvigsson J, Hanas R: Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. *Pediatrics* 111:933–938, 2003
- Chico A, Vidal-Rios P, Subira M, Novials A: The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemia in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. *Diabetes Care* 26:1153–1157, 2003
- Tanenbergh R, Bode B, Lane W, Levetan C, Mestman J, Harmel AP, Tobian J, Gross T, Mastrototaro J: Use of the continuous glucose monitoring system to guide therapy in patients with insulin-treated diabetes: a randomized controlled trial. *Mayo Clin Proc* 79:1521–1526, 2004
- Mastrototaro J: The MiniMed Continuous Glucose Monitoring System (CGMS) (Review). *J Pediatr Endocrinol Metab* 12 (Suppl. 3):751–758, 1999
- Weintrob N, Schechter A, Benzaquen H, Shalitin S, Lilos P, Galatzer A, Phillip M: Glycemic patterns detected by continuous subcutaneous glucose sensing in children and adolescents with type 1 diabetes mellitus treated by multiple daily injections vs continuous subcutaneous insulin infusion. *Arch Pediatr Adolesc Med* 158:677–684, 2004
- Dupont WD, Plummer WD Jr: Power and sample size calculation [article online], 2005. Available at <http://www.mc.vanderbilt.edu/prevmed/ps/index.htm>. Accessed 1 April 2005
- Salardi S, Zucchini S, Santoni R, Ragni L, Gualandi S, Cicognani A, Cacciari E: The glucose area under the profiles obtained with continuous glucose monitoring system relationships with HbA_{1c} in pediatric type 1 diabetic patients. *Diabetes Care* 25:1840–1844, 2002
- Schaepelynck-Belcar P, Vague P, Simonin G, Lassmann-Vague V: Improved metabolic control in diabetic adolescents using the continuous glucose monitoring system (CGMS). *Diabetes Metab* 29:608–612, 2003
- Djakoure-Platonoff C, Radermercker R, Reach G, Slama G, Selam JI: Accuracy of the continuous glucose monitoring system in inpatient and outpatient conditions. *Diabetes Metab* 29:159–162, 2003
- Alemzadeh R, Loppnow C, Parton E,

- Kirby M: Glucose sensor evaluation of glycemic instability in pediatric type 1 diabetes mellitus. *Diabetes Technol Ther* 5: 167–173, 2003
26. Amin R, Ross K, Acerini CL, Edge JA, Warner J, Dunger DB: Hypoglycemia prevalence in prepubertal children with type 1 diabetes on standard insulin regimen: use of continuous glucose monitoring system. *Diabetes Care* 26:662–667, 2003
27. McGowan K, Thomas W, Moran A: Spurious reporting of nocturnal hypoglycemia by CGMS in patients with tightly controlled type 1 diabetes. *Diabetes Care* 25:1499–1503, 2002 [erratum in *Diabetes Care* 26:553, 2003]
28. Diabetes Research in Children Network (DirecNet) Study Group: Accuracy of the GlucoWatch G2 Biographer and the continuous glucose monitoring system during hypoglycemia: experience of the Diabetes Research in Children Network. *Diabetes Care* 27:722–726, 2004 [see comments]
29. Guerci B, Floriot M, Bohme P, Durain D, Benichou M, Jellimann S, Drouin P: Clinical performance of CGMS in type 1 diabetic patients treated by continuous subcutaneous insulin infusion using insulin analogs. *Diabetes Care* 26:582–589, 2003
30. Tansey MJ, Beck RW, Buckingham BA, Mauras N, Fiallo-Scharer R, Xing D, Killman C, Tamborlane WV, Ruedy KJ, the Diabetes Research in Children Network (DirecNet) Study Group: Accuracy of the modified continuous glucose monitoring system (CGMS) sensor in an outpatient setting: results from a Diabetes Research in Children Network (DirecNet) study. *Diabetes Technol Ther* 7: 109–114, 2005