

**Slicing the Pie with Continuous Home Monitoring of Glucose:
Improved Glycemic Control with Real-life use of Continuous Glucose Sensors in Adult
Subjects with Type 1 Diabetes**

Satish K. Garg, MD^{1,2,3}
William C. Kelly, BS¹
Mary K. Voelmle, MS, FNP, CDE^{1,3}
Peter J. Ritchie, BA¹
Peter A. Gottlieb, MD^{1,2,3}
Kim K. McFann, PhD^{1,4}
Samuel L. Ellis, PharmD, CDE^{1,5}

¹Barbara Davis Center for Childhood Diabetes, Aurora, Colorado;
²Internal Medicine, ³Pediatrics, ⁴Preventive Medicine and Biometrics,
⁵University of Colorado at Denver, Aurora, Colorado.

Running Title: Real-life use of CHMG

Correspondence:

Satish K. Garg, MD, Barbara Davis Center for Childhood Diabetes, University of Colorado
at Denver, 1775 North Ursula Street, Aurora, CO 80045, Email: satish.garg@uchsc.edu

Received for publication 24 July 2007 and accepted in revised form 31 August 2007.

Improving metabolic control reduces micro- and macrovascular complications of diabetes. However, intensive insulin therapy increases severe hypoglycemia >3 fold (1-3).

Continuous glucose monitoring (CGM) is being introduced into routine clinical care despite a lack of reimbursement. Registration studies for FDA documented that subjects using real-time CGM are improve glucose excursions, reduce variability, decrease time spent in hypoglycemia and hyperglycemia and improve A1c values (4-9). Despite these reports, there is data unresponsive of new technologies such as CGM (10) or Personal Digital Assistants (11) for reducing hypoglycemia.

This study evaluates glucose control and its relationship to glucose target ranges with Continuous Home Monitoring of Glucose (CHMG).

Research Design and Methods

Inclusion criteria limited analysis to subjects with A1c values and downloaded CHMG data at baseline and 3 months and software to download receivers (not available for first 9 months). Patients who were pregnant or planning a pregnancy were excluded.

Twenty-four subjects on CHMG were included in this analysis. Subjects were computer matched for baseline A1c (\pm 0.3%), gender, age, and duration of diabetes except for one subject in the CHMG group who had diabetes for 57 years. Baseline demographics were similar between groups (Table). This protocol was IRB approved.

Procedures

Subjects initiating CHMG attended a session on glucose trends, features of the CHMG receiver, and proper insertion techniques, conducted by CDE's. All subjects were instructed to not change

treatment based on their first week of CHMG use.

All subjects had baseline and 12 week A1c measurements (DCA 2000 Bayer, Tarrytown, NY). The CHMG data was downloaded prospectively at baseline, 6 (\pm 2), and 12 weeks 12 (\pm 2) weeks, except for one subject who did not have 6 week data. Subjects wore sensors as they felt necessary. Every 3 days subjects were taught to override the receiver and use the same sensor for an additional 3 days.

All subjects in the comparison group received similar diabetes care. No six-week data or finger stick SMBG measurements were available for the comparison group.

CHMG data was analyzed for within (WTR, 60-150 mg/dL), above (ATR, > 150 mg/dL), and below (BTR, < 60 mg/dL) target ranges. The BTR of < 60 mg/dL was used due to clinical observations that subjects using CHMG are more likely to treat glucose values of 60 mg/dL, as opposed to 70 mg/dL, which was used for BTR in our previous SMBG publication (12). The ATR readings were further analyzed for 151-240 mg/dL and > 240 mg/dL. The percentages of readings within each target range were compared between baseline, 6, and 12 weeks. The number of subjects reaching target A1c values were also analyzed. No subject had severe hypoglycemia needing glucagon or ER visits.

Statistical Analysis

Analysis of A1c change from baseline and time within glycemic ranges was performed using SAS 9.1 software (SAS, Cary, NC). Two-tailed tests were used unless otherwise stated. Baseline characteristics were compared using independent samples T-tests. Fisher's Exact tests were performed on the number of subjects reaching target A1c values at baseline. Logistic regression, with baseline

A1c target as a covariate, was used to examine whether the experimental group was more likely than the comparison group to reach A1c targets by 3 months. Mixed model repeated measures analysis was used to evaluate the change over time in A1c, insulin dose, WTR, BTR and ATR within the CHMG group.

Results

Mean (\pm SD) sensor use per subject was 17.6 ± 8.4 days per month. Subjects extended use (despite 3 day approval and now 7 days) of sensors to 6.8 ± 1.6 days.

Changes in A1c

Mean (\pm SD) A1c values at baseline were $7.43 \pm 1.0\%$ and $7.39 \pm 1.0\%$ for the CHMG and comparison groups, respectively ($p = 0.896$, Table). There was a significant decrease in A1c in the CHMG group ($0.4\% \pm 0.5\%$; $p = 0.047$; Mixed Repeated Measures Analysis) at 12 weeks with a non-significant increase in A1c ($0.3 \pm 1.1\%$; $p = 0.0710$) in the comparison group. Also, at 12 weeks there was a difference in A1c values between groups ($p = 0.0385$), despite no change in insulin dose. Number of subjects achieving A1c values $< 7.5\%$ was higher in the CHMG group at 12 weeks (OR = 7.229, $p = 0.0234$) (13).

Glucose Target Ranges

Subjects using CHMG increased mean (\pm SD) glucose readings in WTR by $6.5 \pm 15.0\%$ ($p = 0.0353$), and reduced mean glucose readings in ATR by $5.6 \pm 16.7\%$ ($p = 0.0355$) at 12 weeks compared to baseline. Glucose values in ATR also showed a significant reduction in readings > 240 mg/dL by $6.4 \pm 14.0\%$ ($p = 0.0351$) at 12 weeks. Results were similar for subjects using MDI or insulin pumps.

Conclusions

This study demonstrates that use of real-time CHMG is associated with

improved metabolic control over 12 weeks in adults with type 1 diabetes as documented previously (8, 14-19). This study supports previous findings carrying over to real-life use of CHMG in subjects with reasonable glucose control (A1c $\sim 7.4\%$). The modest improvement in A1c of 0.4% could be due to the subject population, short term nature of the study, and near target baseline A1c values of 7.43%.

Improvements in metabolic control with CHMG were not associated with increased hypoglycemia, supporting earlier findings (8, 14-19).

The mean increase in WTR of 6.5% and decrease in ATR of 5.6% at 3 months corresponded to a 0.4% decline in A1c, which is lower than expected from our previous SMBG data (12). This could be due to lower A1c values at baseline.

Limitations of this study include a small sample size, shorter follow up and lack of a randomized control group. However, the data shows that CHMG use results in a small A1c reduction without increasing hypoglycemia, probably due to behavioral changes.

We conclude that use of CHMG can further improve glucose control in relatively well controlled subjects with type 1 diabetes, with no increase in hypoglycemia. Prospective randomized clinical trials using CHMG with a large sample size need to be conducted.

Acknowledgments

This study was sponsored in part by grant 08 FLA 00250, State of Colorado Public Health and Environment; grant P30 DK575616 Diabetes Endocrine Research Center, National Institutes of Health; grant M01 RR00069 General Clinical Research Centers Program, National Institutes of Health; grant R01 HL61753, RO1 HL079611, RO1 DK32493, and Children's Diabetes Foundation in Denver, CO.

References

- 1: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329:977-86, 1993
- 2: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:837-53, 1998
- 3: Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 290:2159-67, 2003
- 4: Garg SK, Schwartz S and Edelman SV: Improved glucose excursions using an implantable real-time continuous glucose sensor in adults with type 1 diabetes. *Diabetes Care* 27:734-8, 2004
- 5: Garg S and Jovanovic L: Relationship of fasting and hourly blood glucose levels to HbA1c values: safety, accuracy, and improvements in glucose profiles obtained using a 7-day continuous glucose sensor. *Diabetes Care* 29:2644-9, 2006
- 6: Diess D, Bolinder J, Rivelino JP, Battelino T, Bosi E, Tubiana-Rufi N, Kerr D, and Phillip M: Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care* 29:2730-2, 2006
- 7: Bailey T, Zisser H, Garg S: Reduction in hemoglobin A1c with real-time continuous glucose monitoring: results from a 12-week observational study. *Diabetes Technol Ther* 8:203-210, 2007
- 8: Chase HP, Kim LM, Owen SL, MacKenzie TA, Klingensmith GJ, Murtfeldt R and Garg SK: Continuous subcutaneous glucose monitoring in children with type 1 diabetes. *Pediatrics* 107:222-6, 2001
- 9: 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
- 10: Hirsch I, Bode B, Abelseth J, Fischer J, Kaufman F, Mastrototaro J, Wolpert H, and Buckingham B: Sensor augmented pump therapy: results of the first treat-to-target study (Abstract 0090-OR). *Diabetes* 56 (spp1):A24, 2007
- 11: Ellis S, Beatson C, Gottlieb P, Gutin R, Bookout T, Figal C, Snyder B, and Garg S: Improved glycemic control in intensively treated subjects with type 1 diabetes using Accu-Chek® Advisor insulin guidance software (Abstract 0031-OR). *Diabetes* 56 (spp1): A8, 2007
- 12: Brewer KW, Chase HP, Owen S and Garg SK: Slicing the pie. Correlating HbA1c values with average blood glucose values in a pie chart form. *Diabetes Care* 21:209-12, 1998
- 13: American Diabetes Association: clinical practice recommendations 2006. *Diabetes Care* 29 (spp1):S1-S85, 2006
- 14: Bode BW, Gross TM, Thornton KR and Mastrototaro JJ: Continuous glucose monitoring used to adjust diabetes therapy improves glycosylated hemoglobin: a pilot study. *Diabetes Res Clin Pract* 46:183-90, 1999
- 15: Chase HP, Roberts MD, Wightman C, Klingensmith G, Garg SK, Van Wyhe M, Desai S, Harper W, Lopatin M, Bartkowiak M, Tamada J and Eastman RC: Use of the GlucoWatch Biographer in children with type 1 diabetes. *Pediatrics* 111:790-4, 2003

- 16: Ludvigsson J and Hanas R: Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. *Pediatrics* 111:933-8, 2003
- 16: Ludvigsson J and Hanas R: Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. *Pediatrics* 111:933-8, 2003
- 17: Schaepelynck-Belicar P, Vague P, Simonin G and Lassmann-Vague V: Improved metabolic control in diabetic adolescents using the continuous glucose monitoring system (CHMGS). *Diabetes Metab* 29:608-12, 2003
- 18: Schiaffini R, Ciampalini P, Fierabracci A, Spera S, Borrelli P, Bottazzo GF and Crino A: The Continuous Glucose Monitoring System (CHMGS) in type 1 diabetic children is the way to reduce hypoglycemic risk. *Diabetes Metab Res Rev* 18:324-9, 2002
- 19: Tanenberg R, Bode B, Lane W, Levetan C, Mestman J, Harmel AP, Tobian J, Gross T and 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* 79:1521-6, 2004

Table: Demographics and Results						
	Baseline			3 Months		
	CHMG	Comparison	p-value	CHMG	Comparison	p-value
n	24	23	NS*			
Age (years) [†]	45.8 ± 13.2	44.3 ± 13.4	0.703			
Duration (years) [†]	27.2 ± 16.6	24.0 ± 15.8	0.513			
Gender M/F	11/13	10/13	0.871			
BMI (kg/m ²) [†]	26.1 ± 4.1	26.9 ± 4.8	0.565			
Treatment						
MDI	18	16	0.677			
CSII	6	7				
A1c (%) [†]	7.43 ± 1.0 [‡]	7.39 ± 1.0	0.896	7.06 ± 0.8 [‡]	7.73 ± 1.4	0.039
Target A1c						
A1c < 7.5%	14/24	13/23	0.900	20/24	12/23	0.023
A1c < 7.0%	7/24	6/23	0.814	12/24	6/23	0.211
A1c < 6.5%	4/24	4/23	1.000	4/24	3/23	1.000
Insulin Dose [†]	51.9 ± 31.4 [§]	45.7 ± 28.6 [§]	0.413	50.1 ± 31.4 [§]	49.0 ± 33.4 [§]	0.310
Glucose Target Ranges [†]						
WTR (%)	42.6 ± 19.5	n/a	n/a	49.1 ± 16.7	n/a	0.0353 [¶]
ATR (%)	53.2 ± 20.4	n/a	n/a	47.6 ± 17.0	n/a	0.0355 [¶]
BTR (%)	4.2 ± 3.5	n/a	n/a	3.4 ± 6.7	n/a	0.638 [¶]

* Non-significant

† Represents values in ± SD

‡ There was a significant decrease (p= 0.047) in A1c in the CHMG group from baseline to 3 months.

§ There was no significant change in total insulin dose in the CHMG or comparison group from baseline to 3 months.

|| Within the target range (WTR) glycemia was defined as 60-150 mg/dl (3.3-8.3 mmol/L).

¶ These p values represent differences in glucose target ranges from baseline to 3 months in the CHMG group using mixed model repeated measures analysis.